



Review

Environmental Risk Factors and Health: An Umbrella Review of Meta-Analyses

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Abstract: Background: Environmental health is a growing area of knowledge, continually increasing and updating the body of evidence linking the environment to human health. **Aim:** This study summarizes the epidemiological evidence on environmental risk factors from meta-analyses through an umbrella review. **Methods:** An umbrella review was conducted on meta-analyses of cohort, case-control, case-crossover, and time-series studies that evaluated the associations between environmental risk factors and health outcomes defined as incidence, prevalence, and mortality. The specific search strategy was designed in PubMed using free text and Medical Subject Headings (MeSH) terms related to risk factors, environment, health outcomes, observational studies, and meta-analysis. The search was limited to English, Spanish, and French published articles and studies on humans. The search was conducted on September 20, 2020. Risk factors were defined as any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or death. The environment was defined as the external elements and conditions that surround, influence, and affect a human organism or population's life and development. The environment definition included the physical environment such as nature, built environment, or pollution, but not the social environment. We excluded occupational exposures, microorganisms, water, sanitation and hygiene (WASH), behavioral risk factors, and no-natural disasters. **Results:** This umbrella review found 197 associations among 69 environmental exposures and 83 diseases and death causes reported in 103 publications. The environmental factors found in this review were air pollution, environmental tobacco smoke, heavy metals, chemicals, ambient temperature, noise, radiation, and urban residential surroundings. Among these, we identified 65 environmental exposures defined as risk factors and 4 environmental protective factors. In terms of study design, 57 included cohort and/or case-control studies, and 46 included time-series and/or case-crossover studies. In terms of the study population, 21 included children, and the rest included adult population and both sexes. In this review, the largest body of evidence was found in air pollution (91 associations among 14 air pollution definitions and 34 diseases and mortality diagnoses), followed by environmental tobacco smoke with 24 associations. Chemicals (including pesticides) were the third larger group of environmental exposures found among the meta-analyses included, with 19 associations. **Conclusion:** Environmental exposures are an important health determinant. This review provides an overview of an evolving research area and should be used as a complementary tool to understand the connections between the environment and human health. The evidence presented by this review should help to design public health interventions and the implementation of health in all policies approach aiming to improve population health.



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1. Introduction

In 2012, the World Health Organization (WHO) estimated that 12.6 million global deaths, representing 23% (95% CI: 13–34%) of all deaths, were attributable to the environment [1]. Air pollution and second-hand smoke are responsible for 52 million lower-respiratory diseases each year, representing 35% of the global cases [1]. Non-communicable diseases are also related to air pollution, chemicals, and second-hand smoke, which are responsible for 119 million cardiovascular diseases each year, 49 million cancers, and 32 million chronic respiratory diseases [1]. Environmental risks to health include pollution, radiation, noise, land use patterns, or climate change [2].

Environmental health is a growing area of knowledge, continually increasing and updating the body of evidence linking the environment to human health. The Global Burden of Disease project considers 26 environmental and occupational risk factors in their estimations [3]. Such risk factors are those that have enough evidence to be translated with available global exposure data to quantify their impact across the globe. However, these are far from representing the totality of evidence related to environmental exposures and human health.

Global populations are also facing population growth and aging, increasing groups vulnerable to environmental risk factors. Around 10% of the global gross domestic product is spent on healthcare [2], but little is allocated to primary prevention and public health. Be able to identify environmental risk factors is crucial in the decision-making process aiming to protect public health. The investment in measures and policies aiming to reduce environmental risks could help alleviate the health burden that health care systems around the globe are facing.

This study aims to provide an overview of the most recent evidence linking environmental risk factors and health outcomes. Applying an umbrella review approach, this study presents a synthesis of the epidemiological evidence from meta-analyses. The umbrella review systematically identifies and selects the available scientific publications in a research area. The review focuses on meta-analyses from cohort, case-control, case-crossover, and time-series observational studies, relating short and long-term environmental exposures to morbidity and mortality. The review summarizes the statistically significant associations reported in the latest published meta-analysis with the largest available number of individual studies and populations.

2. Methodology

This study is a systematic collection and assessment of multiple systematic reviews with meta-analyses performed on a specific research topic, also known as an umbrella review. The methods of the umbrella review are standardized. In this work, we follow state-of-the-art approaches, as in previously published umbrella reviews on risk factors for health outcomes [4]. The study protocol was developed in accordance with the reporting guidance in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement and registered in the International Prospective Register of Systematic Reviews (PROSPERO—CRD42020196152).

2.1. Literature Search

A search strategy was designed to identify studies published in Medline via PubMed. The search strategy identified systematic reviews of observational studies with a meta-analysis that evaluated the associations between environmental risk factors and health outcomes defined as incidence, prevalence, and mortality. We further hand-searched reference lists of the retrieved eligible publications to identify additional relevant studies.

The specific search strategy included free text and Medical Subject Headings (MeSH) terms related to risk factors, environment, health outcome, observational studies, and meta-analysis. The search was limited to English, Spanish, and French published articles and studies on humans. The last search was conducted on 20 September 2020. The results of the searches were cross-checked to eliminate duplicates.

Search Strategy

(“Risk Factors” [Mesh]) OR risk factor OR Environmental risk factors)
 AND
 (Environment * OR “Environment”[Mesh] OR Environmental pollution OR “Environmental Pollution”[Mesh] OR Environmental exposures OR “Environmental Exposure”[Mesh] OR Environment Design OR “Environment Design”[Mesh] OR Built Environment OR “Built Environment”[Mesh] OR Environmental Medicine OR “Environmental Medicine”[Mesh] OR Decontamination OR “Decontamination”[Mesh])
 AND
 (Health OR “Health”[Mesh] OR Health Outcome OR Population Health OR “Population Health”[Mesh] OR Pathological Conditions OR “Pathological Conditions, Signs and Symptoms”[Mesh] OR Pathologic Processes OR “Pathologic Processes”[Mesh] OR Disease OR “Disease”[Mesh] OR Syndrome OR “Syndrome”[Mesh] OR Morbidity OR “Morbidity”[Mesh] OR Incidence OR “Incidence”[Mesh] OR Prevalence OR “Prevalence”[Mesh] OR Mortality OR “Mortality”[Mesh] OR Death OR “Death”[Mesh] OR Cause of Death OR “Cause of Death”[Mesh] OR Life Expectancy OR “Life Expectancy”[Mesh])
 AND
 (Longitudinal Studies OR “Longitudinal Studies”[Mesh] OR Observational Study OR “Observational Study” [Publication Type] OR Cohort Studies OR “Cohort Studies”[Mesh] OR Case-Control Studies OR “Case-Control Studies”[Mesh] OR Time Series OR “Interrupted Time Series Analysis”[Mesh])
 AND
 (Meta-Analysis OR “Meta-Analysis” [Publication Type])
 NOT
 (“Social Environment” [MeSH Terms] OR Social Environment)

2.2. Selection Criteria

We included meta-analyses of cohort, case-control, case-crossover, and time-series studies examining associations between health outcomes and potential environmental risk factors. Health outcomes were defined as disease incidence, prevalence, cause-specific mortality, and all-cause mortality. Risk factors were defined as any attribute, characteristic, or exposure of an individual that increases the likelihood of developing a disease or death. The environment was defined as the external elements and conditions that surround, influence, and affect a human organism or population’s life and development. The environment definition included the physical environment such as nature, built environment, or pollution, but not the social environment. We excluded occupational exposures, microorganisms, water, sanitation and hygiene (WASH), behavioral risk factors, and no-natural disasters. We only included meta-analyses that reported statistically significant pooled effect estimates and confidence intervals (CI) from observational studies. When two or more meta-analyses existed for an association, we included the most recent meta-analysis with the largest number of studies and populations. We chose eligible articles by consecutively examining the titles, abstracts, and the full-text. Two investigators (DRR and EMZ) independently and blindly screened the titles and abstracts to determine the articles’ inclusion. Eligibility criteria were applied to the full-text articles during the final selection. We manually searched the references of the relevant articles and attempted to identify and include eligible studies. Disagreements were resolved via discussion between reviewers.

2.3. Data Extraction and Analysis

Data extracted from each meta-analysis included the first author, publication year, environmental risk factor, exposure unit or exposure comparator, exposure temporality, study design, population, health outcome, number of studies included, summary meta-analytic estimates (i.e., odds ratio or relative risk) and corresponding 95% CI, random effect p-value, and heterogeneity measure. A narrative synthesis of the included meta-analyses was carried out by environmental risk factors, health outcomes, and population.

To assess the strength of epidemiologic evidence, we considered the estimate's precision and the results' consistency. We noted which associations met the following criteria: (1) precision of the estimate (i.e., $p < 0.001$, a threshold associated with significantly fewer false-positive results), and (2) consistency of results ($I^2 < 50\%$). The strength of the epidemiologic evidence was rated as high (when both criteria were satisfied), moderate (if 1 consistency of results was not satisfied), or low (if both consistencies of results were not satisfied).

3. Results

3.1. Literature Review

We identified 1266 publications in PubMed and 87 publications through a hand search (Figure 1). We excluded 1137 (89%) publications after screening the titles and abstracts for duplications or for not meeting our inclusion criteria. After, we reviewed the full texts of the remaining 216 (11%) publications. From these publications, 1 publication was excluded because it did not report a meta-analysis, 7 because they did not include an environmental risk factor, 10 due to the lack of statistical significance in the pooled meta-estimates, 17 because the meta-analysis did not include cohort, case-control, case-crossover, and time-series studies or combined cross-sectional studies with cohort or case-control studies, 26 because they did not report morbidity (incidence or prevalence) or related mortality estimates, and finally, 52 others because the studies they did not provide the latest available evidence and/or the largest sample size.

In total, 103 publications associating environmental risk factors and health outcomes through were included in this umbrella review. These studies include a total of 69 environmental risk factors that were grouped in air pollutants (14 risk factors), environmental tobacco smoke (6 risk factors), chemicals and heavy metals (25 risk factors), physical exposures (14 risk factors), and surrounding residential exposures (10 risk factors). On average, the meta-analysis included 37 studies ranging from 2 to 652. In terms of study design, 57 included cohort and/or case-control studies, and 46 included time-series and/or case-crossover studies. In terms of the study population, 1 included the elderly, 1 included only men, 13 included only women, 21 included children, and the rest included adult population and both sexes. From all the meta-analyses included, 9 were published before 2013, 13 were published in 2014, 7 in 2015, 11 in 2016, 13 in 2017, 14 in 2018, 24 in 2019, and 12 in 2020. In total, the studies reported 72 different long- and short-term diseases or mortality diagnoses.

3.2. Air Pollution

We identified 14 air pollutants related to 34 diseases and mortality diagnoses. The air pollutant with the most extensive list of health impacts (29 diagnoses) was the particulate matter with less than 2.5 micrometers of diameter (PM_{2.5}), followed by particulate matter with less than 10 micrometers of diameter (PM₁₀) (17), nitrogen dioxide (NO₂) (17), ozone (O₃) (7), household air pollution (5), sulfur dioxide (SO₂) (4), carbon monoxide (CO) (4), solid fuel use (4), nitrogen oxides (2), desert dust (2), biomass burning (2), black carbon (1), and indoor air pollution from solid fuel (1). Air pollution was reported to affect all age groups and both sexes.

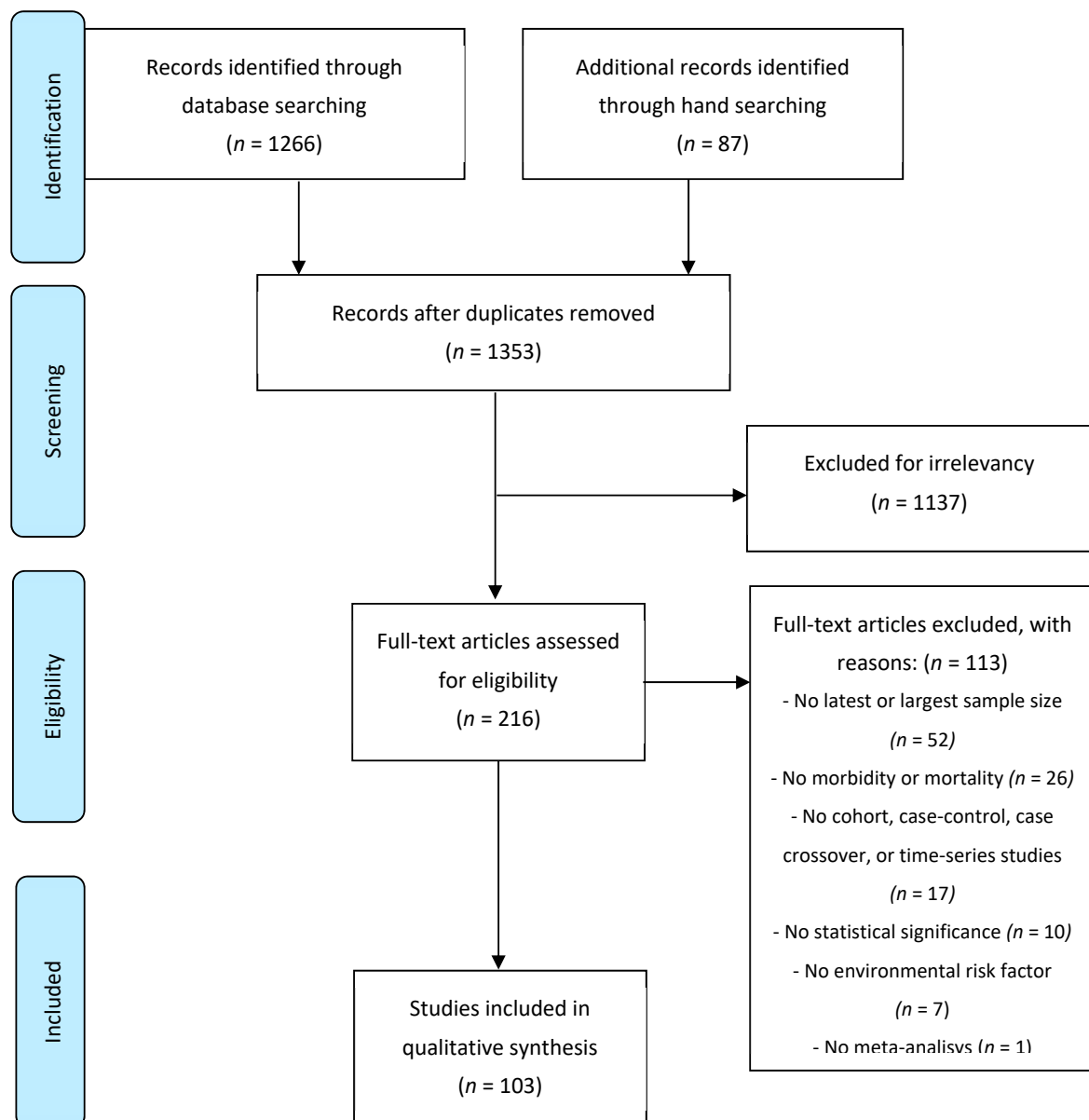


Figure 1. Flow diagram of the study selection.

Long-term impacts of particulate matter (PM_{2.5} and PM₁₀) were reported for 35 diagnoses and causes of death (Tables 1, 9 and 10). Adults exposed to PM_{2.5} or PM₁₀ reported an increased risk of chronic kidney disease [5], type 2 diabetes [6], lung cancer mortality [7,8], and cancer mortality [7]. Adults exposed to PM_{2.5} also reported an increased risk of Alzheimer’s disease [9], all-cause mortality [10], cardiovascular mortality [11], chronic obstructive pulmonary disease (COPD) [8], colorectal cancer mortality [7], dementia [9], depression [12], ischemic heart disease (IHD) mortality [8], liver cancer mortality [7], natural mortality [11], respiratory mortality [11], stroke [13], stroke mortality [8] and Parkinson’s disease [14]. Adults exposed to PM₁₀ reported an increased incidence of coronary events [15] and chronic bronchitis [16]. Pregnant women exposed to PM_{2.5} reported an association with offspring diagnosis of autistic syndrome disorder [17], small for gestational age [18], and those exposed to PM₁₀ reported an association with low birth weight [18] and preterm birth [18]. For children, exposure to PM_{2.5} was associated with asthma [19], acute respiratory infections [8], and autistic spectrum disorder [20]. Moreover, children’s exposure to PM₁₀ was also associated with an increased risk of asthma [19] and autistic spectrum disorder [20].

Table 1. Particulate matter less than 2.5 micrometers of diameter (PM2.5) and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|---------------------------|----------------------------------|----------------------|--------------|--------------------|---------------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|----------|----------------------|
| PM2.5 | per 1 mcg/m ³ | Long-term | Cohort | Adults, both sexes | Alzheimer’s disease | 3 | [9] | 2019 | 86 | 0 | HR | 4.82 | 2.28 | 7.36 | Moderate |
| | | | | | All-cause mortality | 13 | [10]. | 2013 | 65 | 0.001 | RR | 1.06 | 1.04 | 1.08 | Moderate |
| | | | | | Cardiovascular mortality | 17 | [11] | 2014 | 98 | NR | RR | 1.19 | 1.09 | 1.31 | Low |
| | | | | | Chronic kidney disease | 4 | [5] | 2020 | 82 | 0.001 | RR | 1.10 | 1.00 | 1.21 | Low |
| | | | | | Chronic Obstructive Pulmonary Disease | 4 | [8] | 2014 | NR | NR | IRF | F | F | F | Low |
| | Dementia | | | | 4 | [9] | 2019 | 97 | 0 | HR | 3.26 | 1.20 | 5.31 | Moderate | |
| | Depression | | | | 5 | [12] | 2019 | 0 | 0.97 | OR | 1.10 | 1.02 | 1.19 | Moderate | |
| | Ischemic heart disease mortality | | | | 16 | [8] | 2014 | NR | NR | IRF | F | F | F | Low | |
| | Lung cancer mortality | | | | 49 | [8] | 2014 | NR | NR | IRF | F | F | F | Low | |
| | Liver cancer mortality | | | | 2 | [7] | 2018 | 67 | NR | RR | 1.29 | 1.06 | 1.58 | Low | |
| | Colorectal cancer mortality | | | | 2 | [7] | 2018 | 97 | NR | RR | 1.08 | 1.00 | 1.17 | Low | |
| | Cancer mortality | | | | 19 | [7] | 2018 | 97 | <0.001 | RR | 1.17 | 1.11 | 1.24 | Moderate | |
| | Natural mortality | | | | 11 | [11] | 2014 | 87 | NR | RR | 1.05 | 1.01 | 1.01 | Low | |
| | Respiratory mortality | | | | 8 | [11] | 2014 | 61 | NR | RR | 1.05 | 1.01 | 1.09 | Low | |
| | Stroke | | | | 16 | [13] | 2019 | 77 | 0 | HR | 1.11 | 1.05 | 1.17 | Moderate | |
| | Stroke mortality | | | | 16 | [8] | 2014 | NR | NR | IRF | F | F | F | Low | |
| | Type 2 diabetes | | | | 10 | [6] | 2020 | 55 | 0.012 | RR | 1.11 | 1.03 | 1.19 | Low | |
| | Parkinson’s disease | | | | 8 | [14] | 2019 | 86 | <0.001 | RR | 1.06 | 0.99 | 1.14 | Moderate | |

LCI: lower confidence intervals; UCI: upper confidence intervals; NR: No reported; HR: hazard ratios; RR: relative risk; IRF: integrated response function; F: function; OR: odds ratio.

Particulate matter that includes PM_{2.5} and PM₁₀ reported six diagnoses and causes of death related to short-term exposures (Table 9). In adults, short-term exposure to PM_{2.5} and PM₁₀ were associated with out-of-hospital cardiac arrest [21], cardiac arrhythmia [22], daily cardiovascular, respiratory, and natural mortality [23]. In addition, for PM₁₀, suicide was also reported as a short-term impact [12]. In children, short-term exposure to PM_{2.5} or PM₁₀ was associated with pneumonia [24].

Desert dust, an important natural source of particulate matter, was also associated with health impacts (Table 10). This review identified one meta-analysis of adult exposure to desert dust, reporting an increased risk of cardiovascular mortality and natural mortality [25]. Another component of particulate matter is black carbon, which originates from fossil fuel and biomass combustion. We identified one meta-analysis on black carbon in children reporting an increased risk of asthma [19].

Nitrogen oxides (NO_x and NO₂) were associated with 18 different diagnoses and causes of death (Table 11). Pregnant women's exposure to NO_x was associated with low birth weight [18] and preterm birth [18]. For the same group, exposure to NO₂ reported an increased risk of low birth weight [18] and small for gestational age [18]. For adults, long-term exposure to NO₂ was associated with an increased risk of all-cause mortality [11], autistic syndrome disorder [17], cancer mortality [7], cardiovascular mortality [11], chronic kidney disease [5], cancer mortality [7], respiratory mortality [11], and type 2 diabetes [26]. Furthermore, for adults, short-term exposure to NO₂ was associated with an increased risk of out-of-hospital cardiac arrest [21], cardiac arrhythmia [22], conjunctivitis [27], depression [28], and natural mortality [16]. Lastly, children's long-term exposure to NO₂ was associated with an increased risk of asthma [19], and short-term exposure with an increased risk of pneumonia [24].

Ozone (O₃) was found as a risk factor for seven diagnoses and causes of death (Table 7). Long-term exposure to O₃ was reported to increase IHD mortality [29] and Parkinson's disease [14] in adults and for pregnant women with preterm birth [18]. Short-term exposure to ozone was associated as a risk factor for pneumonia in children [24] and in adults with out-of-hospital cardiac arrest [21], all-cause mortality [16], and cardiovascular and respiratory mortality [16].

Sulfur dioxide (SO₂) is a prevalent pollutant and was found as a risk factor for four diagnoses (Table 7). SO₂ is a gas primarily emitted from fossil fuel combustion at power plants and other industrial facilities as well as from fuel combustion in mobile sources like locomotives or ships. In their first trimester, pregnant women exposed to SO₂ reported an increased risk of gestational diabetes mellitus [30]. Pregnant women exposed during any trimester also reported an increased risk of low birth weight [18]. Short-term exposures to SO₂ were associated with pneumonia in children [24] and cardiac arrhythmia in adults [22].

Carbon monoxide (CO) is a gas produced by fuel combustion in motorizing vehicles, small engines, stoves, and fireplaces, among others (Table 7). We identified four health impacts associate with CO exposure. In short term exposures, CO was reported as a risk factor for pneumonia in children [24], and cardiac arrhythmia [22], and out-of-hospital cardiac arrest in adults [21]. CO exposure during pregnancy was also reported as a risk factor for preterm birth [18].

Household air pollution represents indoor air pollution from multiple sources (e.g., cooking and heating) (Table 8). Under this review, we identified five types of cancers related to household air pollution exposure. Specifically, one meta-analysis reported an increased risk for cervical, laryngeal, nasopharyngeal, oral, and pharyngeal cancers [31]. Indoor air pollution from solid fuels was also found as a risk factor for hypertension [32]. Solid fuel use by pregnant women was associated with low birth weight, stillbirth, preterm birth, and intrauterine growth retardation in another meta-analysis [33]. Finally, biomass burning was associated with an increased risk of esophageal squamous cell carcinoma [34] and COPD [35].

Table 2. Ozone (O3), Sulfur Dioxide (SO2), and Carbon Monoxide (CO), long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | |
|---------------------------|-----------------------------|-------------------------|-------------------------|--|----------------------------------|--------------------------------|-----------|------|--------|---------|---------------|-------------|-------|-------|----------------------|----------|
| O3 | per 5 ppb | Long-term | Cohort | Adults, both sexes | Ischemic heart disease mortality | 4 | [29] | 2016 | 67 | 0.02 | RR | 1.02 | 1 | 1.04 | Low | |
| | per 10 mcg/m ³ | | | Pregnant women | Preterm birth | 3 | [18] | 2019 | 0 | NR | OR | 1.04 | 1 | 1.07 | Moderate | |
| | per 10 ppb | | Cohort and Case-Control | Adults, both sexes | Parkinson's disease | 5 | [14] | 2019 | 0 | 0.69 | RR | 1.01 | 1 | 1.02 | Moderate | |
| | per 20 ppb | Short-term | Time-series | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 53 | NR | RR | 1.02 | 1.01 | 1.02 | Low |
| | | | | Children (<18 years) | Pneumonia | 12 | [24] | 2017 | 75 | 0 | RR | 1.02 | 1.01 | 1.03 | Moderate | |
| | | | | Adults | All-cause mortality | 32 | [16] | 2015 | NR | NR | RR | 1.003 | 1.001 | 1.004 | Low | |
| per 10 mcg/m ³ | | | | Cardiovascular and respiratory mortality | 32 | [16] | 2015 | NR | NR | RR | 1.005 | 1.001 | 1.009 | Low | | |
| SO2 | per 5 ppb | 1st pregnancy trimester | Cohort | Pregnant women | Gestational diabetes mellitus | 5 | [30] | 2020 | 93 | 0 | OR | 1.39 | 1.01 | 1.77 | Moderate | |
| | per 10 mcg/m ³ | Long-term | Cohort | Pregnant women | Low birth weight | 5 | [18] | 2019 | 98 | NR | OR | 1.21 | 1.08 | 1.35 | Low | |
| | per 10 ppb | Short-term | Time-series | Adults, both sexes | Cardiac arrhythmia | 10 | [22] | 2016 | 77 | NR | RR | 1.02 | 1 | 1.04 | Low | |
| | | | | Children (<18 years) | Pneumonia | 8 | [24] | 2017 | 48 | 0.04 | RR | 1.03 | 1 | 1.05 | Moderate | |
| CO | per 1 mcg/m ³ | Long-term | Cohort | Pregnant women | Preterm birth | 7 | [18] | 2019 | 89 | NR | OR | 1.06 | 1.04 | 1.08 | Low | |
| | per 1 ppm | Short-term | Time-series | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 44 | NR | RR | 1.06 | 1 | 1.14 | Moderate |
| | | | | Adults, both sexes | Cardiac arrhythmia | 12 | [22] | 2016 | 90 | NR | RR | 1.04 | 1.02 | 1.06 | Low | |
| | | | | Children (<18 years) | Pneumonia | 7 | [24] | 2017 | 68 | 0.004 | RR | 1.01 | 1 | 1.02 | Low | |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

Table 3. Household Air Pollution, indoor air pollution from solid fuel, biomass burning, and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I ² (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|--------------------------------------|-----------------------------|----------------------|-------------------------|--------------------|---------------------------------------|------------------|-----------|------|--------------------|---------|---------------|-------------|------|-------|----------------------|
| Household air pollution | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Cervical cancer | 4 | [31] | 2015 | NR | 0.45 | OR | 6.46 | 3.12 | 13.36 | Low |
| | | | | | Laryngeal cancer | 5 | [31] | 2015 | NR | 0.49 | OR | 2.35 | 1.72 | 3.21 | Low |
| | | | | | Nasopharyngeal cancer | 6 | [31] | 2015 | NR | 0.06 | OR | 1.8 | 1.42 | 2.29 | Low |
| | | | | | Oral cancer | 4 | [31] | 2015 | NR | 0.93 | OR | 2.44 | 1.87 | 3.19 | Low |
| | | | | | Pharyngeal cancer | 4 | [31] | 2015 | NR | 0.99 | OR | 3.56 | 2.22 | 5.7 | Low |
| Indoor air pollution from solid fuel | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Hypertension | 11 | [32] | 2020 | 90 | 0 | OR | 1.52 | 1.26 | 1.85 | Moderate |
| Solid fuel use | Exposed vs. not exposed | Long-term | Cohort | Pregnant women | Low birth weight | 12 | [33] | 2014 | 28 | 0.07 | OR | 1.35 | 1.23 | 1.48 | Moderate |
| | | | | | Stillbirth | 5 | [33] | 2014 | 0 | 0.44 | OR | 1.29 | 1.18 | 1.41 | Moderate |
| | | | | | Preterm birth | 3 | [33] | 2014 | 0 | 0.39 | OR | 1.30 | 1.06 | 1.59 | Moderate |
| | | | | | Intrauterine growth retardation | 2 | [33] | 2014 | 0 | 0.89 | OR | 1.23 | 1.01 | 1.49 | Moderate |
| Biomass burning | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Esophageal squamous cell carcinoma | 16 | [34] | 2019 | 79 | NR | OR | 3.02 | 2.22 | 4.11 | Low |
| | | | Cohort and Case-Control | Adults, both sexes | Chronic Obstructive Pulmonary Disease | 8 | [35] | 2017 | 93 | <0.001 | OR | 2.21 | 1.3 | 3.76 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; OR: odds ratio.

Table 4. Particulate matter less than 2.5 micrometers of diameter (PM2.5), long-term, and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|---------------------------|-----------------------------|----------------------|----------------|---------------------|----------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| PM2.5 | per 10 mcg/m ³ | Long-term | Cohort | Children | Asthma | 10 | [36] | 2017 | 28 | 0.18 | OR | 1.03 | 1.01 | 1.05 | Moderate |
| | | | | | Autism spectrum disorder | 3 | [20] | 2016 | 0 | 0.54 | OR | 2.32 | 2.15 | 2.51 | Moderate |
| | | | | Children (<5 years) | Acute low respiratory infections | 28 | [8] | 2014 | NR | NR | IRF | F | F | F | Low |
| | | | | Pregnant women | Small for gestational age | 5 | [18] | 2019 | 51 | NR | OR | 1.01 | 1.00 | 1.03 | Low |
| | | | | | Autistic syndrome disorder | 9 | [17] | 2020 | 91 | <0.001 | RR | 1.06 | 1.01 | 1.11 | Moderate |
| | per 10 mcg/m ³ | Short-term | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 12 | [21] | 2017 | 70 | NR | RR | 1.04 | 1.01 | 1.07 | Low |
| | | | | | Cardiac arrhythmia | 17 | [22] | 2016 | 78 | NR | RR | 1.15 | 1.01 | 1.03 | Low |
| | | | Time-series | Adults, both sexes | Daily cardiovascular mortality | 652 | [23] | 2019 | NR | NR | RR | 1.36 | 1.30 | 1.43 | Low |
| | | | | | Daily mortality | 652 | [23] | 2019 | NR | NR | RR | 1.68 | 1.59 | 1.77 | Low |
| | | | | | Daily respiratory mortality | 652 | [23] | 2019 | NR | NR | RR | 1.47 | 1.35 | 1.58 | Low |
| | | | | | Children (<18 years) | Pneumonia | 11 | [24] | 2017 | 38 | 0.08 | RR | 1.02 | 1.01 | 1.03 |

LCI: lower confidence intervals; UCI: upper confidence intervals; NR: No reported; HR: hazard ratios; RR: relative risk; IRF: integrated response function; F: function; OR: odds ratio.

Table 5. Particulate matter less than 10 micrometers of diameter (PM10), desert dust, black carbon, long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | | | | | | | | | | | |
|---------------------------|--|----------------------|----------------------|--------------------------|---------------------------------|------------------|----------------|--------------------|--------------------------------|----------|---------------|-------------|------|----------|----------------------|-----------------|------|------|----------|--------------------|----|------|------|------|------|-----|
| PM10 | per 2 mcg/m ³ | Long-term | Cohort | Adults, both sexes | Chronic kidney disease | 4 | [5] | 2020 | 81 | 0.001 | RR | 1.16 | 1.05 | 1.29 | Low | | | | | | | | | | | |
| | | | | | Type 2 diabetes | 6 | [6] | 2020 | 68 | 0.004 | RR | 1.12 | 1.01 | 1.23 | Moderate | | | | | | | | | | | |
| | | | | | Incidence of coronary events | 11 | [15] | 2014 | 0 | 0.81 | HR | 1.12 | 1.01 | 1.25 | Moderate | | | | | | | | | | | |
| | | | | | Lung cancer mortality | 9 | [7] | 2018 | 93 | NR | RR | 1.07 | 1.03 | 1.11 | Low | | | | | | | | | | | |
| | | | | | Cancer mortality | 12 | [7] | 2018 | 91 | <0.001 | RR | 1.09 | 1.04 | 1.14 | Moderate | | | | | | | | | | | |
| | | | | | Incidence of chronic bronchitis | 3 | [16] | 2015 | NR | NR | RR | 1.11 | 1.04 | 1.18 | Low | | | | | | | | | | | |
| | per 10 mcg/m ³ | Long-term | Case-control | Children | Asthma | 12 | [36] | 2017 | 29 | 0.16 | OR | 1.05 | 1.02 | 1.08 | Moderate | | | | | | | | | | | |
| | | | | | Low birth weight | 11 | [18] | 2019 | 73 | NR | OR | 1.06 | 1.02 | 1.09 | Low | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | Preterm birth | 8 | [18] | 2019 | 81 | NR | OR | 1.05 | 1.02 | 1.07 | Low |
| | | | | | per 10 mcg/m ³ | Short-term | Case-crossover | Adults, both sexes | Autism spectrum disorder | 6 | [20] | 2016 | 2 | 0.41 | OR | 1.07 | 1.06 | 1.08 | Moderate | | | | | | | |
| | | | | | | | | | Out-of-hospital cardiac arrest | 9 | [21] | 2017 | 78 | NR | RR | 1.02 | 1.01 | 1.04 | Low | | | | | | | |
| | | | | | | | | | | | | | | | | | | | | Cardiac arrhythmia | 12 | [22] | 2016 | 79 | NR | RR |
| | Daily cardiovascular mortality | 652 | [23] | 2019 | | | | | NR | NR | RR | 1.55 | 1.45 | 1.66 | Low | | | | | | | | | | | |
| | | | | | | | | | | | | | | | | Daily mortality | 652 | [23] | 2019 | NR | NR | RR | 1.44 | 1.39 | 1.5 | Low |
| | | | | | | | | | | | | | | | | | | | | | | | | | | |
| Suicide | 7 | [12] | 2019 | 42 | 0.15 | RR | 1.02 | 1 | 1.03 | Moderate | | | | | | | | | | | | | | | | |
| per 20 mcg/m ³ | Long-term | Cohort | Children (<18 years) | Pneumonia | 10 | [24] | 2017 | 66 | 0 | RR | 1.02 | 1.01 | 1.02 | Moderate | | | | | | | | | | | | |
| | | | | Cardiovascular mortality | 11 | [25] | 2016 | 0 | 0.77 | IR | 1.01 | 1 | 1.02 | Moderate | | | | | | | | | | | | |
| Desert dust | per 10 mcg/m ³ | Short-term | Time-series | Adults, both sexes | Mortality | 11 | [25] | 2016 | 0 | 0.75 | IR | 1.01 | 1 | 1.01 | Moderate | | | | | | | | | | | |
| | | | | | Asthma | 8 | [36] | 2017 | 0 | 0.87 | OR | 1.08 | 1.03 | 1.14 | Moderate | | | | | | | | | | | |
| Black carbon | per 0.5 × 10 ⁻⁵ M ⁻¹ | Long-term | Cohort | Children | Asthma | 8 | [36] | 2017 | 0 | 0.87 | OR | 1.08 | 1.03 | 1.14 | Moderate | | | | | | | | | | | |

LCI: lower confidence intervals; UCI: upper confidence intervals; NR: No reported; HR: hazard ratios; RR: relative risk; IRF: integrated response function; F: function; OR: odds ratio.

Table 6. Nitrogen oxides (NOx), nitrogen dioxide (NO2), long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | | |
|---------------------------|-----------------------------|----------------------|--------------|---------------------------|----------------------------|--------------------|--------------------------------|------|--------|---------|---------------|-------------|----------|----------|----------------------|------|-----|
| NO2 | per 4 mcg/m ³ | Long-term | Cohort | Adults, both sexes | Autistic syndrome disorder | 7 | [17] | 2020 | 58 | 0.007 | RR | 1.02 | 1.01 | 1.04 | Low | | |
| | | | | | Cancer mortality | 16 | [7] | 2018 | 95 | 0.003 | RR | 1.06 | 1.02 | 1.10 | Low | | |
| | | | | | Cardiovascular mortality | 18 | [11] | 2014 | 98 | NR | RR | 1.13 | 1.08 | 1.18 | Low | | |
| | Chronic kidney disease | | | | 3 | [5] | 2020 | 0 | 0.47 | RR | 1.11 | 1.09 | 1.14 | Moderate | | | |
| | All-cause mortality | | | | 12 | [11] | 2014 | 89 | NR | RR | 1.04 | 1.01 | 1.06 | Low | | | |
| | Respiratory mortality | | | | 9 | [11] | 2014 | 0 | NR | RR | 1.02 | 1.02 | 1.03 | Moderate | | | |
| | Type 2 diabetes | | | | 6 | [26] | 2018 | 46 | <0.001 | RR | 1.11 | 1.07 | 1.16 | High | | | |
| | Cancer mortality | | | | 16 | [7] | 2018 | 95 | 0.003 | RR | 1.06 | 1.02 | 1.10 | Moderate | | | |
| | Children | | | | Asthma | 20 | [36] | 2017 | 65 | <0.001 | OR | 1.05 | 1.02 | 1.07 | Moderate | | |
| | Pregnant women | | | Low birth weight | 11 | [18] | 2019 | 32 | NR | OR | 1.02 | 1.00 | 1.04 | Moderate | | | |
| | | | | Small for gestational age | 5 | [18] | 2019 | 87 | NR | OR | 1.02 | 1.01 | 1.03 | Low | | | |
| | per 10 mcg/m ³ | | | Time-series | Adults | Natural mortality | 30 | [16] | 2015 | NR | NR | RR | 1.002 | 1.002 | 1.004 | Low | |
| | per 10 ppb | | | Short-term | Time-series | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 66 | NR | RR | 1.02 | 1.00 | 1.03 | Low |
| | | | | | | | Cardiac arrhythmia | 13 | [22] | 2016 | 93 | NR | RR | 1.04 | 1.01 | 1.05 | Low |
| | | | | | | | Conjunctivitis | 12 | [27] | 2019 | NR | NR | RR | 1.02 | 1.01 | 1.04 | Low |
| | Depression | 7 | [28] | 2020 | 65 | 0.008 | RE | 1.02 | 1.00 | 1.04 | Low | | | | | | |
| per 20 ppb | | Children (<18 years) | Pneumonia | 10 | [24] | 2017 | 71 | 0 | RR | 1.01 | 1.00 | 1.02 | Moderate | | | | |
| NOx | per 20 ppb | Long-term | Cohort | Pregnant women | Low birth weight | 3 | [18] | 2019 | 58 | NR | OR | 1.03 | 1.01 | 1.05 | Low | | |
| | | | | | Preterm birth | 5 | [18] | 2019 | 88 | NR | OR | 1.02 | 1.01 | 1.03 | Low | | |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

3.3. Environmental Tobacco Smoke

Environmental tobacco smoke is an involuntary exposure to tobacco smoke, also known as passive smoke or secondhand smoke. Environmental tobacco smoke is generated by tobacco products' combustion and is a complex mixture of over 4000 compounds. These include more than 40 known or suspected human carcinogens, such as 4-aminobiphenyl, 2-naphthylamine, benzene, nickel, and various polycyclic aromatic hydrocarbons (PAHs) and N-nitrosamines. Furthermore present are several irritants, such as ammonia, nitrogen oxides, sulfur dioxide, and aldehydes, and cardiovascular toxicants, such as carbon monoxide, nicotine, and some PAHs [37,38].

This review identified 23 diseases and causes of death related to environmental tobacco smoke, parental, and prenatal smoke (Table 12). Specifically, environmental tobacco smoke was reported to be associated in adults with stroke [39], lung cancer in women [40], and in pregnant women with low birth weight [37] and small for gestational age [37]. Passive smoking was associated in adults with an increased risk of breast cancer [41], cardiovascular disease [42], cervical cancer [43], lung cancer, lung adenocarcinoma, large cell lung cancer, small cell lung cancer, squamous cell carcinoma [44], all-cause mortality [42], and type 2 diabetes [45]. In pregnant women, passive smoking was associated with neural tube defects [46]. In children, passive smoking was associated as a risk factor for asthma [47] and otitis media [48]. Prenatal smoke was found to be associated with schizophrenia [49], offspring depression [50], and attention-deficit/hyperactivity disorder [51]. Parental smoke with childhood obesity [52], maternal smoke with neuroblastoma [53], and paternal smoke with acute myeloid leukemia [54] and acute lymphoblastic leukemia [55].

3.4. Chemicals, Pesticides, and Heavy Metals

This review identified two health outcomes associated with childhood exposure to 1,3-butadiene (Table 13). 1,3-Butadiene is a synthetic gas used primarily as a monomer to manufacture many different polymers and copolymers and as a chemical intermediate in industrial chemical production. Motor vehicle exhaust is also a source of 1,3-butadiene. One meta-analysis found that long-term exposure to 1,3-Butadiene during childhood increased the risk of acute lymphoblastic leukemia and all leukemias [56]. Another group of chemicals found to be associated with health impacts were the hydrocarbons (Table 13). Hydrocarbons are present in a broad range of products, including petroleum and other fuels, solvents, paints, glues, and cleaning products [57]. A meta-analysis of 14 studies showed that long-term exposure to hydrocarbons was associated with Parkinson's disease [58]. Organic solvents and other solvents were also found to be associated with neurological and rheumatological diseases (Table 13). Specifically, long-term exposure to organic solvents was associated with multiple sclerosis [59] and Parkinson's disease [58]. Long-term exposure to solvents was also found to be associated with an increased risk of systemic sclerosis [60]. Organic solvents are used in many industries. They are used in paints, varnishes, lacquers, adhesives, glues, and degreasing and cleaning agents, and the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals.

Table 7. Ozone (O3), Sulfur Dioxide (SO2), and Carbon Monoxide (CO), long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | |
|---------------------------|-----------------------------|-------------------------|-------------------------|--|----------------------------------|--------------------------------|-----------|------|--------|---------|---------------|-------------|-------|-------|----------------------|----------|
| O3 | per 5 ppb | Long-term | Cohort | Adults, both sexes | Ischemic heart disease mortality | 4 | [29] | 2016 | 67 | 0.02 | RR | 1.02 | 1 | 1.04 | Low | |
| | per 10 mcg/m ³ | | | Pregnant women | Preterm birth | 3 | [18] | 2019 | 0 | NR | OR | 1.04 | 1 | 1.07 | Moderate | |
| | per 10 ppb | | Cohort and Case-Control | Adults, both sexes | Parkinson's disease | 5 | [14] | 2019 | 0 | 0.69 | RR | 1.01 | 1 | 1.02 | Moderate | |
| | per 20 ppb | | Short-term | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 53 | NR | RR | 1.02 | 1.01 | 1.02 | Low |
| | | | | Time-series | Children (<18 years) | Pneumonia | 12 | [24] | 2017 | 75 | 0 | RR | 1.02 | 1.01 | 1.03 | Moderate |
| | | | | | Adults | All-cause mortality | 32 | [16] | 2015 | NR | NR | RR | 1.003 | 1.001 | 1.004 | Low |
| per 10 mcg/m ³ | | | | Cardiovascular and respiratory mortality | 32 | [16] | 2015 | NR | NR | RR | 1.005 | 1.001 | 1.009 | Low | | |
| SO2 | per 5 ppb | 1st pregnancy trimester | Cohort | Pregnant women | Gestational diabetes mellitus | 5 | [30] | 2020 | 93 | 0 | OR | 1.39 | 1.01 | 1.77 | Moderate | |
| | per 10 mcg/m ³ | Long-term | Cohort | Pregnant women | Low birth weight | 5 | [18] | 2019 | 98 | NR | OR | 1.21 | 1.08 | 1.35 | Low | |
| | per 10 ppb | Short-term | Time-series | Adults, both sexes | Cardiac arrhythmia | 10 | [22] | 2016 | 77 | NR | RR | 1.02 | 1 | 1.04 | Low | |
| | | | | Children (<18 years) | Pneumonia | 8 | [24] | 2017 | 48 | 0.04 | RR | 1.03 | 1 | 1.05 | Moderate | |
| CO | per 1 mcg/m ³ | Long-term | Cohort | Pregnant women | Preterm birth | 7 | [18] | 2019 | 89 | NR | OR | 1.06 | 1.04 | 1.08 | Low | |
| | per 1 ppm | Short-term | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 44 | NR | RR | 1.06 | 1 | 1.14 | Moderate | |
| | | | Time-series | Adults, both sexes | Cardiac arrhythmia | 12 | [22] | 2016 | 90 | NR | RR | 1.04 | 1.02 | 1.06 | Low | |
| | | | | Children (<18 years) | Pneumonia | 7 | [24] | 2017 | 68 | 0.004 | RR | 1.01 | 1 | 1.02 | Low | |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

Table 8. Household Air Pollution, indoor air pollution from solid fuel, biomass burning, and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|--------------------------------------|-----------------------------|----------------------|-------------------------|--------------------|---------------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|-------|----------------------|
| Household air pollution | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Cervical cancer | 4 | [31] | 2015 | NR | 0.45 | OR | 6.46 | 3.12 | 13.36 | Low |
| | | | | | Laryngeal cancer | 5 | [31] | 2015 | NR | 0.49 | OR | 2.35 | 1.72 | 3.21 | Low |
| | | | | | Nasopharyngeal cancer | 6 | [31] | 2015 | NR | 0.06 | OR | 1.8 | 1.42 | 2.29 | Low |
| | | | | | Oral cancer | 4 | [31] | 2015 | NR | 0.93 | OR | 2.44 | 1.87 | 3.19 | Low |
| | | | | | Pharyngeal cancer | 4 | [31] | 2015 | NR | 0.99 | OR | 3.56 | 2.22 | 5.7 | Low |
| Indoor air pollution from solid fuel | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Hypertension | 11 | [32] | 2020 | 90 | 0 | OR | 1.52 | 1.26 | 1.85 | Moderate |
| Solid fuel use | Exposed vs. not exposed | Long-term | Cohort | Pregnant women | Low birth weight | 12 | [33] | 2014 | 28 | 0.07 | OR | 1.35 | 1.23 | 1.48 | Moderate |
| | | | | | Stillbirth | 5 | [33] | 2014 | 0 | 0.44 | OR | 1.29 | 1.18 | 1.41 | Moderate |
| | | | | | Preterm birth | 3 | [33] | 2014 | 0 | 0.39 | OR | 1.30 | 1.06 | 1.59 | Moderate |
| | | | | | Intrauterine growth retardation | 2 | [33] | 2014 | 0 | 0.89 | OR | 1.23 | 1.01 | 1.49 | Moderate |
| Biomass burning | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Esophageal squamous cell carcinoma | 16 | [34] | 2019 | 79 | NR | OR | 3.02 | 2.22 | 4.11 | Low |
| | | | Cohort and Case-Control | Adults, both sexes | Chronic Obstructive Pulmonary Disease | 8 | [35] | 2017 | 93 | <0.001 | OR | 2.21 | 1.3 | 3.76 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; OR: odds ratio.

Table 9. Particulate matter less than 2.5 micrometers of diameter (PM2.5), long-term, and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I ² (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | |
|---------------------------|-----------------------------|----------------------|--------------|---------------------|----------------------------------|--------------------------------|-----------|------|--------------------|---------|---------------|-------------|------|------|----------------------|-----|
| PM2.5 | per 10 mcg/m ³ | Long-term | Cohort | Children | Asthma | 10 | [36] | 2017 | 28 | 0.18 | OR | 1.03 | 1.01 | 1.05 | Moderate | |
| | | | | | Autism spectrum disorder | 3 | [20] | 2016 | 0 | 0.54 | OR | 2.32 | 2.15 | 2.51 | Moderate | |
| | | | | Children (<5 years) | Acute low respiratory infections | 28 | [8] | 2014 | NR | NR | IRF | F | F | F | Low | |
| | | | | Pregnant women | Small for gestational age | 5 | [18] | 2019 | 51 | NR | OR | 1.01 | 1.00 | 1.03 | Low | |
| | | | | | Autistic syndrome disorder | 9 | [17] | 2020 | 91 | <0.001 | RR | 1.06 | 1.01 | 1.11 | Moderate | |
| | per 10 mcg/m ³ | Short-term | Time-series | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 12 | [21] | 2017 | 70 | NR | RR | 1.04 | 1.01 | 1.07 | Low |
| | | | | | | Cardiac arrhythmia | 17 | [22] | 2016 | 78 | NR | RR | 1.15 | 1.01 | 1.03 | Low |
| | | | | Adults, both sexes | Daily cardiovascular mortality | 652 | [23] | 2019 | NR | NR | RR | 1.36 | 1.30 | 1.43 | Low | |
| | | | | | Daily mortality | 652 | [23] | 2019 | NR | NR | RR | 1.68 | 1.59 | 1.77 | Low | |
| | | | | | Daily respiratory mortality | 652 | [23] | 2019 | NR | NR | RR | 1.47 | 1.35 | 1.58 | Low | |
| Children (<18 years) | Pneumonia | 11 | [24] | 2017 | 38 | 0.08 | RR | 1.02 | 1.01 | 1.03 | Moderate | | | | | |

LCI: lower confidence intervals; UCI: upper confidence intervals; NR: No reported; HR: hazard ratios; RR: relative risk; IRF: integrated response function; F: function; OR: odds ratio.

Table 10. Particulate matter less than 10 micrometers of diameter (PM10), desert dust, black carbon, long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|-----------------------------|--|----------------------|----------------|--------------------|---------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| PM10 | per 2 mcg/m ³ | Long-term | Cohort | Adults, both sexes | Chronic kidney disease | 4 | [5] | 2020 | 81 | 0.001 | RR | 1.16 | 1.05 | 1.29 | Low |
| | | | | | Type 2 diabetes | 6 | [6] | 2020 | 68 | 0.004 | RR | 1.12 | 1.01 | 1.23 | Moderate |
| | | | | | Incidence of coronary events | 11 | [15] | 2014 | 0 | 0.81 | HR | 1.12 | 1.01 | 1.25 | Moderate |
| | | | | | Lung cancer mortality | 9 | [7] | 2018 | 93 | NR | RR | 1.07 | 1.03 | 1.11 | Low |
| | | | | | Cancer mortality | 12 | [7] | 2018 | 91 | <0.001 | RR | 1.09 | 1.04 | 1.14 | Moderate |
| | | | | | Incidence of chronic bronchitis | 3 | [16] | 2015 | NR | NR | RR | 1.11 | 1.04 | 1.18 | Low |
| | | | | | Asthma | 12 | [36] | 2017 | 29 | 0.16 | OR | 1.05 | 1.02 | 1.08 | Moderate |
| | per 10 mcg/m ³ | | Pregnant women | Low birth weight | 11 | [18] | 2019 | 73 | NR | OR | 1.06 | 1.02 | 1.09 | Low | |
| | | | | Preterm birth | 8 | [18] | 2019 | 81 | NR | OR | 1.05 | 1.02 | 1.07 | Low | |
| | | | Case-control | Children | Autism spectrum disorder | 6 | [20] | 2016 | 2 | 0.41 | OR | 1.07 | 1.06 | 1.08 | Moderate |
| | | | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 9 | [21] | 2017 | 78 | NR | RR | 1.02 | 1.01 | 1.04 | Low |
| | | | | | Cardiac arrhythmia | 12 | [22] | 2016 | 79 | NR | RR | 1.01 | 1 | 1.02 | Low |
| | | | | | Daily cardiovascular mortality | 652 | [23] | 2019 | NR | NR | RR | 1.55 | 1.45 | 1.66 | Low |
| | | | | | Daily mortality | 652 | [23] | 2019 | NR | NR | RR | 1.44 | 1.39 | 1.5 | Low |
| Daily respiratory mortality | 652 | [23] | | | 2019 | NR | NR | RR | 1.74 | 1.53 | 1.95 | Low | | | |
| per 20 mcg/m ³ | Children (<18 years) | Suicide | 7 | [12] | 2019 | 42 | 0.15 | RR | 1.02 | 1 | 1.03 | Moderate | | | |
| | | Pneumonia | 10 | [24] | 2017 | 66 | 0 | RR | 1.02 | 1.01 | 1.02 | Moderate | | | |
| Desert dust | per 10 mcg/m ³ | Short-term | Time-series | Adults, both sexes | Cardiovascular mortality | 11 | [25] | 2016 | 0 | 0.77 | IR | 1.01 | 1 | 1.02 | Moderate |
| | | | | | Mortality | 11 | [25] | 2016 | 0 | 0.75 | IR | 1.01 | 1 | 1.01 | Moderate |
| Black carbon | per 0.5 × 10 ⁻⁵ M ⁻¹ | Long-term | Cohort | Children | Asthma | 8 | [36] | 2017 | 0 | 0.87 | OR | 1.08 | 1.03 | 1.14 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals; NR: No reported; HR: hazard ratios; RR: relative risk; IRF: integrated response function; F: function; OR: odds ratio.

Table 11. Nitrogen oxides (NOx), nitrogen dioxide (NO2), long-term and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence | | |
|---------------------------|-----------------------------|----------------------|--------------------|---------------------------|----------------------------|--------------------|--------------------------------|------|--------|---------|---------------|-------------|------|----------|----------------------|-------|------|
| NO2 | per 4 mcg/m ³ | Long-term | Cohort | Adults, both sexes | Autistic syndrome disorder | 7 | [17] | 2020 | 58 | 0.007 | RR | 1.02 | 1.01 | 1.04 | Low | | |
| | | | | | Cancer mortality | 16 | [7] | 2018 | 95 | 0.003 | RR | 1.06 | 1.02 | 1.10 | Low | | |
| | Cardiovascular mortality | | | | 18 | [11] | 2014 | 98 | NR | RR | 1.13 | 1.08 | 1.18 | Low | | | |
| | Chronic kidney disease | | | | 3 | [5] | 2020 | 0 | 0.47 | RR | 1.11 | 1.09 | 1.14 | Moderate | | | |
| | All-cause mortality | | | | 12 | [11] | 2014 | 89 | NR | RR | 1.04 | 1.01 | 1.06 | Low | | | |
| | Respiratory mortality | | | | 9 | [11] | 2014 | 0 | NR | RR | 1.02 | 1.02 | 1.03 | Moderate | | | |
| | Type 2 diabetes | | | | 6 | [26] | 2018 | 46 | <0.001 | RR | 1.11 | 1.07 | 1.16 | High | | | |
| | Cancer mortality | | | | 16 | [7] | 2018 | 95 | 0.003 | RR | 1.06 | 1.02 | 1.10 | Moderate | | | |
| | Children | | | Asthma | 20 | [36] | 2017 | 65 | <0.001 | OR | 1.05 | 1.02 | 1.07 | Moderate | | | |
| | Pregnant women | | | Low birth weight | 11 | [18] | 2019 | 32 | NR | OR | 1.02 | 1.00 | 1.04 | Moderate | | | |
| | | | | Small for gestational age | 5 | [18] | 2019 | 87 | NR | OR | 1.02 | 1.01 | 1.03 | Low | | | |
| | per 10 mcg/m ³ | | | Short-term | Time-series | Adults | Natural mortality | 30 | [16] | 2015 | NR | NR | RR | 1.002 | 1.002 | 1.004 | Low |
| | per 10 ppb | | | | Case-crossover | Adults, both sexes | Out-of-hospital cardiac arrest | 11 | [21] | 2017 | 66 | NR | NR | RR | 1.02 | 1.00 | 1.03 |
| per 20 ppb | | Time-series | Adults, both sexes | | Cardiac arrhythmia | 13 | [22] | 2016 | 93 | NR | NR | RR | 1.04 | 1.01 | 1.05 | Low | |
| | Conjunctivitis | | | | 12 | [27] | 2019 | NR | NR | RR | 1.02 | 1.01 | 1.04 | Low | | | |
| | Children (<18 years) | | Depression | | 7 | [28] | 2020 | 65 | 0.008 | RE | 1.02 | 1.00 | 1.04 | Low | | | |
| NOx | per 20 ppb | Long-term | Cohort | Pregnant women | Low birth weight | 3 | [18] | 2019 | 58 | NR | OR | 1.03 | 1.01 | 1.05 | Low | | |
| | | | | | Preterm birth | 5 | [18] | 2019 | 88 | NR | OR | 1.02 | 1.01 | 1.03 | Low | | |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

3.5. Environmental Tobacco Smoke

Environmental tobacco smoke is an involuntary exposure to tobacco smoke, also known as passive smoke or secondhand smoke. Environmental tobacco smoke is generated by tobacco products' combustion and is a complex mixture of over 4000 compounds. These include more than 40 known or suspected human carcinogens, such as 4-aminobiphenyl, 2-naphthylamine, benzene, nickel, and various polycyclic aromatic hydrocarbons (PAHs) and N-nitrosamines. Furthermore present are several irritants, such as ammonia, nitrogen oxides, sulfur dioxide, and aldehydes, and cardiovascular toxicants, such as carbon monoxide, nicotine, and some PAHs [37,38].

This review identified 23 diseases and causes of death related to environmental tobacco smoke, parental, and prenatal smoke (Table 12). Specifically, environmental tobacco smoke was reported to be associated in adults with stroke [39], lung cancer in women [40], and in pregnant women with low birth weight [37] and small for gestational age [37]. Passive smoking was associated in adults with an increased risk of breast cancer [41], cardiovascular disease [42], cervical cancer [43], lung cancer, lung adenocarcinoma, large cell lung cancer, small cell lung cancer, squamous cell carcinoma [44], all-cause mortality [42], and type 2 diabetes [45]. In pregnant women, passive smoking was associated with neural tube defects [46]. In children, passive smoking was associated as a risk factor for asthma [47] and otitis media [48]. Prenatal smoke was found to be associated with schizophrenia [49], offspring depression [50], and attention-deficit/hyperactivity disorder [51]. Parental smoke with childhood obesity [52], maternal smoke with neuroblastoma [53], and paternal smoke with acute myeloid leukemia [54] and acute lymphoblastic leukemia [55].

3.6. Chemicals, Pesticides, and Heavy Metals

This review identified two health outcomes associated with childhood exposure to 1,3-butadiene (Table 13). 1,3-Butadiene is a synthetic gas used primarily as a monomer to manufacture many different polymers and copolymers and as a chemical intermediate in industrial chemical production. Motor vehicle exhaust is also a source of 1,3-butadiene. One meta-analysis found that long-term exposure to 1,3-Butadiene during childhood increased the risk of acute lymphoblastic leukemia and all leukemias [56]. Another group of chemicals found to be associated with health impacts were the hydrocarbons (Table 13). Hydrocarbons are present in a broad range of products, including petroleum and other fuels, solvents, paints, glues, and cleaning products [57]. A meta-analysis of 14 studies showed that long-term exposure to hydrocarbons was associated with Parkinson's disease [58]. Organic solvents and other solvents were also found to be associated with neurological and rheumatological diseases (Table 13). Specifically, long-term exposure to organic solvents was associated with multiple sclerosis [59] and Parkinson's disease [58]. Long-term exposure to solvents was also found to be associated with an increased risk of systemic sclerosis [60]. Organic solvents are used in many industries. They are used in paints, varnishes, lacquers, adhesives, glues, and degreasing and cleaning agents, and the production of dyes, polymers, plastics, textiles, printing inks, agricultural products, and pharmaceuticals.

Table 12. Environmental Tobacco Smoke and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|-----------------------------|-----------------------------|-------------------------|-------------------------|--|------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|-------|----------|----------------------|
| Environmental tobacco smoke | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Stroke | 23 | [39] | 2017 | NR | NR | RR | 1.15 | 1.06 | 1.24 | Low |
| | | | Cohort and Case-Control | Women | Lung cancer | 41 | [40] | 2018 | NR | <0.05 | RR | 1.33 | 1.17 | 1.51 | Low |
| | | | | Pregnant women | Low birth weight | 10 | [37] | 2008 | 54 | 0.009 | OR | 1.32 | 1.07 | 1.63 | Moderate |
| | | | | | Small for gestational age | 9 | [37] | 2008 | 0 | 0.004 | OR | 1.21 | 1.06 | 1.37 | Moderate |
| Parental smoking | Exposed vs. not exposed | Long-term | Cohort | Children | Childhood obesity | 6 | [52] | 2014 | 0 | NR | RR | 1.33 | 1.23 | 1.44 | Moderate |
| Paternal smoking | Exposed vs. not exposed | Long-term | Case-controls | Children | Acute myeloid leukemia | 17 | [54] | 2019 | 0.5 | 0.003 | OR | 1.15 | 1.038 | 1.275 | Moderate |
| | Exposed vs. not exposed | Long-term | Case-controls | Children | Acute lymphoblastic leukemia | 10 | [55] | 2012 | 28 | 0.18 | OR | 1.15 | 1.06 | 1.24 | Moderate |
| Maternal smoking | Exposed vs. not exposed | Long-term | Case-controls | Children | Neuroblastoma | 14 | [53] | 2019 | 17 | NR | OR | 1.1 | 1.0 | 1.3 | Moderate |
| Passive smoking | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Lung adenocarcinoma | 18 | [44] | 2014 | NR | 0.26 | OR | 1.35 | 1.23 | 1.48 | Low |
| | | | | | Lung cancer | 18 | [44] | 2014 | NR | 0.01 | OR | 1.34 | 1.24 | 1.45 | Low |
| | | | | | Lung large cell cancer | 18 | [44] | 2014 | NR | 0.68 | OR | 1.36 | 1.04 | 1.79 | Low |
| | | | | | Lung small cell cancer | 18 | [44] | 2014 | NR | 0.98 | OR | 1.63 | 1.31 | 2.04 | Low |
| | | | | | Lung squamous cell carcinoma | 18 | [44] | 2014 | NR | 0.06 | OR | 1.36 | 1.17 | 1.58 | Low |
| | | | Pregnant women | Neural tube defects | 11 | [46] | 2018 | 50 | 0.02 | OR | 1.90 | 1.56 | 2.31 | Low | |
| | | | Cohort | Adults, both sexes | Cardiovascular disease | 38 | [42] | 2015 | 66 | 0 | RR | 1.23 | 1.16 | 1.31 | Moderate |
| | | | | | All-cause mortality | 11 | [42] | 2015 | 69 | 0 | RR | 1.18 | 1.10 | 1.27 | Moderate |
| | | | | | Type 2 diabetes | 7 | [26] | 2018 | 31 | <0.001 | RR | 1.22 | 1.10 | 1.35 | High |
| | | | Cohort and Case-Control | Women | Breast cancer | 51 | [41] | 2014 | 75 | <0.001 | OR | 1.62 | 1.39 | 1.85 | Moderate |
| Cervical cancer | 14 | [43] | | | 2018 | 64 | 0 | OR | 1.70 | 1.40 | 2.07 | Moderate | | | |
| Cohort | Children | Asthma | 41 | [47] | 2020 | 86 | <0.01 | OR | 1.21 | 1.15 | 1.26 | Low | | | |
| | | Otitis Media | 9 | [48] | 2014 | 80 | 0.04 | OR | 1.39 | 1.02 | 1.89 | Low | | | |
| | | Schizophrenia | 7 | [49] | 2020 | 71 | NR | OR | 1.29 | 1.10 | 1.51 | Low | | | |
| | | Offspring depression | 4 | [50] | 2017 | 54 | 0.084 | OR | 1.20 | 1.08 | 1.34 | Low | | | |
| | | Cohort and Case-Control | Pregnant women | Attention-deficit/hyperactivity disorder | 20 | [51] | 2017 | 79 | 0.000 | OR | 1.60 | 1.45 | 1.76 | Moderate | |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

Table 13. Chemicals and long-term health impacts.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|---|------------------------------|----------------------|-------------------------|--------------------|------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| 1,3-Butadiene | High exposed vs. low exposed | Long-term | Case-controls | Children | Acute lymphoblastic leukemia | 2 | [56] | 2019 | 0 | 0 | RR | 1.31 | 1.11 | 1.54 | High |
| | | | | | All leukemia | 2 | [56] | 2019 | 28 | 0.025 | RR | 1.45 | 1.08 | 1.95 | Moderate |
| Bisphenol A | High exposed vs. low exposed | Long-term | Cohort | Adults, both sexes | Diabetes | 3 | [64] | 2015 | 0 | 0.55 | OR | 1.47 | 1.21 | 1.80 | Moderate |
| | | | | | Obesity | 3 | [64] | 2015 | 0 | 0.44 | OR | 1.67 | 1.41 | 1.98 | Moderate |
| Dioxins | High exposed vs. low exposed | Long-term | Cohort | Women | Endometriosis | 10 | [62] | 2019 | 72 | <0.01 | OR | 1.65 | 1.14 | 2.39 | Low |
| Hydrocarbon exposure | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Parkinson's disease | 14 | [58] | 2016 | 28 | NR | OR | 1.36 | 1.13 | 1.63 | Moderate |
| Mono (2-ethyl-5-hydroxyhexyl) phthalate | High exposed vs. low exposed | Long-term | Cohort and Case-Control | Women | Endometriosis | 6 | [65] | 2019 | 44 | 0.11 | OR | 1.24 | 1.00 | 1.54 | Moderate |
| Organic solvents | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Multiple sclerosis | 15 | [59] | 2015 | 77 | 0.06 | RR | 1.54 | 1.03 | 2.29 | Low |
| | | | | | Parkinson's disease | 18 | [58] | 2016 | 43 | NR | OR | 1.22 | 1.01 | 1.47 | Moderate |
| Polychlorinated biphenyls (PCBs) | High exposed vs. low exposed | Long-term | Control Cohort | Women | Endometriosis | 9 | [62] | 2019 | 78 | <0.01 | OR | 1.70 | 1.20 | 2.39 | Low |
| | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | Non-Hodgkin Lymphoma | 7 | [61] | 2012 | NR | NR | OR | 1.43 | 1.31 | 1.55 | Low |
| Polychlorinated biphenyls 153 | per log2 ng/L | Long-term | Cohort | Children | Bronchitis | 7 | [63] | 2014 | NR | 0.89 | RR | 1.06 | 1.01 | 1.12 | Low |
| Solvents | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Systemic sclerosis | 11 | [60] | 2018 | 55 | <0.001 | OR | 2.41 | 1.73 | 3.37 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

In adults, long-term exposure to polychlorinated biphenyls (PCBs) were found to be associated with non-Hodgkin lymphoma [61], in women with endometriosis [62], and in children (<18 months of age), PCB 153 was found to be associated with increase risk of bronchitis [63] (Table 13). Polychlorinated biphenyls are a large group of human-made organic chemicals that, due to their properties like non-flammability, chemical stability, high boiling point, and electrical insulating capacity, are widely used industrial and commercial applications. Bisphenol A (BPA), a chemical used primarily in the production of polycarbonate plastics and epoxy resins, for example, in food and drink packaging, was found to be a risk factor for diabetes [64] and obesity in adults [64] (Table 13). Women's exposure to mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP) has been found as a risk factor for endometriosis [65] (Table 13). MEHHP is a metabolite of phthalate acid esters (PAEs). MEHHP is often found in the blood and tissues of the general population. Studies have shown that women are more likely to be exposed to PAEs through products such as perfume, cosmetics, and personal care products. The review found evidence of dioxins as a risk factor for endometriosis [62] (Table 13). Dioxins are a group of chemically-related compounds that are persistent environmental pollutants (POPs). Dioxins are unwanted by-products of a wide range of manufacturing processes, including smelting, chlorine bleaching of paper pulp, manufacturing some herbicides and pesticides, and incinerators.

Pesticide exposure also was found by multiple meta-analyses as a risk factor for several diseases in adults and children (Tables 14 and 15). In adults, pesticides, in general, were found to be associated with Alzheimer's disease [66], amyotrophic lateral sclerosis [67], brain tumors [68], myelodysplastic syndromes [69], and Parkinson's disease [70]. Organochlorine pesticides were associated with endometriosis [62]. Paraquat, a dichloride pesticide, was also found to be related to Parkinson's disease [71]. Non-Hodgkin lymphoma was also associated with multiple types of pesticides, like organophosphate [72], organochlorine [73], chlordane [73], diazinon [72], hexachlorobenzene [73], hexachlorocyclohexane [73], and dichlorodiphenyldichloroethylene (DDE) pesticides [73]. Finally, children (<18 months of age) reported a higher risk of bronchitis when exposed to DDE [63], and children's residential exposure to pesticides was reported as a risk factor for acute lymphoblastic leukemia, acute myeloid leukemia, and childhood leukemia [74].

In terms of mineral and heavy metals, aluminum, asbestos, cadmium, chromium, arsenic, lead, and silica, were also associated with multiples health outcomes (Table 16). Aluminum was associated with dementia in adults [45]. Non-occupational asbestos was associated with mesothelioma [75]. Cadmium exposure was associated with cancer, especially lung cancer [76]. Chromium exposure was associated with schizophrenia [77]. Inorganic arsenic was associated with type 2 diabetes [78]. Lead exposure to amyotrophic lateral sclerosis [79] and mild mental retardation [80]. Silica exposure with systemic sclerosis [60].

Table 14. Pesticides and health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|--------------------------------|--------------------------------------|----------------------|-------------------------|--------------------|-------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| Pesticides | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Alzheimer’s disease | 7 | [66] | 2016 | 0 | 0.885 | OR | 1.34 | 1.08 | 1.67 | Moderate |
| | High exposed vs. low exposed | | Cohort and Case-Control | Adults, both sexes | Amyotrophic lateral sclerosis | 7 | [67] | 2016 | 41 | 0.16 | RR | 1.20 | 1.02 | 1.41 | Moderate |
| | High exposed vs. low exposed | | Case-controls | Children | Brian tumors | 18 | [68] | 2017 | 0 | NR | OR | 1.26 | 1.13 | 1.14 | Moderate |
| | Exposed vs. not exposed | | Case-controls | Adults, both sexes | Myelodysplastic Syndromes | 11 | [69] | 2014 | 80 | 0 | OR | 1.95 | 1.23 | 3.09 | Moderate |
| | 10 years of exposure vs. no exposure | | Cohort | Adults, both sexes | Parkinson’s disease | 10 | [70] | 2018 | 50 | 0.032 | OR | 1.11 | 1.05 | 1.18 | Low |
| Residential pesticide exposure | High exposed vs. low exposed | Long-term | Case-controls | Children | Acute lymphoblastic leukemia | 8 | [74] | 2019 | NR | NR | OR | 1.42 | 1.13 | 1.80 | Low |
| | | | | | Acute myeloid leukemia | 5 | [74] | 2019 | NR | NR | OR | 1.90 | 1.35 | 2.67 | Low |
| | | | | | Childhood leukemia | 15 | [74] | 2019 | 73 | NR | OR | 1.57 | 1.27 | 1.95 | Low |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

Table 15. Pesticides and health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure temporality | Study Design | Population | Health outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|--|------------------------------|----------------------|-------------------------|--------------------|----------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| Chlordane | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | non-Hodgkin lymphoma | 8 | [73] | 2016 | 17 | 0.29 | OR | 1.93 | 1.51 | 2.48 | Moderate |
| Diazinon | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | non-Hodgkin lymphoma | 7 | [72] | 2017 | 0 | 0.668 | OR | 1.39 | 1.11 | 1.73 | Moderate |
| Dichlorodiphenyldichloroethylene (DDE) | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | non-Hodgkin lymphoma | 11 | [73] | 2016 | 0 | 0.94 | OR | 1.38 | 1.14 | 1.66 | Moderate |
| | per log2 ng/L | Long-term | Cohort | Children | Bronchitis | 7 | [63] | 2014 | NR | 0.38 | RR | 1.05 | 1.00 | 1.11 | Low |
| Hexachlorobenzene | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | non-Hodgkin lymphoma | 7 | [73] | 2016 | 0 | 0.64 | OR | 1.54 | 1.20 | 1.99 | Moderate |
| Hexachlorocyclohexane | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | non-Hodgkin lymphoma | 6 | [73] | 2016 | 34 | 0.17 | OR | 1.42 | 1.08 | 1.87 | Moderate |
| Organochlorine pesticides | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | non-Hodgkin lymphoma | 13 | [73] | 2016 | 12 | 0.253 | OR | 1.40 | 1.27 | 1.56 | Moderate |
| | | | Cohort | Women | Endometriosis | 5 | [62] | 2019 | 65 | 0.02 | OR | 1.97 | 1.25 | 3.13 | Low |
| Organophosphate pesticides | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | non-Hodgkin lymphoma | 10 | [72] | 2017 | 41 | 0.032 | OR | 1.22 | 1.04 | 1.43 | Moderate |
| Paraquat | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Parkinson's disease | 14 | [71] | 2019 | 31 | 0.126 | OR | 1.70 | 1.28 | 2.25 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; OR: odds ratio.

Table 16. Heavy metals, minerals and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|-----------------------------|------------------------------|----------------------|-------------------------|--------------------|-------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|-------|----------------------|
| ALUMINUM | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Dementia | 8 | [45] | 2017 | 6.2 | <0.001 | OR | 1.72 | 1.33 | 2.21 | High |
| Asbestos (non-occupational) | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Mesothelioma | 27 | [75] | 2018 | 99 | NR | RR | 5.33 | 2.53 | 11.23 | Low |
| Cadmium | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | Cancer | 3 | [76] | 2015 | 0 | 0.84 | RR | 1.22 | 1.13 | 1.31 | Moderate |
| | | | | | Lung Cancer | 3 | [76] | 2015 | 0 | 0.41 | RR | 1.68 | 1.47 | 1.92 | Moderate |
| Chromium | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | Schizophrenia | 7 | [77] | 2019 | >50 | <0.01 | SMD | 0.32 | 0.01 | 0.63 | Moderate |
| Inorganic arsenic | High exposed vs. low exposed | Long-term | Cohort | Adults, both sexes | Type 2 diabetes | 3 | [78] | 2014 | 39 | 0.18 | RR | 1.39 | 1.06 | 1.81 | Moderate |
| Lead | High exposed vs. low exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Amyotrophic lateral sclerosis | 3 | [79] | 2020 | 51 | 0.01 | RR | 1.46 | 1.16 | 1.83 | Low |
| | Blood levels in mg/L | Long term | Cohort | Children | Mild mental retardation | 7 | [80] | 2005 | NR | NR | OR | F | F | F | Low |
| Silica exposure | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Systemic sclerosis | 16 | [60] | 2018 | 96 | 0.002 | OR | 2.96 | 1.65 | 5.29 | Low |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio; SMD: standard median difference; F: function.

3.7. Physical Exposures

Physical exposures refer to environmental factors such as temperature, noise, or radiation. Our review identified 21 meta-analyses covering 14 physical environmental exposures and 27 different diseases or causes of death among children, women, adults, and elderly populations. Ambient temperature and extreme weather were the most common physical environmental risk factor studied among the meta-analysis found in this review (Table 17). Changes in ambient temperature (increases or decreases) were related to short-term health impacts. Particularly in adults, increases in the ambient temperature above the 93rd percentile were found to be a risk factor of suicide [81], those exposed to temperatures above 90th percentile or below 10th percentile to diabetes mortality [82], and those under orthopedic procedure during warmer weather periods of the year had an increased risk of postoperative infection [83]. Comparing high versus low temperatures, high temperature increases the risk of low birth weight and stillbirth among pregnant women [84]. Furthermore, changes in diurnal temperature by increases of 10 degrees Celsius were related to increased mortality [85]. Furthermore, heatwaves, defined as a high temperature lasting for several days, were associated with cardiovascular and respiratory mortality in adults [86] and preterm birth [84]. For the elderly populations, heat changes by 1 Celsius degree increment above a threshold were related to acute renal failure, cardiovascular disease mortality, cerebrovascular mortality, diabetes, ischemic heart disease mortality, respiratory disease, and respiratory mortality [87]. In terms of cold temperatures, reductions of 1 Celsius degree during winter times were related to an increased risk of cardiovascular mortality, cerebrovascular mortality, intracerebral hemorrhage, pneumonia, and respiratory mortality [87]. Cold waves were also associated with cardiovascular mortality [88]. For children, reductions of 1 degree Celsius during cold weather were related to an increased risk of asthma (<12 years old) [89].

Natural and artificial light exposure was also associated with positive and negative health impacts (Table 18). Outdoor light exposure was found as a protective factor for myopia in children [90]. The main explanation for this effect is the impact of sunlight on eyeball size, neurotransmitters released in the retina, and vitamin D synthesis. In contrast, artificial light exposure at night was associated as a risk factor for women's breast cancer [91]. The main explanation for the increased risk of breast cancer is the impact of artificial light on reducing sleep duration and melatonin release. Melatonin is suggested as a carcinogenesis inhibitor; thus, low melatonin concentrations could contribute to breast cancer development. Ultraviolet radiation was found to be a protective factor for positive Epstein–Barr Virus Hodgkin lymphoma in adults [92], and recreational sun exposure was associated with non-Hodgkin lymphoma [93].

The noise was another environmental risk factor that was found to be associated with non-communicable diseases (Table 18). In particular, noise exposure from any source was found to be a risk factor for diabetes [94], and each increment of 5 decibels of ambient noise was associated with an increased risk of hypertension [95]. In addition, road traffic noise increments were associated with diabetes [94], hypertension in men [96], and ischemic heart disease [97].

Table 17. Ambient temperature and short-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|-------------------------------|---|----------------------|--------------|--------------------|----------------------------------|------------------|-----------|------|--------|----------|---------------|-------------|------|----------|----------------------|
| Ambient temperature | Maximum suicide temperature 93rd percentile vs. minimum suicide temperature | Short-term | Time-series | Adults, both sexes | Suicide | 341 | [81] | 2019 | 3.3 | NR | RR | 1.33 | 1.30 | 1.36 | Moderate |
| | Orthopedic procedures during warmer periods of the year | Short-term | Time-series | Adults, both sexes | Post-operative infection | 12 | [83] | 2019 | 65 | 0.001 | OR | 1.16 | 1.04 | 1.30 | Moderate |
| | High versus low temperatures | Short-term | Time-series | Pregnant women | Low birth weight | 9 | [84] | 2020 | NR | NR | OR | 1.07 | 1.05 | 1.16 | Low |
| Stillbirth | | | | | 2 | [84] | 2020 | 27.8 | NR | OR | 3.39 | 2.33 | 4.96 | Moderate | |
| Cold | per 1 Celsius degree decrease | Short-term | Time-series | Children <12 years | Asthma | 13 | [89] | 2017 | NR | NR | OR | 1.07 | 1.01 | 1.12 | Low |
| | | | | | Cardiovascular disease mortality | 9 | [87] | 2016 | 98 | <0.0001 | RR | 1.01 | 1.00 | 1.00 | Moderate |
| | | | | | Cerebrovascular mortality | 3 | [87] | 2016 | 60 | 0.001 | RR | 1.01 | 1.00 | 1.01 | Low |
| | | | | Elderly | Intracerebral hemorrhage | 2 | [87] | 2016 | 0 | 0.39 | RR | 1.01 | 1.01 | 1.02 | Moderate |
| | | | | | Pneumonia | 5 | [87] | 2016 | 94 | <0.0001 | RR | 1.06 | 1.01 | 1.12 | Moderate |
| | | | | | Respiratory disease mortality | 8 | [87] | 2016 | 90 | <0.0001 | RR | 1.02 | 1.00 | 1.00 | Moderate |
| | | | | | Diabetes mortality | 9 | [82] | 2016 | NR | NR | RR | 1.11 | 1.03 | 1.19 | Low |
| Cold wave | Exposed vs. not exposed | Short-term | Time-series | Adults, both sexes | Cardiovascular mortality | 31 | [88] | 2020 | 84.3 | <0.001 | OR | 1.54 | 1.21 | 1.97 | Moderate |
| Diurnal temperature range | per 10 Celsius degrees | Short-term | Time-series | Adults, both sexes | Mortality | 308 | [98] | 2018 | NR | NR | RR | 1.03 | 1.02 | 1.03 | Low |
| Heat | 90th and the 99th percentile vs. 75th percentile of temperature | Short-term | Time-series | Adults, both sexes | Diabetes mortality | 9 | [82] | 2016 | NR | NR | RR | 1.20 | 1.12 | 1.3 | Low |
| | | | | | Acute renal failure | 2 | [87] | 2016 | 16 | 0.27 | RR | 1.01 | 1.01 | 1.02 | Moderate |
| | | | | | Cardiovascular disease mortality | 15 | [87] | 2016 | 99 | <0.0001 | RR | 1.03 | 1.03 | 1.04 | Moderate |
| | | | | Elderly | Cerebrovascular mortality | 3 | [87] | 2016 | 72 | 0.03 | RR | 1.01 | 1.00 | 1.02 | Low |
| | | | | | Diabetes | 3 | [87] | 2016 | 25 | 0.26 | RR | 1.01 | 1.00 | 1.01 | Moderate |
| | | | | | Ischemic heart disease mortality | 3 | [87] | 2016 | 81 | 0.004 | RR | 1.01 | 1.00 | 1.03 | Low |
| | | | | | Respiratory disease | 11 | [87] | 2016 | 82 | <0.0001 | RR | 1.02 | 1.01 | 1.04 | Moderate |
| Respiratory disease mortality | 9 | [87] | 2016 | 92 | <0.0001 | RR | 1.00 | 1.00 | 1.00 | Moderate | | | | | |
| Heatwave | Exposed vs. not exposed | Short-term | Time-series | Adults, both sexes | Cardiovascular mortality | 36 | [86] | 2019 | 99 | <0.01 | RE | 1.15 | 1.09 | 1.21 | Low |
| | | | | | Respiratory mortality | 27 | [86] | 2019 | 97 | <0.01 | RE | 1.18 | 1.09 | 1.28 | Low |
| | | | | Pregnant women | Preterm birth | 6 | [84] | 2020 | 44.7 | 0.11 | OR | 1.16 | 1.10 | 1.23 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio.

Table 18. Light, noise, radon, electromagnetic fields, and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|--|---|----------------------|-------------------------|--------------------|--|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| Artificial light exposure at night | High exposed vs. low exposed | Long-term | Case-controls | Women | Breast cancer | 6 | [91] | 2014 | 1.9 | 0.4 | RR | 1.17 | 1.11 | 1.24 | Moderate |
| Outdoor light exposure | High exposed vs. low exposed | Long-term | Cohort | Children | Myopia | 4 | [90] | 2019 | 91 | 0.02 | OR | 0.57 | 0.35 | 0.92 | Low |
| Ultraviolet radiation | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | Epstein–Barr Virus positive Hodgkin lymphoma | 4 | [92] | 2013 | NR | 0.10 | OR | 0.59 | 0.36 | 0.96 | Low |
| Recreational sun exposure | High exposed vs. low exposed | Long-term | Case-controls | Adults, both sexes | Non-Hodgkin lymphoma | 4 | [93] | 2008 | NR | 0.001 | OR | 0.76 | 0.63 | 0.91 | Moderate |
| Extremely low-frequency electromagnetic fields | High exposed vs. low exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Amyotrophic lateral sclerosis | 5 | [67] | 2016 | 58 | 0.34 | RR | 1.30 | 1.10 | 1.60 | Low |
| | High vs. low current wiring configuration codes | Long-term | Cohort and Case-Control | Children | Childhood leukemia | 6 | [99] | 1999 | NR | NR | OR | 1.46 | 1.05 | 2.04 | Low |
| Indoor radon | Exposed vs. not exposed | Long-term | Case-controls | Adults, both sexes | Lung cancer | 31 | [100] | 2019 | NR | NR | OR | 1.14 | 1.08 | 1.21 | Low |
| | High exposed vs. low exposed | Long-term | Case-controls | Children | Leukemia | 7 | [101] | 2012 | 9 | 0.36 | OR | 1.37 | 1.02 | 1.82 | Moderate |
| Noise | High exposed vs. low exposed | Long-term | Cohort | Adults, both sexes | Diabetes | 5 | [94] | 2018 | 31 | 0.18 | HR | 1.04 | 1.02 | 1.07 | Moderate |
| | per 5 dB | | | | Hypertension | 5 | [95] | 2017 | 51 | 0.086 | RR | 1.20 | 1.09 | 1.31 | Low |
| Road traffic noise | per 5 dB | Long-term | Cohort | Adults, both sexes | Diabetes | 3 | [94] | 2018 | 33 | 0.222 | HR | 1.07 | 1.02 | 1.12 | Moderate |
| | per 10 dB (Lden) | | | | Ischemic heart disease | 7 | [97] | 2018 | NR | NR | RR | 1.08 | 1.01 | 1.15 | Low |
| | | | | | Men | Hypertension | 2 | [96] | 2018 | 0 | <0.001 | RR | 1.62 | 1.02 | 1.09 |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio; HR: hazard ratio.

Radon, a radioactive natural, was found in a recent meta-analysis as a risk factor for lung cancer [100] at indoor radon exposure levels above 100 Bq/m³ (Table 18). In another meta-analysis, indoor radon exposure was also associated as a risk factor for childhood leukemia [101]. Finally, long-term exposures to extremely low-frequency electromagnetic fields were also found associated as a risk factor for amyotrophic lateral sclerosis [67] and childhood leukemia [99] (Table 18). Extremely low-frequency (ELF) magnetic fields are alternating fields generated by the distribution and supply of electricity.

3.8. Residential Surroundings

In this category, we summarized the environmental exposures related to residential surroundings, such as greenness, proximity to roadways and petrochemical complexes, or the degree of urbanization. We also located other residential exposures, such as the presence of pets that are suggested as a protective factor for non-communicable diseases. We identified two meta-analyses associating residential greenness as a protective factor for adults and newborns health (Table 19). Specifically, we found evidence that greenness in a 300 m buffer around homes was associated with a reduced risk for mortality in adults [102] and a reduced risk of low birth weight [103]. In addition, residential greenness in a 500 m buffer from homes was also associated with a reduced risk of newborns being small for their gestational age [103]. Living near major roadways or being exposed to traffic around homes was found as a risk factor for type 2 diabetes in adults [104] and leukemia in children [105] (Table 19). Living near petrochemical industrial complexes was also found to produce multiple types of leukemias (Table 19). Specifically, living in an 8 km radius from a petrochemical complex was found to be a risk factor for acute myeloid leukemia, chronic lymphocytic leukemia, and all leukemias [106].

The degree of urbanization was also related to several health impacts (Table 20). Specifically, living in a highly urbanized area was found to be associated with schizophrenia [107]. Urban exposure during childhood has been associated with an increased risk of Crohn's disease and inflammatory bowel disease [108]. Live in a modern house was (compared to traditional house) was found to be a protective factor for clinical malaria [109]. In contrast, living in rural areas has been suggested as a risk factor from Parkinson's disease [58]. Finally, having pets at home has been suggested to be a protective factor for non-communicable diseases in children and adults (Table 20). Specifically, being exposed to pets in the first year of life was found to reduce the risk of acute lymphoblastic leukemia [110]. For adults, being exposed to a pet was suggested to reduce Crohn's disease and ulcerative colitis [108].

Table 19. Greenness, major roads, petrochemical, and long-term health outcomes.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|------------------------------------|--|----------------------|-------------------------|--------------------|------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| Petrochemical industrial complexes | Residence >8 km distance from petrochemical industrial complexes | Long-term | Cohort and Case-Control | Adults, both sexes | Acute myeloid leukemia | 7 | [106] | 2020 | 50 | 0.01 | RR | 1.61 | 1.12 | 2.31 | Low |
| | | | | | Chronic lymphocytic leukemia | 7 | [106] | 2020 | 92 | 0.048 | RR | 1.85 | 1.01 | 6.42 | Low |
| | | | | | Leukemia | 13 | [106] | 2020 | 73 | 0.001 | RR | 1.36 | 1.14 | 1.62 | Low |
| Proximity to major roadways | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Type 2 diabetes | 6 | [104] | 2017 | 36 | 0.025 | RR | 1.13 | 1.02 | 1.27 | Moderate |
| Residential traffic exposure | High exposed vs. low exposed | Long-term | Case-controls | Children | Childhood leukemia | 7 | [105] | 2014 | 57 | 0.02 | OR | 1.39 | 1.03 | 1.88 | Low |
| Residential greenness | per 0.1 NDVI within 300 m buffer from residence | Long-term | Cohort | Adults, both sexes | All-cause mortality | 9 | [102] | 2019 | 95 | <0.001 | HR | 0.96 | 0.94 | 0.97 | Low |
| | | | | | Low birth weight | 10 | [103] | 2020 | 41 | <0.001 | RR | 0.98 | 0.97 | 0.99 | High |
| | | | | | Small for gestational age | 13 | [103] | 2020 | 59 | 0.037 | RR | 0.99 | 0.98 | 1.00 | Low |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio; HR: hazard ratio.

Table 20. Urbanization, pets, and long-term health impacts.

| Environmental Risk Factor | Exposure Unit or Comparator | Exposure Temporality | Study Design | Population | Health Outcome | Studies Included | Reference | Year | I2 (%) | p-Value | Risk Estimate | Effect Size | LCI | UCI | Strength of Evidence |
|---------------------------------|---------------------------------|----------------------|-------------------------|--------------------|------------------------------|------------------|-----------|------|--------|---------|---------------|-------------|------|------|----------------------|
| Rural living | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Parkinson’s disease | 31 | [58] | 2016 | 78 | NR | OR | 1.32 | 1.18 | 1.48 | Low |
| Urban exposure during childhood | Rural exposure during childhood | Long-term | Case-controls | Adults, both sexes | Crohn’s disease | 12 | [108] | 2019 | 71 | 0 | OR | 1.45 | 1.14 | 1.85 | Moderate |
| | | | Cohort and Case-Control | Adults, both sexes | Inflammatory bowel disease | 4 | [108] | 2019 | 71 | 0 | OR | 1.35 | 1.15 | 1.58 | Moderate |
| Urbanicity | Highest vs. lowest category | Long-term | Cohort | Adults, both sexes | Schizophrenia | 8 | [107] | 2018 | 99 | 0 | OR | 2.39 | 1.62 | 3.51 | Moderate |
| Modern housing | Exposed vs. not exposed | Long-term | Cohort | Adults, both sexes | Clinical malaria | 3 | [109] | 2015 | 67 | 0.05 | OR | 0.55 | 0.36 | 0.84 | Low |
| Pet in the first year of life | Exposed vs. not exposed | Long-term | Case-controls | Children | Acute lymphoblastic leukemia | 12 | [110] | 2018 | 39 | 0.08 | OR | 0.91 | 0.82 | 1.00 | Low |
| Pet | Exposed vs. not exposed | Long-term | Cohort and Case-Control | Adults, both sexes | Crohn’s disease | 14 | [108] | 2019 | 67 | 0 | OR | 0.77 | 0.59 | 0.94 | Moderate |

LCI: lower confidence intervals; UCI: upper confidence intervals NR: No reported; RR: relative risk; OR: odds ratio; HR: hazard ratio.

4. Discussion

This umbrella review found 193 associations among 68 environmental exposures and 83 diseases and death causes reported in 101 meta-analyses. The environmental factors found in this review were air pollution, environmental tobacco smoke, heavy metals, chemicals, ambient temperature, noise, radiation, and urban residential surroundings. Among these, we identified 64 environmental exposures defined as risk factors and 4 environmental protective factors. This review offers a comprehensive overview of the latest available evidence on environmental exposures and health outcomes. This, to our knowledge, is the first umbrella review on environmental risk factors and health. We included the most recent meta-analyses that summarize the largest number of individual studies and populations in each research area. We also selected only those meta-estimates that reported statistically significant associations between environmental exposures and health outcomes. In contrast with previous reviews in the area, which only focused on a single exposure or a single health outcome, we provided a general overview of multiples exposures and multiples health outcomes. Furthermore, we focused on observational studies with short and long-term environmental exposures.

Most of the meta-analyses found were focused on adults (80), 57 included cohorts or case-control studies, and 44 included case-crossover or time series analysis and form all meta-analyses included 79 were published in the last five years. In this review, the largest body of evidence was found in air pollution (91 associations among 14 air pollution definitions and 34 diseases and mortality diagnoses). That could be a reflection of two main factors: a) the relevance of air pollution as the most important environmental risk factor worldwide being one of the top 10 global health risk factors accounting for 4.8 million deaths globally in 2017 [3]; and combined with b) the available research funding, interest, and knowledge to integrate air pollution as an exposure factor in epidemiological studies compared to other pollutants. In terms of air pollution, in this review, particulate matter (PM_{2.5} and PM₁₀) was the leading pollutant group that reported the largest number of associations (45). Environmental tobacco smoke was the second-largest exposure included in meta-analyses, with 24 associations among 6 exposure definitions. Chemicals (including pesticides) were the third larger group of environmental exposures found among the meta-analyses included, with 19 associations. Four environmental exposures were found to be protective for different health outcomes. These protective factors were residential greenness, modern housing, pet exposure, UV radiation, and recreational sun exposure. Despite the evidence on protective environmental factors, the largest body of evidence found in this review was on environmental risk factors (64 exposure definitions). Most of the meta-analyses included in this review reported observational studies from multiple geographical locations and multiple nations. Although some meta-analyses on specific geographical regions or countries were found during the screening step, we only selected those that included the largest number of observational studies. In all cases, this led to select those meta-analyses that do not restrict by geographical location.

In terms of the strength of evidence, we only found six associations that were assessed with “high” strength of evidence (defined as those associations that reported precision of the estimate ($p < 0.001$) and consistency of results ($I^2 < 50\%$)). The associations with “high” strength of evidence were NO₂ and Type 2 diabetes; passive smoking and Type 2 diabetes; 1,3 Butadiene and acute lymphoblastic leukemia; aluminum and dementia; road traffic noise and hypertension; and residential greenness and low birth weight. In all the cases, but 1,3 Butadiene (case-control in children), the associations were reported in cohort studies from adult populations. Based on our definition of the strength of evidence, we consider that those six associations will be the only ones that we do not expect to change in direction (i.e., risk vs. protective factor) or magnitude of the association even if new studies on these topics are published.

This study encountered several limitations that should be considered. As with any systematic review, publication bias was the main limitation. To mitigate this, we focused our research on PubMed publications, where we searched for free text and medical subhead-

ings (MESH) terms. A hand search complemented this effort. One important limitation of this review is the inclusion of a single literature database (Medline via PubMed). We acknowledge that this review will probably only capture the literature published primarily in health journals. Other data sources (i.e., Web of Science) could capture other sectoral journals (i.e., environment). Due to the limited resources and the large scope of this review, we decided to concentrate our resources on “PubMed” because it was considered the primary data source on health evidence. Another limitation we found was the quality of the included studies as most of the examined meta-analyses had a large heterogeneity. This review aimed to include studies focusing on the “environment” defined as the external elements and conditions which surround, influence, and affect the life and development of a human organism or population. While this review considers physical environments such as nature, the built environment, and pollution, it does not consider social environments. This review does not include occupational exposures; water, sanitation, and hygiene (WASH) exposures; behavioral risk factors (e.g., physical activity or diet); or exposure to microorganisms and no-natural disasters. This review selected only those meta-analysis that includes disease prevalence, incidence, and causes of death. The current epidemiological evidence provides a large body of studies (e.g., on biomarkers, metabolic and cardiovascular risk factors, symptoms, signs, hospitalizations, and emergency room visits, among others) that were beyond the scope of this review. We favored health evidence on defined diseases and causes of death that could be more easily translated into public health interventions and practices, although we acknowledge that preclinical and symptomatic health indicators could affect the largest portion of the population. In addition, there are several environmental exposures that were not included in this umbrella review based on the inclusion criteria. For example, large single observational studies were not included in the scope of this review. Furthermore, in the case that several observational studies on the similar exposure and outcome were published this study would be not able to include those type of evidence if those were not combined in a meta-analysis. For those reasons this umbrella review should be considered as a complementary tool to understand the universe of evidence available on environmental health.

Although this umbrella review found several publications and associations among environmental exposures and health outcomes, we also identified several evidence gaps. Most of the studies focus on identifying environmental risk factors, and only a few studies have been focusing on identifying environmental protective factors. Furthermore, few studies have focused on vulnerable and disadvantaged populations (children, elders, social disadvantaged, ethnic minorities, etc.). Furthermore, most studies do not provide a clear definition of the health outcomes using the international classification of diseases (ICD), nor a comparable exposure definition when the same pollutant is used. In terms of the meta-analysis, we exclude several studies from this review because, in the analyses, cross-sectional studies were mixed with other observational studies (i.e., cohorts). Additionally, several studies did not report heterogeneity values (i.e., I²) or do not provide dose-response functions essential for population risk assessment, health impact assessments and policy translation. We have summarized a list of recommendations for future research in environmental health studies based on these gaps, and we have listed those recommendations in Table 21.

Table 21. Recommendations on observational studies and meta-analyses in environmental health.

| Recommendations |
|---|
| Observational studies:< |
| - Increase studies on protective environmental risk factors |
| - Increase studies on vulnerable and disadvantaged populations |
| - Provide international classification of diseases (ICD) codes as part of the definitions for health outcomes |
| - Use comparable exposure definitions for environmental risk factors |
| - Support longitudinal study designs |

Table 21. Cont.

| Recommendations |
|---|
| Meta-analyses |
| - Avoid combining cross-sectional studies with cohort or case-control studies in the meta-estimates |
| - Provide heterogeneity values (i.e., I ²) |
| - Provide dose-response functions to support populational risk assessment, quantitative health impact assessments, and policy translation |

5. Conclusions

Environmental exposures are an important health determinant. This umbrella review identified 68 environmental exposures that were associated to 83 health outcomes. This review provides an overview of an evolving area of research and should be used as a complementary tool to understand the connections between the environment and human health. This review also found the need of research prioritization using longitudinal approaches with harmonized exposure and outcome definitions, including vulnerable and susceptible populations in environmental health. The evidence presented by this review should help to design public health interventions and the implementation of a health in all policies approach aiming to improve populational health.

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