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Environmental pollution and risk of psychotic disorders: A review of the science to date

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ABSTRACT

Environmental pollution is a global problem with diverse and substantial public health implications. Although many environmental (i.e., non-genetic) risk factors for schizophrenia and other psychotic disorders have been identified, there has been comparatively little research on pollution as a possible risk factor. This is despite the fact that gene-by-environment interactions and epigenetic mechanisms are now recognized as likely facets of the etiology of schizophrenia, and the fact that pollution could potentially mediate the association between urban birth/upbringing and elevated risk. We conducted a review of the literature to date in order to summarize and synthesize work in this area. We identified 13 research reports and 16 review articles. Based on the extant knowledge in this area and what is known about the pathophysiology of schizophrenia, it is feasible that exposure to xenobiotic heavy metals such as lead and cadmium, constituents of air pollution such as particulate matter and nitrogen and sulfur oxides, organic solvents, and other constituents of environmental pollution could be component causes. Further research—from the cellular to epidemiological levels—is clearly needed. If causation is proven, enhancements of policy intended to reduce human exposure to environmental pollution could reduce the burden of schizophrenia and possibly other mental illnesses.

1. Introduction

Environmental pollution is a subject of increasing worldwide public health concern. According to the World Health Organization (WHO, 2014), in 2012 approximately 7 million premature deaths were attributable to air pollution exposure, confirming that air pollution is presently the world's major environmental risk for health, having an impact on several diseases (e.g., coronary artery disease, cerebrovascular accidents, obstructive lung disease, lung carcinoma, and acute lower respiratory infections in childhood). Ambient particulate matter (PM) pollution was the ninth principal risk factor in 2010 with regard to the global burden of disease (Lim et al., 2012). Air pollution commonly takes origin from combustion of fossil fuels, as well as industrial and agricultural processes. Air pollutants of main public health interest involve PM (e.g., organic and elemental carbon, metals [e.g., lead], and polycyclic aromatic hydrocarbons), carbon monoxide (CO), ozone (O_3), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2) (Suades-González et al., 2015). Associations between air pollutants and central nervous system (CNS) diseases have being shown (Block et al., 2012).

Risk for psychosis is linked to both genetic and environmental factors, with increasing evidence that the environment can largely influence genetic effects (e.g., through gene-by-environment interactions and epigenetic mechanisms) and vice versa (van Os and Sham, 2003). Interestingly, both past and current studies show that urbanicity of birthplace and upbringing is related to a higher incidence of schizophrenia and other non-affective psychoses (Heinz et al., 2013). Air pollution could conceivably be one of the candidate factors to explain this association. Yet, relatively little attention has been given to the question of the role of pollution as a risk factor for psychosis. The aim of our work is to briefly review all of the studies (including both review articles and original research) in which the relationship between pollution and psychotic illness was examined.

2. Methods

We searched the Pubmed electronic database for all articles up to February 19, 2016. Search terms included “schizophrenia” or “psychosis” or “psychoses” or “psychotic” or “schizophreniform” or “schizoaffective” or “delusional” or “catatonia” combined with “pollution” or “pollutants” or “polluting” or “particulate” or “smog.” The

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search included all languages. 98 articles were identified. We selected 29 studies related to pollution's effects on human subjects: 13 were research reports, and 16 were review articles. We excluded 69 articles, on the basis of the following exclusion criteria: a) studies unrelated to the topic, b) studies related to pollution's effects on animals, c) studies on cigarette smoke or on passive tobacco smoke, and d) letters or general comment papers not reporting research findings.

3. Results

Main findings from the research reports are presented in Table 1, in descending chronological order, and also described narratively below. Main conclusions from the review articles are briefly summarized narratively below.

3.1. Review articles

Thirteen of the 16 review articles (Brown Dzubow et al., 2010; Cirla and Gilioli, 1978; Guilarte et al., 2012; Holden, 1995; Kelly et al., 2010; Marchetti, 2014; McGrath and Scott, 2006; Mena, 1974; Mortensen, 2001; Opler and Susser, 2005; Orisakwe, 2014; Padhy et al., 2014; Terry et al., 2011) explicitly refer to a possible association between environmental pollution and an increased risk of schizophrenia/psychosis; the other three review articles are less specific, relating to a possible role of environmental pollution in increasing the risk of mental disorders (Landrigan, 1983; Lederbogen et al., 2013), or of emotional and behavioral dysfunctions (Dumont, 1989). Among all environmental pollutants, lead (Pb), a xenobiotic heavy metal, is certainly the most mentioned potential candidate linked to an increased risk of schizophrenia/psychosis ($n = 7$ dedicated review articles) (Guilarte et al., 2012; Landrigan, 1983; Marchetti, 2014; Mortensen, 2001; Opler and Susser, 2005; Orisakwe, 2014; Terry et al., 2011). A xenobiotic substance is an element or chemical compound foreign to a particular organism or biological system; a xenobiotic is not normally endogenously produced by or expected to be found within that organism or biological system. The second most mentioned candidate is air pollution ($n = 5$ dedicated review articles) (Kelly et al., 2010; McGrath and Scott, 2006; Mortensen, 2001; Padhy et al., 2014; Terry et al., 2011), a more general term used to describe the introduction of particulates, biological molecules, or other harmful substances into earth's atmosphere that can have adverse effects on humans and the ecosystem. The third most mentioned pollutant that may play a role in schizophrenia is cadmium (Cd), a xenobiotic heavy metal similar to Pb ($n = 2$ dedicated review articles) (Marchetti, 2014; Orisakwe, 2014).

3.2. Research reports

All 13 research reports describe a possible connection between environmental pollution and an increased risk of schizophrenia/psychosis. Most of the studied pollutants belong to the group of air pollutants ($n = 11$ research reports) (Bowler et al., 1991; Kelly et al., 2010; Kiselev et al., 1997; Lary et al., 2015; Lundberg et al., 2009; Pedersen et al., 2004; Perrin et al., 2007; Sanders, 1964; Tong et al., 2016; Vaneckova and Bambrick, 2013; Yackerson et al., 2014). Among air pollutants, particulates, referred to as particulate matter or PM (i.e., microscopic matter suspended in the earth's atmosphere), appear to play an influential role recently (Lary et al., 2015; Tong et al., 2016; Vaneckova and Bambrick, 2013; Yackerson et al., 2014). Also, oxides of nitrogen (NO_x), particularly NO_2 (Pedersen et al., 2004; Tong et al., 2016), and organic solvents (Bowler et al., 1991) like tetrachloroethylene, also known under the name perchloroethylene (Perc or PCE) (Perrin et al., 2007), seem to have a significant role. We found only one research report related to risk of schizophrenia induced by PCE-contaminated water (Aschengrau et al., 2012), and one research report in which the risk of schizophrenia was related to reactive oxygen species whose generation can be induced by exposure to different environmental pollutants (Korotkova et al., 2011). A complete list of pollutants identified in the 13 research reports (and their role for an increased risk of schizophrenia/psychosis) is presented in Table 1.

4. Discussion

Schizophrenia is a complex, debilitating, and clinically heterogeneous neurodevelopmental syndrome, associated with variable functional impairments in social, emotional, perceptual, and cognitive domains (Green and Glausier, 2016; Mittal et al., 2016; Owen et al., 2016;). To date, no single factor has been found to characterize all patients with schizophrenia; this holds for potential etiological factors, as well as clinical manifestations. Patients with schizophrenia differ in clinical presentations and features, developmental and family backgrounds, cognitive functioning, and even neuropathology and neurochemical processes (Mittal et al., 2016). The etiologies of schizophrenia are indeed multifactorial, with different patients probably having very different constellations of "component causes," or risk factors, both genetic and environmental (Green and Glausier, 2016; Owen et al., 2016; Sawa and Snyder, 2002). Multiple developmental pathways eventually lead to disease onset and both genetic and environmental factors are sources of constitutional vulnerability, having implications for prenatal and postnatal brain development (Mittal et al., 2016). Therefore, the complex clinical features of schizophrenia are underpinned by an equally complex pathogenesis, in which a likely genetic susceptibility confers a vulnerability to a number of environmental menaces, especially during particular developmental periods (Green and Glausier, 2016).

A number of "environmental" risk factors, both biological and psychosocial, have been identified (Owen et al., 2016) in addition to genetic risk factors that still remain poorly understood. A role of epigenetic processes is suggested by the fact that data on consistently replicated genetic effects are absent, and by the evidence for stable modifications in gene expression after certain environmental hazards (Cariaga-Martinez et al., 2016). Several environmental risk factors, affecting early neurodevelopment or having an effect at later timepoints, contribute to schizophrenia (Owen et al., 2016). Those observed most commonly and frequently include obstetric complications, maternal illnesses during pregnancy (above all infections such as maternal influenza), early-life CNS infections, and nutritional deficiencies. Additionally, negative family emotional environment and childhood maltreatment, adolescent cannabis use, socioeconomic factors, immigration, and urbanicity (being born or raised in cities), have been commonly described as risk factors for schizophrenia (Green and Glausier, 2016; Laurens et al., 2015; Owen et al., 2016).

Urbanicity, specifically urban birth and upbringing, is a well-defined risk factor for schizophrenia; in this field, hypothesized mediators like neighborhood fragmentation, low social cohesion and social capital, and the psychological stress of urban life, have been singled out (Green and Glausier, 2016; Haddad et al., 2015; Heinz et al., 2013; Krabbendam and van Os, 2005; Laurens et al., 2015; Owen et al., 2016; Torrey and Bowler, 1990). Urbanicity could also potentially be related, at least in part, to environmental pollution (Heinz et al., 2013; Kelly et al., 2010; Lundberg et al., 2009; McGrath and Scott, 2006; Mortensen, 2001), which has been largely neglected compared to some of the other non-genetic environmental risk factors.

The findings from our review show that both recent and less recent studies link environmental pollution and especially air pollution exposure, to an increased risk of schizophrenia or psychosis. There are feasible biological mechanisms by which some of the specific pollutants could affect brain development in a way that could increase risk for schizophrenia. Epidemiological and observational studies have shown that air pollution has well-defined adverse effects on the respiratory and cardiovascular systems (Genc et al., 2012), and recently emerging data from both human and animal studies suggest that certain CNS diseases, such as Alzheimer's and Parkinson's diseases, cerebrovascular insults, and neurodevelopmental disorders, may be related to air pollutant

Table 1

Research reports			
Study	Study characteristics	Types of pollution	Main findings
Tong et al., 2016	A time-series analysis on the short-term association between the daily disease (psychosis and non-accidental) morbidity and air pollutants was conducted in Tianjin for the period 2008–2011. Country: China.	Air pollutants including PM10, SO_2, and NO_2	An increase of 10 μg/m^3 in 2-day average concentration of PM10, SO_2, and NO_2 corresponded to 0.06%, 0.10%, and 0.10% increases of all psychosis morbidity (daily counts of hospital admissions for psychosis), respectively.
Lary et al., 2015	An analysis of Baltimore, Maryland, emergency room admissions for schizophrenia in 2002 was presented in terms of the levels of ambient pollution. The data for mental disorders was considered in monthly increments. The total number of cases classified under the category of mental disorders was 13,163. The number of admissions in each month for each of the disorders was then correlated with air quality observations in Baltimore. The US Environmental Protection Agency data were considered for every hour of every day of 2002. The monthly average of the daily maxima was used. Country: USA.	Ground-level airborne PM2.5	Unspecified schizophrenia ($r = 0.61$, $p = 0.03$), drug psychosis ($r = 0.8$, $p = 0.001$), and alcoholic psychosis ($r = 0.7$, $p = 0.009$) were significantly related to PM2.5.
Yackerson et al., 2014	The study evaluated the role of the concentration of solid air-suspended particles in the incidence of mental disorders. Data for the study came from cases registered in the Beer-Sheva mental health center during a 16-month period, from 2001 to 2002. Country: Israel.	Solid air-suspended particles	A trend towards positive correlation ($\rho > 0.2$, $p < 0.1$) between the solid air-suspended particle number concentration and number of persons with exacerbation of schizophrenia (as manifested in an acute psychotic episode) was observed in periods with dominant eastern winds.
Vaneckova and Bambrick, 2013	Daily hospital admissions for mental diseases and for other medical diseases, and the effects of heat and light were analyzed in Sydney between 1991 and 2009. The sensitivity to heat of subcategories within the major disease groups was investigated. A time-stratified, case-crossover analysis was applied to examine the hospital admissions on hot days ("case") with those on non-hot ("control") days. Country: Australia.	Air pollutants including O_3 and PM10 as potential modifiers/confounders of the analysis	On all case days, the average temperature was higher and the relative humidity was lower than on the control days. O_3 and PM10 concentrations were higher on case days. Within mental diseases, hospital admissions increased significantly only for psychoses on hot days (odds ratio [OR] = 1.03).
Aschengrau et al., 2012	A retrospective cohort study examined whether early-life exposure to PCE-contaminated drinking water affected the incidence of mental disorders among adults from Cape Cod, Massachusetts. 1512 subjects born from 1969 to 1983 were examined, including 831 individuals with both prenatal and early childhood PCE exposure. Country: USA.	PCE-contaminated drinking water	Subjects with prenatal and early childhood exposure had a 2.1-fold increased risk of schizophrenia.
Korotkova et al., 2011	The quantity of oxygen radicals, such as $OH^{\bullet}$ radical in human serum, was investigated. $OH^{\bullet}$ radicals' concentrations in serum of healthy subjects and schizophrenia patients were analyzed. Country: Russia.	Reactive oxygen species (whose generation can be induced by exposure to environmental pollutants)	Concentrations of $OH^{\bullet}$ radicals in healthy people were considerably lower than in schizophrenia patients.
Kelly et al., 2010	The incidence of schizophrenia and other psychoses in urban (South Dublin) and rural (Counties Cavan and Monaghan) catchment areas (over four years and seven years, respectively) was prospectively compared. Country: Ireland.	Air pollution as one of the candidates underlying the urbanicity risk factor	The risk of schizophrenia in males from urban areas was found to be twice that of males from rural areas (incidence rate ratio [IRR] = 1.92); an analogous model was found at trend level for females (IRR = 1.34). The occurrence of affective psychosis was reduced in urban compared to rural areas for both males (IRR = 0.48) and females (IRR = 0.60).
Lundberg et al., 2009	The potential association between urbanicity of place of birth and symptoms of psychosis was investigated in rural (Mbarara) and urban (Kampala) districts. Country: Uganda.	Air pollution as one of the candidates underlying the urbanicity risk factor	Urban birth was associated with more lifetime psychotic experiences (adjusted OR = 2.1) and more psychotic symptoms during the past week (adjusted OR = 1.9). Maternal pollution exposures during pregnancy or exposures during childhood could be more common or relevant in urban than in rural areas and could be a possible explanation.
Perrin et al., 2007	The relationship between parental work as a dry cleaner and risk for schizophrenia was examined in a prospective population-based cohort of 88,829 offspring born in Jerusalem between 1964 and 1976, followed-up to age 21–33 years. Country: Israel.	PCE	An increased incidence of schizophrenia in offspring of parents who worked as dry cleaners (a surrogate for PCE exposure) was observed (RR = 3.4, $p = 0.01$).
Pedersen et al., 2004	The association between air pollution from traffic and schizophrenia risk was examined in a cohort based on data on air pollution at birth on 7455 children followed from 1970 until 2001. Country: Denmark.	Air pollution from traffic including benzene, CO, NOx and NO_2 (benzene and CO were closely correlated with Pb emissions from traffic in the past)	The risk for schizophrenia increased with increasing levels of all air pollution variables and traffic density, but only significantly for benzene (RR = 3.20), CO (RR = 3.07), and traffic (RR = 5.55). When the variables were adjusted for the level of urbanization, only the traffic level at birth remained relevant: children exposed to the highest traffic level had a risk of 4.40 as compared to children exposed to the lowest traffic level.
Kiselev et al., 1997	The degree of psychiatric disorders in workers exposed to components of synthetic hydrocarbon fuel was investigated. Country: Russia.	Synthetic hydrocarbon fuel	The symptoms included mild emotional problems, premorbid psychotic disturbances, or a full psychiatric syndrome of chronic occupational poisoning.
Bowler et al., 1991	A sample of women, former microelectronics workers raised in the USA, were examined for affective and personality disturbance with the Minnesota Multiphasic Personality Inventory (MMPI). Country: USA.	Organic solvents (used in the production and manufacture of microelectronic components)	MMPI profile classification revealed the presence of a psychotic clinical diagnostic group in 14.3% of the sample.
Sanders, 1964	Case reports of acute poisoning with tetraethyl lead. Country: USA.	Tetraethyl lead	A severe acute intoxication causes symptoms including auditory and visual hallucinations, and speech disorders.

Abbreviations used in the table (in order of appearance): PM10: particulate matter with diameters of 10 μm or less; SO_2: sulfur dioxide; NO_2: nitrogen dioxide; PM2.5: particulate matter with diameters of 2.5 μm or less; O_3: ozone; PCE: tetrachloroethylene; OH•: hydroxyl radicals; CO: carbon monoxide; NOx: oxides of nitrogen; Pb: lead.

exposure (Allen et al., 2014, 2015; Genc et al., 2012). Brain is a target of air pollutants through multiple pathways (for example, through the nasal pathway, pollutants can reach the bulbus olfactorius and the fifth cranial nerve, and then the brain; through respiratory intake, pollutants can reach the systemic circulation, the blood-brain barrier, and the vagal nerves, and then the brain) (Genc et al., 2012). Once translocated to the CNS, air pollutants can trigger immune responses; the CNS can also be affected by systemic inflammation originating from the cardiovascular and respiratory systems. Several processes by which air pollutants can affect CNS health have been hypothesized: inflammation of the nervous tissue, oxidative stress, microglial activation, protein aggregation, subclinical cerebrovascular disease, and disruption of the blood-brain barrier (Block and Calderón-Garcidueñas, 2009; Genc et al., 2012). Recent animal studies by Allen et al. (2014, 2015) suggest that air pollution exposure (especially after exposure to ultrafine concentrated particles) during periods of rapid neurogenesis and gliogenesis may be a risk factor for neurodevelopmental disorders that share features with autism-spectrum disorders, such as schizophrenia. Inflammation/microglial activation, reductions in size and hypomyelination of the corpus callosum, aberrant white matter development, ventriculomegaly (i.e., lateral ventricle dilation), increased amygdala astrocytic activation, and elevated glutamate and an altered ratio of glutamate and GABA (with resulting excitatory/inhibitory imbalance), have been observed after air pollutant exposure, especially in male mice; these neuropathological features have been frequently described both in schizophrenia- and autism-spectrum disorders. Furthermore, the role of an altered ratio of glutamate and GABA in schizophrenia has been hypothesized in studies on exposures to environmental pollutants such as xenobiotic heavy metals, especially lead (Pb) (Guilarte et al., 2012; Marchetti, 2014). Xenobiotic metals can gain access to the body via contaminated air, water, and food, can have a direct effect on the glutamate and $GABA_A$ neurotransmitter receptors, and so induce neurotransmitter dysfunction. In schizophrenia and in developmental Pb exposure, substantial evidence for hypofunction of the NMDA subtype of glutamate receptors (NMDAR) exist. A possible neurobiological relationship between Pb exposure and schizophrenia may be that Pb potently antagonize the NMDAR (Guilarte et al., 2012; Marchetti, 2014), and NMDAR hypofunction seems to be involved in the schizophrenia's pathophysiology (Owen et al., 2016).

However, this initial "biological plausibility" needs to be followed up with research on specific mechanisms, and caution is needed before inferring causality. There are numerous potential confounders and covariates that need to be taken into account and there does not yet exist a strong case from animal studies to support the hypothesis. Moreover, the evidence presented of relationships between pollution and psychosis is mostly cross-sectional and most of the prospective studies use proxy measures of pollution, such as urban birth. There are many different pollutants being considered, each of which may operate through very different mechanisms and have different associations with the outcome. Future research also needs to combine environmental factors with measures of genetic risk. To fully understand the causal role of the environmental risk factors, the integration of genomics with large-scale epidemiological studies is warranted (Owen et al., 2016).

If environmental (e.g., air) pollution is determined to act as an independent risk factor for schizophrenia, policy measures should be expanded to address this risk factor, which is also a risk factor for diverse other health conditions. Regulatory interventions are needed in order to reduce ambient pollution levels and, therefore, negative health effects. The goals should be the development of a new evidence-based, interdisciplinary public health governance and the incorporation of more robust evidence-based research and models addressing current knowledge gaps, in order "to move from good intentions, to proven interventions" (Giles et al., 2011).

Future research on this subject is likely to focus on recognizing the neurotoxic components of environmental pollution, revealing their cellular and molecular mechanism driving neuropathology, and investigating the effects of specific components of environmental pollution on increased risk for mental, neurodevelopmental, and neurodegenerative diseases in humans. Establishing critical periods, identification of at-risk subjects, and using environmentally relevant, lifetime exposures will become necessary, through a large research program requiring the collaboration between researchers and scientists from different fields, in order to understand this human health issue (Block et al., 2012).

Conflict of interest

None.

Contributors

LA conceived the study. LA, FB and RG managed the literature searches and analyses. LA and FB wrote the manuscript. MTC supervised the entire work. All authors contributed to and have approved the final manuscript.

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