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Environmental Exposures and Depression: Biological Mechanisms and Epidemiological Evidence

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Abstract

Mental health and well-being are consistently influenced—directly or indirectly—by multiple environmental exposures. In this review, we have attempted to address some of the most common exposures of the biophysical environment, with a goal of demonstrating how those factors interact with central structures and functions of the brain and thus influence the neurobiology of depression. We emphasize biochemical mechanisms, observational evidence, and areas for future research. Finally, we include aspects of contextual environments—city living, nature, natural disasters, and climate change—and call for improved integration of environmental issues in public health science, policies, and activities. This integration is necessary for reducing the global pandemic of depression.

1. INTRODUCTION

Depression is a leading contributor to global disability (133). The disease is characterized by sustained symptoms of sadness, low energy, sleep disturbances, anxiety, and feelings of worthlessness. Depression is a potentially fatal disease, with suicide as an ultimate outcome. The risk of depression varies with sex, age, income, and education, and its incidence and prevalence display different patterns and trends in different countries (65). A high comorbidity exists with various physical disorders, such as cancer and cardiovascular diseases.

The etiology of depression is complex, partly unknown, and determined by multiple influences, including genetic, social, and environmental (65, 139). The biological and genetic underpinnings display a high clinical heterogeneity. Social and environmental factors are often modifiable and thus targets for public health actions. The developing brain is influenced by social deprivation factors (58), and poor social environments, including economic instability and unemployment, increase the risk of depression. Recent research suggests that more physical aspects of the environment, such as noise and chemical pollutants, may also have a neurobiological impact and influence the risk of depression, especially among genetically susceptible individuals (130). Other environmental exposures, such as the natural environment, may potentially increase resilience and prevent depression (19).

Social and physical environments are highly interrelated, but in this review we evaluate mostly physical exposures. We aim to address how external factors directly interfere with neurobiological mechanisms and functions involved in the development of depression and what empirical evidence exists to support a relation. This knowledge must then be incorporated into more complex models of how our living environment—including social and cultural aspects—may increase or decrease the risk of depression and how this level of risk varies depending on genetic vulnerability (see **Figure 1**).

2. THE NEUROBIOLOGY OF DEPRESSION

Depression is associated on the systems level with a hypoactivation of prefrontal cortical (PFC) areas (both in lateral and anterior cingulate cortex) together with hyperreactivity of the amygdala, a key signaling site for neural threat response, negative emotion, and anxiety (see the sidebar titled Terms and Definitions). This pattern can be interpreted as an impaired PFC regulation of the amygdala and linked limbic structures (e.g., hippocampus and hypothalamus) (30). This dysregulation is accompanied by alterations in neurotransmitter systems, including noradrenergic, cholinergic, serotonergic, and dopaminergic pathways (86, 124). Some environmental exposures have the capacity to alter these systems and may thus induce depression or depressive symptoms. Several exposures can also influence the specific gene expression for depression vulnerability and subsequently have an impact on correlating brain structures, such as the PFC (116). A related biological pathway is through chronic stress and the corresponding dysregulation of the hypothalamic pituitary axis (HPA). HPA dysregulation can induce changes in neural positive reward pathways (124) and alter levels of serotonergic and noradrenergic receptors, thus influencing the risk of depression (72). Chronic stress is also related to reduced neuronal plasticity, which may contribute to systems-level abnormalities and the pathophysiology of depression (130). Many environmental exposures have the potential to affect the HPA function and to contribute to chronic stress.

Chronic stress induces a state of chronic inflammation, and an inflammatory pathway to depression has been suggested (121). Recent research has found an association between depression and inflammatory biomarkers (107), such as proinflammatory cytokines and C-reactive protein (CRP), though the causality is unclear, and it is possible that depression itself may induce an inflammatory state with the release of biomarkers rather than vice versa (123).

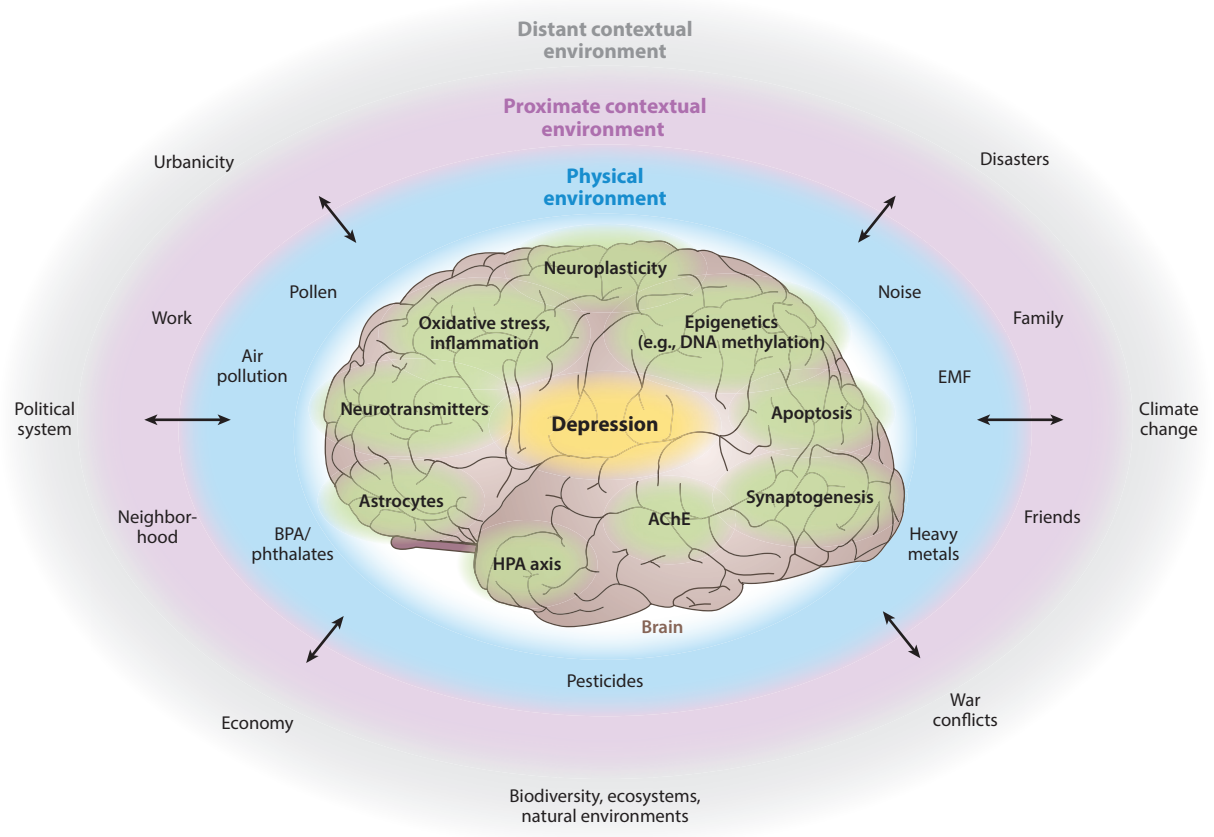

Figure 1

The effect of the environment on the pathophysiology of depression is a complex set of interactions between multiple exposures that, alone or more commonly interdependently, affect various structures and functions of the brain. The figure illustrates how physical environmental exposures have a direct impact on specific brain structures, resulting in cell damage or functional changes of CNS mechanisms. These physical exposures are influenced by and interrelated with multiple proximate and distant contextual factors. While the figure illustrates external impacts, internal and individual factors, such as genetic material, age, gender, ethnicity, and behavior, also interact with and eventually determine exposure, dose, and any subsequent response and effect. Abbreviations: HPA, hypothalamic-pituitary-adrenal axis; AChE, acetylcholinesterase; BPA, bisphenol-A; CNS, central nervous system; EMF, electromagnetic fields. Figure adapted from image provided by Henry Y. Lu, Department of Pediatrics and Experimental Medicine Program, British Columbia Children's Hospital and The University of British Columbia, Vancouver.

3. REVIEW PROCESS AND DEFINITIONS OF DEPRESSION AND PHYSICAL ENVIRONMENT

This narrative review is complemented by a quasi-systematic search in Scopus and PubMed of peer-reviewed articles of observational studies or controlled trials for a predefined set of common environmental exposures to and associations with depression. For a full description of the search strategy and references to all included articles, see the **Supplemental Material**. This review of empirical evidence is supplemented by a discussion of plausible biochemical mechanisms for each exposure.

Supplemental Material >

TERMS AND DEFINITIONS

Brain Structures

Limbic system: brain system that regulates inborn and acquired behaviors and is the origin of instinctive behaviors, motivation, and emotions. The hippocampus, hypothalamus, and amygdala are part of the limbic system.

Prefrontal cortex (PFC): part of the frontal lobe of the cerebral cortex, carrying out higher reasoning executive functions, such as complex cognitive behavior and decision making, as well as guiding thoughts, actions, and emotions. The PFC is made up of several distinct areas, including the lateral and anterior cingulate cortices. Impaired function of the PFC is associated with many mental disorders, including depression.

Striatum: a cluster of neurons in the forebrain. It has connections to several other parts of the brain, including the limbic system, and is involved in feelings of reward, empathy, and social behaviors.

Brain Systems and Functions

Apoptosis: programmed cell death.

Glial cells: nonneuronal cells in the central nervous system (CNS) that surround and support neurons, with specific functions for maintaining internal, physiological balance (known as homeostasis).

Astrocytes: the most common type of glia cells, regulating, for example, neurotransmitter concentrations.

Hypothalamic-pituitary-adrenal axis (HPA axis): a hormonal stress response system, which through a cascade mechanism, initiated from the hypothalamus, releases cortisol. In a healthy individual, negative feedback loops inhibit further cortisol secretion after the immediate response to an acute stressor.

Neuronal migration: a complex process in the fetal brain whereby different classes of developing neurons are spatially brought together so they can interact appropriately.

Neuronal plasticity: adaptive responses in the adult brain to internal or external stimuli. Negatively affected by, for example, chronic stress. In a healthy individual, the PFC has high capacity for neuronal plasticity.

Neurotransmitter systems: the noradrenergic, dopaminergic, and serotonergic neurotransmitter systems often work interactively and are important for overall regulation of behaviors. They have all been related to depression and suicide and are often targets for antidepressants.

Noradrenergic system (concerns the neurotransmitter noradrenaline): associated with activity in, for example, the PFC, amygdala, and hypothalamus. Noradrenaline modulates several behaviors, such as stress, attention, and decision making.

Dopaminergic system (concerns the neurotransmitter dopamine): influences, for example, the limbic system and striatum. It is involved in emotional regulation and feelings of reward.

Serotonergic system (concerns the neurotransmitter serotonin): associated with activity in the hippocampus and the PFC, and its function is important for most cognitive functions, decision making, and social relationships.

Cholinergic system (concerns the neurotransmitter acetylcholine): part of the parasympathetic nervous system. It is important for memory, learning, attention, and other higher brain functions. It is also associated with neural plasticity. The cholinergic system has many receptors and synapses in, for example, the thalamus, striatum, and limbic system, which are all critical structures in the pathophysiology of depression.

Synapse: the point of contact between neurons (axons and dendrites) where information is passed by release of neurotransmitters.

Synaptogenesis: the formation and maintenance of synapses in the developing brain.

We focused on depression as a single entity, excluding literature on, for example, general mental illness, anxiety, or psychotic disorders. It should be borne in mind, however, that most environmental exposures usually have multiple, related or unrelated effects on various psychiatric illnesses (139). We refer to depression as defined with ICD-10 (International Statistical Classification of Diseases and Related Health Problems, tenth revision) or DSM-IV (*Diagnostic and Statistical Manual of Mental Disorders*, 4th Edition, Text Revision) criteria, with validated scales for depression screening or with proxy indicators such as suicide, suicide ideation, or prescription of antidepressants. See the **Supplemental Material** for details.

Supplemental Material >

We have reviewed environmental exposures that are abundant in daily lives, are modifiable, and may have a possible impact on human neurobiology. These include harmful exposures, such as air pollution, noise, heavy metals, toxic chemicals, and environmental radiation. We have also considered the physical aspects of a few contextual environments, including urbanization, natural environments, natural disasters, and climate change. In the following discussion, we present the current evidence for an association between each exposure and depression, including the state of the science for biological mechanisms. For a description of the search strategy with a full list of keywords, search terms, and references, see the **Supplemental Material**.

4. HARMFUL ENVIRONMENTAL EXPOSURES

4.1. Airborne Pollution

Airborne pollutants, such as diesel emissions, carbon monoxide (CO), nitrogen oxides (NOx), sulfur dioxide (SO_2), ozone (O_3), particulate matter (PM), and a wide array of hazardous substances such as benzene are emitted from, for example, vehicles, industries, residential heating, and cooking with biofuels, or they are formed through complex secondary reactions in the atmosphere from the emission of precursor pollutants. They enter the body primarily through inhalation, but some can also enter through the skin. Among the various pollutants, fine particulate matter of $\leq$2.5 microns in aerodynamic diameter ($PM_{2.5}$) appears especially harmful because the particles enter the circulation and reach the brain directly (23). Recent research has increasingly explored the direct neurophysiological effects of air pollutants, including prenatal exposure and impacts on the developing brain. Prenatal exposure has been associated with reductions in brain white matter volume, cognitive impairments, and increases in attention-deficit hyperactivity disorder symptoms (103) in a dose-dependent fashion, possibly by inducing neuroinflammatory and autoimmune responses. For example, exposure to air pollution complex mixture among children and teens (24) has been associated with systemic and central nervous system (CNS) inflammation, production of autoantibodies to key neural proteins, and disturbances of the integrity of neurovascular units and barriers. In highly exposed children, a misfolding and aggregation of neural proteins can occur, which coincides with the anatomical maldistribution observed in the early stages of both Alzheimer and Parkinson diseases (24), indicating a direct effect on important brain functions.

Air pollutants can influence neurotransmitter function, such as serotonin (10, 49) and dopaminergic neuron activity (132). Studies also show that air pollutants can affect inflammatory cytokines and neuronal morphology in the hippocampus (42) and induce oxidative stress in, for example, the PFC and striatum (31, 88). Air pollution may influence neural plasticity, with implications for cognition, memory performance, and various behavioral outputs. For example, one study found that biking along a heavily polluted road did not contribute to an increase in the brain-derived neurotrophic factor (BDNF) normally seen after physical activity (17). BDNF is important for neural plasticity and is altered in many psychiatric diseases, including depression.

Physical diseases consistently associated with air pollution—such as cardiovascular diseases (80), diabetes (125), and asthma (82)—may, through comorbidity, increase the prevalence of

depression in air-polluted environments. Depression also shows comorbidity with other neuropsychiatric disorders that are associated with air pollution, such as cognitive disturbance and Alzheimer disease (122, 127, 143). In addition, air pollution may cause oxygen deficiency, which can alter a variety of neural systems, including serotonin synthesis (21, 93, 119). Some studies have found an association between hypoxia and suicide (21).

A recent review (106) on the link between suicide and exposure to air pollution and aeroallergens showed that PM_{10} and $PM_{2.5}$ were consistently associated with an increased prevalence of completed and attempted suicide (7 studies of 7), whereas the results were more inconclusive for NO, O_3, CO, and SO_2. A 2018 review by Zhao et al. (144) on O_3 exposure and mental health came to a similar conclusion. Another review demonstrated a relation between air pollution exposure and depression, but this review included only two studies (109). In our review, air pollution was the single physical exposure that yielded most hits, and we included 26 epidemiological studies (published between 2007 and 2018), 24 of which showed a positive association between air pollution and depression, whereas two (135, 145) showed inconsistent or nonsignificant results of long-term exposure. Of the 26 included studies, 9 concerned short-term exposure and 11 analyzed the effects of long-term exposures. We found only one study on indoor air pollution, showing that cooking with biomass, and related long-term exposure to $PM_{10,}$ $PM_{2.5}$, and CO, was associated with a higher risk of depression (25). Taken together, the relatively large number of studies, including a few longitudinal studies, from a wide array of locations, a majority of which show a positive association, confirms the hypothesis that exposure to air pollution increases the risk of depression. This finding is supported by evidence of plausible neurobiological mechanisms.

4.2. Pollen (Aeroallergens)

Pollens, some of which provoke allergy, are emitted from plants when they are ready to flower, contributing to the seasonality of this exposure. The biochemical mechanisms behind aeroallergens and increased risk of depression are not entirely elucidated but may be mediated by immunoglobulin E (IgE) release in response to pollen (79), with an increase of inflammatory cytokines (129) that affect the brain and thus may increase the risk of depression. Another hypothesis suggests that pollen allergy increases CNS cholinergic-system sensitivity and thereby induces depression (83).

Relatively few studies have analyzed the association between depression and pollen exposures. Some studies indicate that suicide rates peak in late spring when pollen counts are highest (111). Any seasonality of suicide prevalence may be due to several factors though, such as meteorological variables. However, the evidence of seasonal variation in depression and suicide is inconsistent (78, 99), and pollen counts peak in late spring when any effects of seasonal affective disorder should be lower. In the 2017 review by Ragguett et al. (106), four studies showed an increased risk of suicide associated with pollen exposure, but the heterogeneity was large in terms of pollen type and confounder control.

Pollen allergy is likely associated with impaired mood due to physical symptoms and fatigue that arise from allergic symptoms, and this indirect pathway may explain an association between pollen exposure and depression. In general, the low number of both biochemical and observational studies hinders any scientific conclusions.

4.3. Noise

Noise is a common environmental stressor and complaint in urban environments following, for example, large traffic volumes and construction. Noise activation of the acoustic nerve may disturb related structures in the CNS, including the HPA axis (8), which may be an endogenous pathway

between noise and depression (15). Noise can also result in annoyance or other negative emotions, and these experiences can induce psychophysiological stress responses (37, 136); these responses, in turn, are related to depression (121).

Several studies report on objectively measured noise levels and an association with depressive symptoms (e.g., Reference 94). In some cases, the only association found is between noise sensitivity and depression, while objectively measured noise levels are nonrelated (97). The most commonly reported nuisance related to noise is sleep disturbance (126), which is related to depression.

A recent, large case-control study (117) used objective noise modeling estimates and found an increased risk of physician-diagnosed depression or antidepressant prescription from exposure to aircraft, railway, or traffic noise. Another recent, longitudinal study found that residential noise exposure increased the risk of depression, as measured by antidepressant prescription and a validated scale (94). Although these studies need to be replicated, the rigid designs and large sample sizes provide some evidence for a relation between noise exposure and depression, though further studies are needed to establish biological pathways and causal relationship.

4.4. Human-Made Electromagnetic Fields

In the everyday environment, human-made electromagnetic fields (EMFs) are emitted from, for example, power sockets, Wi-Fi networks, and mobile phones. EMFs affect various organ systems by interfering with the functional electrical currents inducing heat in, for example, the CNS. Recent reviews on health effects of Wi-Fi exposure show that EMFs from Wi-Fi induce, for example, oxidative stress (134), neuropsychiatric effects, and endocrine changes (96). The area has gained increasing concern owing to the rapidly growing use of mobile phones and widely distributed Wi-Fi networks.

Neuropsychiatric effects of EMFs could be caused by radiation-induced damages to the brain and neuronal structures (95). Most biochemical models of these relationships are based on animal studies. The harmful effect on the CNS could be a result of the high concentration of voltage-gated calcium ion channels (VGCCs) in the brain (95). EMFs have a high affinity for VGCCs and can act through those channels. Because a core function of VGCCs is to release neurotransmitters and neuroendocrine hormones, any disturbance of this system may produce neuropsychiatric effects, including depression (95). Studies on rat and mice brains show EMF-related disturbances in the neurotransmitter system, including serotonin, dopamine, and norepinephrine (1). A 2013 study by Kitaoka et al. (67) indicated that EMF exposures induce depression-like corticosterone secretion and behavior in mice. Increases of reactive oxygen species (ROS), oxidative stress, and genetic damage have also been found in populations living near mobile towers (50). A small number of studies, on the other hand, show that oxidative stress decreases after exposure to EMFs, likely dependent on the type and frequency of radiation (134).

A few epidemiological studies suggest that exposure to EMFs, by for example living close to transceiver stations or frequent use of mobile phones, increases the risk of depression, but causality is obscure (110). A general issue in epidemiological studies on EMFs is a lack of standardized exposure assessment measures. The exposure to EMFs is increasing dramatically, and more research, including analyses of biochemical reactions in humans, should be encouraged.

4.5. Endocrine Disrupting Substances

People are exposed to endocrine disrupting substances (EDCs) by inhalation, by ingestion, or through dermal uptake. They act via several neural receptor classes and may alter transmission and the formation of networks in the brain, which may influence brain function and induce neural

degeneration (63). Because EDCs interrupt the normal action of hormones, they may affect the function of hormone-sensitive organs, including the brain. Low doses of EDCs have also been postulated to cause incomplete methylation of specific gene regions in the young brain, impairing neural growth and brain functions across generations (63) with a potential impact on the development of depression. Bisphenol A, phthalates, and pesticides are common groups of EDCs.

4.5.1. Bisphenol A and phthalates. Bisphenol A (BPA) and phthalates are sometimes called "everywhere chemicals" because of their widespread use. They are both used to synthesize and manufacture polycarbonate plastics and polyepoxides. Studies on rats and nonhuman primates have demonstrated that BPA disturbs brain function by interfering with gonadal steroid-induced synaptogenesis, resulting in severe loss of hippocampal and prefrontal spine synapses (53). Phthalate exposure also seems to induce hippocampal disturbance in mice (142), inducing down-regulation of BDNF expression (114). This behavior could explain various neurodevelopmental symptoms, and several animal studies show an increase of depressive symptoms in test subjects (28, 141). Another suggested pathway is that BPA would induce hyperactivity in the HPA axis (28).

Several studies have analyzed prenatal exposures, including preconception paternal BPA exposure and negative outcomes in offspring (39), possibly acting through epigenetic mechanisms. Kundakovic et al. (71) showed that prenatal BPA exposure induced DNA methylation changes in transcriptionally relevant regions of hippocampal genes, changes that were shown to be consistent with BDNF changes in human cord blood. Lab studies on cell lines have demonstrated that BPA at low concentrations induces differential transcript levels of biomarker genes for depression (112). A link between high concentrations of phthalates in urine and raised levels of oxidative stress (40) and inflammatory biomarkers in blood (9) has also been demonstrated. Several animal studies show correlations between exposure to phthalates and depressive symptoms (140), including prenatal exposure (142).

Observational studies have shown a relation between prenatal BPA exposure and depressive symptoms among children (101). With few exceptions, the effects seem to be more pronounced among boys (102). A review from 2015 (91) suggested a potential link between prenatal exposure to BPA and neurodevelopmental impairment with increased risk of depression. A review from 2017 (35) came to similar conclusions, i.e., that limited observational evidence suggests a link between prenatal exposure to BPA and depressive symptoms among children. Both reviews concluded that prospective cohort studies are needed to clarify these associations.

Epidemiological studies on phthalates and risk of depression are less common, but recent studies show associations between urinary phthalate levels and depressive symptoms among adults (118) and elderly (75). Given that there is a biologically plausible pathway, further observational studies are warranted.

4.5.2. Pesticides. Pesticides, such as organophosphates, glyphosate, and cyanide, are used for crop protection, preservation of food and materials, and prevention of some vector-borne diseases. They are toxic by design and target systems or enzymes in insects, weeds, fungi, or rodents but may also damage human systems. Children are particularly vulnerable to exposure, prenatally and in early life when organ systems, including the brain, are under development. Pesticides are ubiquitous, are often persistent in the environment, and are quickly absorbed through the skin, mucous membranes, gastrointestinal and respiratory tracts, and the placenta. Pesticides inhibit the enzyme acetylcholinesterase (AChE), which results in decreased degradation of the neurotransmitter acetylcholine with disturbed axonal (nerve fiber) outgrowth and neuronal differentiation as consequences. This behavior may increase the risk for psychiatric disorders. Various pesticides interfere with the serotonergic and dopaminergic systems (61, 77).

The induction of depression by exposure to pesticides may also be related to DNA methylation in specific genes with potential impact on neurodevelopment (62). Animal studies have shown links to oxidative stress, astrocyte dysfunction, and impaired hippocampal neurotransmission (27, 104).

Several studies have found an association between pesticide exposure and increased risk of depression (26, 137). The evidence of a link is increasing, including an augmented risk of suicide, but the results are inconsistent, and insufficient understanding exists on the effects of long-term low-dose exposure (44). Many studies have analyzed effects of high-dose exposure, such as after pesticide poisoning (11). Many studies use self-reported depression as outcome data, but studies analyzing data on prevalence or incidence of physician-diagnosed depression or hospitalization are scarce. Most studies also use self-reported exposure to pesticides, making detailed analyses of effect sizes and effect thresholds difficult.

A systematic review from 2013 (44) concluded that most studies were cross-sectional in design, and causal relationships remain to be confirmed. A few recent longitudinal studies have demonstrated that exposure to pesticides prenatally and in adulthood increases the risk for depression at follow-up (12, 45, 68). Pesticides are highly toxic substances with a wide range of possible impacts on brain structure and function, but further well-designed epidemiological studies are required to establish causality.

4.6. Heavy Metals

Exposure to heavy metals can occur through, for example, diet, traffic, and industrial emissions, including dust in industrial and urban areas. They may induce neurotoxic effects and may also increase the risk of neurodevelopmental disturbance and depression through epigenetic mechanisms (7). In the following, we discuss a few of the most toxic heavy metals: cadmium, lead, and mercury.

4.6.1. Cadmium. Cadmium is among the most toxic environmental pollutants, inducing disturbances across organ systems, including neurotoxicity. It may impair mental health through oxidative stress, alterations in neurotransmitter release, damage to the blood–brain barrier, and induction of neuron apoptosis (87). A few studies have shown an association between cadmium in blood and depressive symptoms (13, 54), but the results are inconclusive. The association between depression and cadmium levels in urine is unclear (118).

4.6.2. Lead. Lead is a potent neurotoxic metal and is associated with numerous adverse health effects, including impaired brain functioning. Especially in developing brains, lead exposure is detrimental for synaptic trimming, neuron migration, and neuron–glia interactions (22). On depression, most observational studies (18, 73) show an increased risk associated with lead exposure, but the results are inconsistent (47) and the only prospective longitudinal study identified in this review (85) was unable to confirm an association.

4.6.3. Mercury. Mercury blocks normal biological functions and exerts neurotoxic effects through disturbed neurotransmission, oxidative stress, and accumulation of neurotoxic molecules (59). A relatively recent review (64) suggested that chronic, low-level exposure to mercury (e.g., from dental amalgam fillings) is associated with depression and suicide.

The evidence for a relation between heavy metals and depression is, in general, inconsistent and the area must be explored further. A biological risk is very likely, considering their highly toxic characteristics.

5. CONTEXTUAL PHYSICAL ENVIRONMENTS

While this review has focused mainly on direct environmental exposures and biological pathways to depression, a few contextual exposures deserve mention because of their potentially major role in the physical realm of daily lives: urban and natural environments, natural disasters, and climate change. Although natural disasters may not be part of regular daily life, they are expected to increase in severity and frequency owing to climate change; existing studies suggest that they are likely to have a profound effect on mental health and risk of depression. A few hypotheses, including some empirical support, suggest direct impacts on biological functions of these contextual environments, but many pathways appear linked to behavioral mechanisms. In this section, we briefly outline the current understanding of biological and behavioral linkages, starting with an overview of urbanization and city environments.

5.1. Urbanization: A Global Change in Environmental Exposure

Urbanization is one of the most notable changes in environmental experience and subsequent exposures. Currently, 55% of the global population is urbanized, and by 2050 roughly 70% are likely to live in urban areas (32). The most rapid urbanization is now occurring in low- and middle-income countries, as high-income countries are already highly urbanized (around 80% in North America and Europe). Urban living entails many health benefits: City dwellers, on average, are wealthier and have access to improved sanitation, nutrition, and health care (32). At the same time, urban living is associated with a more multifaceted, demanding, and stressful environment and sometimes with greater spatial divides and social disparities, especially for the estimated one billion people who live in slums (32), creating a complex landscape of risk and protective factors.

Multiple environmental exposures, for example, increased exposure to air pollution and noise, are altered in cities, which may contribute to increased risk of depression. This assumption is supported by some neuroscience studies (128). Recent work has demonstrated that city upbringing impacts on the structure and function of brain regions critical for the processing of emotion, social cognition, and stress (51, 74). On the functional level, research has shown that city size may predict amygdala activation in a social stress challenge (74), mirroring the amygdala hyperreactivity seen in depression. Urban upbringing in the first 15 years of life has been associated with increased pregenual anterior cingulate cortex activation (74) and decreased gray matter volume in the PFC. The anterior cingulate cortex and the PFC are prime neural regions where alterations are often seen in depression (105), which suggests that urban upbringing may alter the developmental trajectory of higher-order stress regulatory areas. This altered trajectory increases the risk of mental disorders.

In observational studies, poor mental health is a commonly reported negative health effect of city living, with a 34% increase in the prevalence of psychiatric disorders in urban relative to rural areas after adjustment for confounders (100). Depression is one of the mental disorders in which the incidence is consistently found elevated in city dwellers or in populations that have been exposed to urban environments early in life (see the **Supplemental Material** for additional references), though some of this may be explained by, for example, self-selection due to greater access to health care in urban areas or more undiagnosed cases in rural areas (48). Most research, however, seems to suggest that an etiologic effect of urban living on psychiatric diseases exists that is not attributable to reverse causation or service utilization (81). This proposition is also supported by biological findings of changes in brain structures and functions associated with city living. Any causal mechanisms are likely manifold, though, and replication of experimental studies and larger prospective studies are needed to improve the evidence and confirm whether city living is a causal risk factor of depression.

Supplemental Material >

5.2. Natural Environments

The pathways between natural environments and depression have often referred to the promotion of healthy behaviors (131), such as stress relief, physical activity, and social interactions—all related to improved mood and reduced risk of depression. Studies analyzing biomarkers have suggested physiological changes, indicating biological stress recovery from exposure to nature (34). In the brain, nature exposure has been linked to cingulate cortex activity (20), which is the brain area identified as compromised in the urban born, and to reduced lateral prefrontal activation (60). The latter is associated with less rumination, a common symptom in depression. Another suggested link relates to perceptual fluency (the ease with which a stimulus is processed in the brain), where individuals seem to prefer the type of fractal patterns (having high internal repetition of visual information) that are displayed in nature, responding to those with stress relief, as compared with nonnatural, less random, or nonfractal patterns (52). Other hypothetical pathways refer to the immune system, suggesting that the stress relief experienced from nature exposure averts telomere shortening (138) and prevents chronic inflammation (16), but these effects are also experienced through direct exposure to biodiverse microorganisms. This microbial exposure contributes to the diversity of the intestinal microbiota, which then influences brain development and function through the gut–brain axis (113).

With few exceptions (92), results from a large number of observational studies and one twin study (29) indicate a relation between exposure to natural environments and reduced risk of depression (46, 115), but limitations in terms of cross-sectional study designs, risk of self-selection effects, uncertainty about actual use of green space, and scarce knowledge around the relative impact of different nature types remain a source of uncertainty in these reported associations. A few recent studies have used longitudinal design and mostly confirmed a protective effect of natural environments (4, 6), though results are inconsistent (33). Studies evaluating impact on suicide have found a protective effect (89).

The most recent review (70) of urban nature and health outcomes concluded that, while a positive association existed between exposure to nature and positive mood, the results were inconclusive for diagnosed depression. This review included only longitudinal or quasi-experimental design studies, thus addressing causality.

Like many of the environmental exposures and the impact on human health, improved evidence of the impact of natural environments on human health may play an important role for policy and decision makers. To provide knowledge for evidence-based decisions, any causal relation between natural environments and depression should be confirmed through longitudinal or experimental study designs, including analyses of biochemical reactions to nature exposure. Equally, contextualization and quantification of various nature types, including biodiversity, are necessary to analyze relative impact on depression.

5.3. Natural Disasters

The most commonly studied natural disasters in relation to depression are earthquakes and hurricanes, followed by tsunamis, floods, and droughts (98). Recent studies and reviews suggest that depression can be a long-term sequel after these phenomena (5, 41, 90), and increasing suicidal rates have been associated with natural disasters (69). Mental health effects are most likely mediated through factors such as acute and secondary stress responses (including post-traumatic stress disorder), socioeconomic losses, psychological trauma, and physical injuries. A specific phenomenon, solastalgia, may also increase the risk of depression (3, 57). This phenomenon is defined as the distress produced by change to a home environment to which people are closely connected (3). This area of research needs to be further investigated. Various prevention and intervention approaches

should be evaluated, especially as natural disasters can be expected to increase in frequency, owing to climate change.

5.4. Climate Change

The potentially increased risk of depression from climate change has been less explored than have many of the physical health impacts, such as heat stroke and famine. Berry et al. (14) suggested a few mediating factors that would contribute to an increased risk of poor mental health and higher prevalence of depression as a result of climate change. These factors refer to both direct effects following stress or trauma after extreme events and indirect effects such as food insecurity, poverty, or impaired mood due to physical health effects from climate change. The risk of depression may also follow solastalgia (36), similar to the effect of a natural disaster. Climate change–induced violence and forced migration may also expose individuals to stress and thereby increase the risk of depression (120), but long-term effects are poorly understood. A direct, biological effect of climate change is increased heat stress. Whereas a relatively large evidence base for harmful neurological and inflammatory effects of heat exposure exists and the related consequences for cognitive function are well studied (55, 66, 76), the association with depression is less explored.

Recent reviews have concluded that there are substantial gaps in the literature around the association between climate change and depression (38, 108), including potentially increased vulnerability among the elderly, children, and the socioeconomically disadvantaged (2). Several studies indicate that an association exists between climate change, increased heat in particular, and suicide (43, 56). For example, a recent study from Greece showed that the correlation between heat exposure and completed suicides was stronger than the effect of unemployment on completed suicides (43). As climate change proceeds and larger populations are directly affected, more studies will be possible to conduct and should be prioritized.

6. EVIDENCE LEVEL

In this review, we have discussed how various environmental exposures influence the brain and interact with the neurobiology of depression. We can conclude that biological pathways between depression and exposure to air pollution, BPA, phthalates, pesticides, and heavy metals are likely, on the basis of a relatively large number of studies on biological mechanisms that explain how these exposures may induce depression. A substantial number of epidemiological studies have considered air pollution ($n = 26$); 24 of these studies, including longitudinal and case-crossover studies, reported positive associations between depression and short- and long-term exposure to air pollution, indicating an effect. BPA, phthalates, pesticides, and heavy metals have all been associated with depression in observational studies, but further longitudinal, large population-level studies are required for establishing causality and evidence level. The impact of EMFs on human neurofunction and depression has been insufficiently studied, and the epidemiological evidence is inconsistent. Although there are likely indirect pathways to depression, such as stress, nuisance, or reduced well-being, the neurobiological impact of pollen and noise is less clear and should be further investigated in combination with epidemiological studies to confirm causality and evidence level. On contextual environments, urban living is suggested as a risk factor of depression. This proposed effect is supported by studies showing a direct impact on the structure and function of vulnerable brain structures such as the amygdala and PFC. Several longitudinal studies also confirm that depression is more common in cities than in rural areas, but there is some debate regarding causality. The association is most likely due to a complex mixture of social and environmental exposures and stressors associated with city living. A small amount of evidence

Table 1 Assessed strength of evidence for a biological mechanism and epidemiologically confirmed association with depression for each exposure

Environmental exposure	Biological mechanisms		Epidemiological association	
	Current evidence level[a]	Number of studies	Current evidence level[a]	Number of studies
Air pollution	S	13	S	26
BPA, phthalates	S	11	M	13
Pesticides	S	5	M	17 (published after 2011)
Heavy metals	M/S	4	M	16
Noise	L	3	M	8
Pollen	L	3	M/S	11
EMFs	M/S	6	L	2
Urban living	L/M	2	S	53
Natural environments	L/M	4	M	30
Natural disasters	L	0	M	Only previous review articles considered ($n = 4$)
Climate change	L	0	L/M	13

Abbreviations: BPA, bisphenol A; EMFs, electromagnetic fields; L, low; M, moderate; S, strong.

[a]The evidence level was estimated by evaluating study design, sample size, and control of confounders. See the **Supplemental Material** for details on quality assessment.

Supplemental Material >

for a direct, neurobiological link between natural environments and depression exists, and several epidemiological studies confirm an association; however, more research is needed before causality can be confirmed. Natural disasters and climate change have been associated with depression in a few studies, but neurobiological pathways have not been analyzed.

In future research around environment and depression, it will be important to analyze multiexposures and how different exposures interact, specific neurobiological effects of different exposures, and effect differences depending on population group and sociocultural context. The inflammatory pathway is also critical to investigate further as a link between environmental exposures and depression. Many studies suggest that the increased inflammation from environmental exposures can cause depression. While most studies seem to confirm this causal pathway, further prospective studies are warranted (84).

Based on the literature discussed in this review, **Table 1** presents an overview of the estimated evidence for biological pathways and epidemiological associations, respectively, for each environmental exposure.

7. LIMITATIONS

A major limitation of this review is the artificial divide between physical and social environments. From a vast array of scholarly knowledge and scientific studies, we know that such a division does not exist but that these dimensions are mutually influencing one another and act interdependently to a higher or lower extent. This relation is similar to the complex interrelation between body and mind, for example, demonstrated when toxic substances absorbed by the gut increase the risk of depression by reaching vulnerable neurological structures, such as the amygdala and PFC, through the gut–brain axis. It is also why some diseases that are traditionally categorized as somatic are closely related to depression and vice versa. This somewhat reductionist approach was necessary for covering the broad physical environment, but we urge the reader to take this

review as a first stepping stone and to incorporate the evidence into a much wider framework where scientific knowledge on sociocultural and behavioral interactions are included to improve our understanding of the etiology of depression and to determine how healthier environments can be created for those at highest risk.

8. CONCLUSIONS

This review has shown that a plethora of biophysical environmental exposures may contribute to the formation or prevention of depression through direct or indirect pathways. The effects are likely results of interrelated mechanisms and interactions of various causal factors at multiple levels (individual, family, neighborhood, city, nation, and global).

We have outlined how specific components of pollutants and toxic compounds may interfere with delicate structures and functions of the brain with sometimes long-lasting effects on mental health, particularly depression. We have also aimed to highlight how urbanization and a disconnection from our evolutionary origin—natural environments—may result in depressive mood. Finally, we have discussed how natural disasters and continued climate change will most likely increase the prevalence of depression through numerous sociobiological pathways.

Environmental exposures lack the immediate stability and clarity that characterize many individual risk factors. The situation is further complicated by accounting for the original purpose of some of the agents. For example, many pesticides have been developed with the goal of improving agricultural yields, and thereby reducing poverty and famine, or for preventing vector-borne diseases. This knowledge means that careful trade-off analyses must be conducted together with increased international investments in finding alternative strategies and protection measures, especially for vulnerable groups such as outdoor workers, pregnant women, and children.

We can conclude that the evidence for causal effects of environmental factors on depression ranges from exposures such as air pollution, which seem to have strong biological plausibility and observational support, to those that are currently relatively poorly understood, such as climate change. Given the large complexity of and uncertainties related to environmental exposures, however, it is necessary to apply the precautionary principle: Until proof of harmlessness is established, exposure should be limited and well-designed studies conducted, perhaps in a systems science paradigm, to prevent a further increase in an already alarming rate of depression, a potentially fatal disease with major implications for global public health.

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Annual Review of Public Health

Volume 40, 2019

Contents

Social Environment and Behavior

Environmental and Occupational Health

Public Health Practice and Policy

Health Services

Indexes

Errata

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