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Environment As Risk Factors of Schizophrenia: A Systematic Review

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Abstract

Schizophrenia is a costliest mental disorder regarding human suffering and social expenditure. Schizophrenia is a severe mental illness caused by a gene-environment interaction. An environment has an important role in schizophrenia. It is important to know which environmental factor has related to schizophrenia for the prevention and control of schizophrenia. The study was done by using a systematic review to identify which environmental risk factor and variables associated with schizophrenia. The reviewed articles are from Pro quest, Science Direct, and Scopus database, published on a peer review journal, in English, with human subject, physical and chemical environment factor related with schizophrenia studies. There were 99 articles, and seven selected articles reviewed systematically. An extreme hot ambient temperature, born in winter or early spring, air pollution especially with PM_{10}, $PM_{2,5}$, SO_2 dan NO_2, lead, and tetrachlorethylene exposure had a significant correlation with schizophrenia. Female had higher risk than male. Older age corra elates with the risk of schizophrenia. Urban people have a higher risk than rural people.

Further studies required to confirm these correlations. Season of birth and schizophrenia studies for two seasons countries may be required. This study limitations only compared two articles for each environmental factor, and the metal exposure had no comparison. The next studies are necessary to review specific exposure-related schizophrenia with more articles.

Keywords: Schizophrenia, Environment, Systematic Review

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1. Introduction

Schizophrenia is a mysterious severe mental disorder, with a high cost of care, required lifelong treatment. Untreated schizophrenia may cause a social problem from homeless even homicide and suicide [1]. Their family does not take many people with schizophrenia care whereas the success of treatment depends on the closes persons around them.

The incidence of schizophrenia increases may be because of urbanization, air pollution, and heavy metal exposure [1-5]. Schizophrenia causes not only mental disorders but also physical disorders. The incidence of schizophrenia was 15 per 100,000, point prevalence reaching 4.5 per 1000 population. People with schizophrenia have 12-15 years shorter lifetime than the general population [6]. Researches on schizophrenia

widely practiced, but the exact cause of the disease was unclear. Tsuang (2000) said that genetic/hereditary had a role in the occurrence of schizophrenia. Children whose both parents had schizophrenia had a 48% risk for schizophrenia, 17% if only one parent had schizophrenia.

Schizophrenia occurs due to the interference of dopamine neurotransmitters in the brain causing hallucinations and delusions in people with schizophrenia [1]. The disorder occurs due to an environmental exposure that disrupts the process of brain development in the fetus and early life. Schizophrenia arises from the interaction between genetic and environmental. The environment exposure also affects the brain-forming disorder which is the originator of schizophrenia [1-5].

An environment is a media of a disease so that environmental conditions have a lot contribution to the incidence of disease [5]. Contamination in water, air, soil, food, and air temperature affects the health and the occurrence of schizophrenia might one of the effects [7-9]. Many kinds of pollutants might cause schizophrenia. Tong et al. (2016) stated that there was an association between air pollution with the morbidity of Psychosis in which one of the psychosis is schizophrenia. Air pollution is one of the problems faced by all countries especially developed and developing countries [10]. Along with urbanization, people who lived in cities have a higher risk to suffered from schizophrenia than in a village where one of the contributing factors was air pollution [7, 11]. Exposure to heavy metals, chemical, a season of birth, a climate was related to the occurrence of schizophrenia [7,10,12-17].

This systematic review was done to identify which physical and chemical exposures could be as the risk factor of schizophrenia and which variables affected it. This research was expected to be able to give important information related to the risk factors of schizophrenia and as a recommendation in the control and prevention of schizophrenia.

2. Methods

The systematic review done by using the Preferred Reporting Items for Systematic-Meta-Analysis (PRISMA) method 2009 [18].

2.1. Article search

The reviewed articles published articles that examined environmental health impacts/ environmental in 2000-2017 and studied the association between physical and chemical exposure with the incidence of schizophrenia.

The articles obtained from ProQuest, science direct and Scopus database by using remote library University of Indonesia facilities. The keywords were the combination of "schizophrenia" and "environmental pollution," "mental disorder" and "environmental pollution," "environmental pollution" and "psychosis." The searching was on March until May 8, 2017.

2.2. Article collection and selection

Information collected from the articles then tabulated. The articles inclusion criteria published in peer-reviewed journals, the subject was human, discussing the impact of physical and chemical exposure to the incidence of schizophrenia, in English. Articles that were inconsistent with topics, criteria, and duplicates excluded. The content of selected articles then analyzed.

3. Results

There were 99 articles. The chosen articles by title, topic, abstract review and the overall content of the articles. Sequentially, 4, 64, 24 articles excluded.

3.1. Researchs characteristics

Wang et al. (2014) examined the associated of extreme temperature with the incidence of schizophrenia. The population was the population of Toronto from April 1, 2002, to March 31, 2010, identified by using the provincial computer database of NACRS (National Ambulatory Care Reporting System). The ambient air temperature data obtained from health and climate data from 2002-2010. The results showed a strong correlation between schizophrenia emergency room visit and hot temperature with average ambient air temperature was 28^0 C. The cumulative period was seven days after exposure to high temperature, 149% increase (RR = 2.49 95% CI 1.69-3.69). There was no significant association between cold temperature and visitation in an emergency.

Tong et al. (2016) examined the association between season, air pollution and the incidence of schizophrenia in Tianjing, China. Daily air pollution data PM_{10}, SO_2, and NO_2 obtained from the Tianjin Environmental Monitoring Center database. The daily average data on temperature and humiditywere collected from the China Meteorological Data Sharing Service System. Schizophrenia data were obtained from the Centers for Disease Contol (CDC) and the Prevention of Urban District in Tianjin. The history of the disease, sex, age, family address data taken. Time series analysis was conducted to explore the association of seasons, age, gender with air pollution to the morbidity of psychiatric disorders in Tianjin from 2008-2011. The effects based on age and gender, indicated with elevated levels of 10 µg/m^3 of air pollution concentration, there was no significant effect on 5-44-year-olds or 45-64 years. Among the age of 65 years and over, the effect was predicted to significantly with the increase of SO_2 levels. Female had a higher risk than male. The level of SO_2, NO_2 was 12 and 13 times higher in cold seasons (October-March) than in Warm season (April-September). Increased of 10 µg/m^3 levels of SO_2, NO_2, and PM_{10} had a higher risk to Psychosis 0.15%, 0.49%, and 0.57% respectively.

Oudin et al. (2016) examined the association of air pollution (NO_2, PM_{10}, and $PM_{2.5}$) and the risk of schizophrenia in Sweden. The data were from the Swedish National Register. The data used in the study were the form of drugs for disorders of psychiatric include sedatives, sleeping pills and antipsychotics as well as socioeconomic, demographic and residential data using regression models for air pollution concentrations for NO_2, PM_{10}

and PM $_{2.5}$. Average NO_2 levels 9.8 μg/m3, children and adolescents who lived in the higher-grade level were likely to receive psychiatric disorders during follow-up (RR= 1.09, 95% CI 1.06-1.12), in line with the increase of 10 μg/m^3 NO_2.

Research conducted by Wang&Zhang(2017) studied the association between the season of birth and schizophrenia. The study focused on the differences based on geographic area, urban/rural residences, and sex. The results showed that people born in spring had the highest risk for schizophrenia compared to those born in winter (OR = 0.95, 95% CI-0.89-1.0, p> 0.05), summer (OR = 0.92, 95%, CI = 0.86-0.98, p <0.001) or autumn (OR = 0.88, CI = 0.83-0.94, p <0.001). People living in the northern (region with central heating system) had a smaller risk for schizophrenia than the southern (region with no central heating system) (OR = 0.79, 95% CI = 0.76-0.83). People who lived in urban areas had a higher risk for schizophrenia than those who lived in rural. Male had a lower risk than female (OR 0.94, 95% CI = 0.90-0.99, p <0.001). The interaction between the season of birth and the geographic showed that people in the north who was born in spring had the highest risk than others, followed by those in summer, winter, and fall. In the Southern, born in spring still had the highest risk of schizophrenia, then winter, summer, and fall. The interaction between seasons of birth and urban, rural residencies indicated that people born in spring had the highest risk of schizophrenia but only significantly in rural. The interaction between the season of birth and gender suggests that people born in spring had the highest risk for experienced schizophrenia for both men and women.

Aschengrau, Weinberg, P. a Janulewicz, et al. (2012) studied 1,512 people who were born in between 1969 and 1983, including 831 respondents who exposed to tetrachloroethylene, contaminated water (from water pipes) and 547 unexposed respondents. Retrospective cohorts were performed to determine whether early exposure to contaminated drinking water with the incidence of depression, bipolar, post-traumatic disorder and schizophrenia. The results showed that exposure to tetrachlorethylene was 2.1 times for schizophrenia risk (n = 3 cases of exposed, 95%, CI: 0.2-20.0).

A study in Jerusalem, conducted by Perrin et al. (2007a) examined the exposure of tetrachloroethylene with schizophrenia to 88,829 children born in Jerusalem in 1964-1976. They were followed from birth to age 21-33 years with Population-Based Cohort Study method. The results showed that relative risk (RR) for schizophrenia to the offspring whose parents were dry cleaner (had exposed with tetrachloroethylene) was 3.4 (95% CI 1.3-9.2, p = 0.01).

Modabbernia et al. (2016) examined the association of metals exposure with schizophrenia. A total of 14 people as control (9 people with schizophrenia and five people) investigated by using Proof_of concept study design. The study was conducted by using tooth-matrix biomarkers and analyzed to determine the association between early metal exposure and psychiatric abnormalities. The metals which were analyzed were lead, manganese, cadmium, copper, magnesium, and zinc. The results showed a positive correlation between early lead exposure and schizophrenia. Lead levels were higher in schizophrenia compared with controls while manganese and copper were negatively correlated.
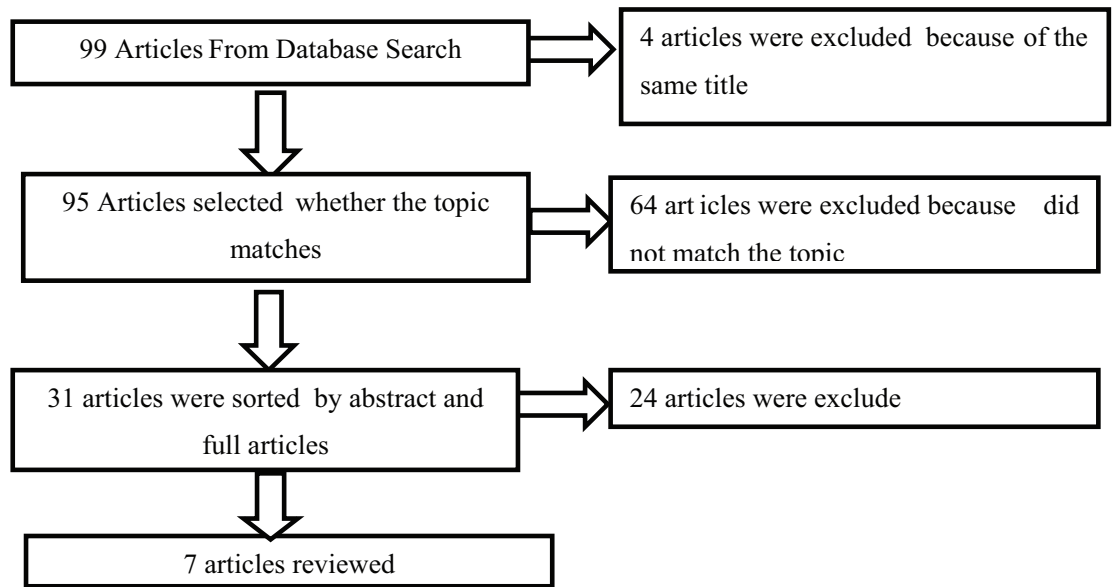
Figure 1: Data Collection Process.

TABLE 1: Research Characteristics.

Researchers	Country	Study Object	Research design	Year
Wang, X. et.al	Canada	Extreme Temperature	Time Series Study	2013
Tong, L. et al	China	Air pollution	Time Series Study	2016
Wang, C & Zhang, Y	China	Season of Birth	Cross Sectional Study	2017
Aschengrau, A. et. al	Massachusetts, US	Tetrachloroethylene	Retrospective Cohort Study	2012
Perrin, A. et. al	Israel	Tetrachloroethylene	Population Based Cohort Study	2006
Oudin, A. et.al	Swedia	Air pollution	Cohort Study	2016
Modabbernia, A. et.al	U.S	Metal	Proof -of-Concept Study	2016

4. Discussion

Air pollution, climate/season, tetrachloroethylene exposure and lead exposure had an association with the occurrence of schizophrenia based on the result of a review.

4.1. Air pollution

The results of Oudin et al. study showed a significant association between elevated air pollution levels and schizophrenia (NO_2). Tong et al. found no significant association between high air pollution levels (PM_{10}, SO_2, and NO_2) by age and sex, only in the age group of 60 years and above was estimated that increase of SO_2 levels significantly related to the incidence of schizophrenia. This result may be due to the age group may experience more prolonged exposure to pollutants and weaker immune system [21]. Increased of 10 µg/m^3 levels of SO_2, NO_2, and PM_{10} had a higher risk to Psychosis

0.15%, 0.49%, and 0.57% respectively. Although the increase was not too high, the risk increased along with the length of exposure. The incidence of a disease influenced by duration and the dose of the exposure [21].

In the cold season (October-March), it showed the elevation levels of PM_{10}, SO_2, and NO_2 had a significant association with the incidence of schizophrenia whereas during the warmer months (April-September) there was no significant association. The differences in the association between seasons might be because during the cold season the levels of PM_{10}, SO_2, and NO_2 reach 12 to 13 times more than the warm season. It might be come from the emission of coal combustion that was used as a heating system in a cool season [7]. Some studies suggested that schizophrenia was more common in people born in winter or early spring [22, 23]. Those may correlate and needs to be proven with further research.

4.2. Climate/Season

Research on ambient air temperature and seasons done by Wang et al. in Canada and Wang & Zhang in Canada. Wang & Zhang found that people born in the spring, lived in cold areas, and in urban areas had the highest risk for schizophrenia. Male had a lower risk than female; this condition was different from the risk factor for schizophrenia in which male had higher risk than female [24]. This difference might be due to the presence of other risk factors that supported the incidence of schizophrenia such as genetic factors, individual characters, living and working pressure [7]. Smoking habit might have an association with this result. Non-smokers were more sensitive to air pollution than smoker (most of female are non-smokers) [7]. Wang et al. found that hot temperatures increased the risk of exacerbation of schizophrenia while cold temperatures did not have a significant association. Psychiatric disorder/illness could increase an individual's physiological vulnerability to extreme temperature if specific neurotransmitter involved in thermoregulation were also involved in the disease process [19]. Further research is needed to analyze the other factors than extreme temperatures to schizophrenia exacerbations.

4.3. Chemical (Tetrachloroethylene)

The studied that examined the association between tetrachloroethylene schizophrenia done by Perrin et al. in Jerusalem and Aschengrau et al. in America. Perrin et al. showed that people who exposed to tetrachloroethylene in early life had a risk of schizophrenia 3, four times higher than those who were not exposed. Aschengrau et al. found that tetrachlorethylene exposure at the beginning of life were 2.1 times to have a higher risk than those who did not. From the results of these two studies, the risk level differed considerably; this might be due to differences in study design. Aschingrau et al. study conducted with a retrospective cohort study found three subjects suffered from schizophrenia. It was not enough to get the conclusions [14]. The number of samples should be on the minimum sample number criteria. Population-Based Cohort Study prospectively performed on a study by Perrin et al.[15]. Prospective investigators were

considered to be more minimal in causing bias in the study than cross-sectional and retrospective studies [25].

4.4. Heavy metals

The lead had a positive correlation with the incidence of schizophrenia whereas other metals, manganese and copper had a negative correlation. The study analyzed teeth metal exposure biomarkers of 9 people with schizophrenia and four controls. The number of controls was less than the case so the results, of cours was, significant because the number of cases was more than the control. The number of control should be minimal 1:1 with the case [25]. The biomarker examination might show a more definite metal exposure compared to other such as the use of a questionnaire [26].

5. Conclusions

Environmental factors such as extreme hot temperatures, air pollution (SO2, NO_2, PM_{10}, $PM_{2.5}$) season of birth on winter or early spring, tetrachlorethylene and lead exposure could increase the risk for schizophrenia. The variables that affected the association between environment and schizophrenia were geographic location, gender, age, and urban/rural residences.

Further researches are needed to be done to reinforce the results of the above studies by using a study design that can show the exact cause, design and sample size, represent the situation in the population, biomarker examination that can ensure which exposure and other factors that may be the risk of schizophrenia. This systematic review only compared two research articles for each environmental factor/condition because the research related to the topic was limited. Further research might be needed for season of birth related to schizophrenia in two season countries.

Acknowledgement

Ethical Approval

This is systematic review, no need ethical approval

Competing Interst

Authors declare that there is no competing interest.

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