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BMJ Open Global environmental risk factors of schizophrenia: a study protocol for systematic review and meta-analysis of cohort studies

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ABSTRACT

Introduction Schizophrenia is a chronic, complex and severe psychiatric disorder affecting millions of people every year and inflicting different costs to the individual, family and community. A growing body of evidence has introduced several genetic and environmental factors and their interactions as aetiological factors of schizophrenia. The goal of this systematic review and meta-analysis is to present an updated representation of the global environmental risk factors of schizophrenia.

Method and analysis This protocol is developed and reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guideline. We will systematically search the databases such as PubMed, Scopus, Web of Science, PsycINFO and Embase until 30 September 2022. We include Cohort studies that have reported one or more risk factors of schizophrenia. We will also search Google Scholar search engine and references lists of included articles. Extracting the relevant data and assessing the quality of the included studies will be independently performed by different authors of our team. The risk of bias for the included studies will be evaluated using Newcastle-Ottawa Scale. Subgroup analysis, meta-regression or sensitivity analysis will be our solution to deal with heterogeneity between studies. We will use a funnel diagram as well as Begg and Egger tests to check for possible publication bias.

Ethics and dissemination Ethical approval is not required because there will be no primary data collection or human involvement. The results of this study will be published in an international peer-reviewed journal.

PROSPERO registration number CRD42022359327.

INTRODUCTION

Schizophrenia is a chronic, complex and severe psychiatric disorder. The estimated number of people suffering from this disease was approximately 24 000 000 in 2019. Schizophrenia is prevalent in all societies as well as all socioeconomic levels with differences in terms of diagnosis, clinical symptoms and prognosis.^{1 2} According to Diagnostic and Statistical Manual of Mental Disorders (DSM) criteria, clinical manifestations of schizophrenia are positive (eg, hallucinations,

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ Our aim will be to conduct a systematic review and meta-analysis focusing on the epidemiology of environmental risk factors of schizophrenia in the world.
- ⇒ We will search only articles written in English language, which may increase the publication bias.
- ⇒ Data of the updated publications from different communities will increase the generalisability of results.
- ⇒ We will just include cohort studies to reduce heterogeneity.
- ⇒ We will develop and report this protocol in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols guideline.

delusions and disturbed behaviour) and negative (eg, deficits in emotional expression, social impulsivity, social withdrawal and difficulty experiencing pleasure).³

Due to the high costs of treatment, loss of work ability of affected people and the fact that schizophrenia causes severe despair and depression in patients and families, the costs of this disorder for society are beyond the material resources spent for the patients.⁴ From this perspective, schizophrenia is a public health problem rather than an ‘illness’ only for patients, relatives and mental health workers.⁴

Although the exact causes of schizophrenia are unclear, various genetic and epidemiological studies have indicated multiple genetic and environmental risk factors for this disorder.⁵ The role of genetic factors in the occurrence of schizophrenia has been demonstrated⁶; however, the role of environmental factors cannot be ignored.^{7 8} The development of schizophrenia is likely to be a function of interaction between genetic and environmental risk factors rather than the result of their independent effects.⁹ Therefore, it may be possible to distinguish the importance of genetic factors of schizophrenia with the help

of environmental factors. Considering the importance of environmental factors, various studies have indicated the role of multiple environmental risk factors in the development of schizophrenia: cannabis use in adolescence,¹⁰ childhood adversities and injuries,¹¹ migration,¹² father's age,¹³ low socioeconomic status,¹⁴ single-parent families,¹⁴ urban residence,¹⁵ etc.

Due to the high number of people afflicted with schizophrenia, the problems arising for patients and their families, as well as the high costs it imposes on society, schizophrenia is considered a crucial matter, the importance of which has been reported in many studies.^{16 17}

Despite the importance of environmental risk factors related to schizophrenia, up to our knowledge, no worldwide study has been conducted in this regard. Therefore, our aim will be to conduct a systematic review and meta-analysis focusing on the epidemiology of environmental risk factors of schizophrenia in the world. We hope that our findings provide a comprehensive report that will be useful for future studies.

METHODS AND ANALYSIS

Review question

What environmental risk factors can be associated with schizophrenia?

Main objective

Evaluation of the risk factors associated with schizophrenia.

Condition or domain under study

Regularisation of data, which have reported the risk factors related with schizophrenia.

Patient and public involvement

No patient was involved.

Study design

We will develop and report this protocol in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guideline¹⁸ for study design, search protocol, screening and reporting. The protocol is registered with the International Registration of Systematic Reviews. The completed systematic review and meta-analysis will be reported following the PRISMA guidelines.¹⁹

Search strategy to identify relevant studies

We will perform both electronic and manual searching. In the first step, two members of our team will conduct the search independently and export the articles in an EndNote file. In the second step, we will remove the duplicates. In this way, the possibility of human error will be reduced because two researchers perform the literature search. All search steps will be done under supervision of a health informatics expert. We will do a systematic search of international databases such as Web of Science, PubMed, Scopus, PsycINFO and Embase until 30 September 2022. We also use Google Scholar

search engine to find grey literature of this area. The search strategy includes keywords and Medical Subject Headings terms as follows: ('Dementia Praecox' OR 'Schizophre*' OR 'psychosis') AND (Risk OR 'Population at Risk' OR 'Populations at Risk' OR 'Risk factor' OR 'Risk factors' OR 'Risk Score' OR 'Risk Scores' OR 'Risk Factor Score' OR 'Risk Factor Scores' OR 'Relevant factor' OR 'Relevant factors') AND (Cohort OR 'longitudinal studies').

Each database will be searched without restrictions on publication year and region. Due to resource limitations and authors' linguistic competence, only articles published in English will be included in the study. References list of all included studies will be manually checked to identify any other eligible studies that may have been excluded from literature searches.

Types of studies to be included

Cohort studies.

Risk of bias (quality) assessment

The quality of each included study will be assessed independently by two authors using Newcastle-Ottawa Scale checklists. This scale ranges from 1 (lowest quality) to 9 (highest quality) stars, which judges each study regarding group selection, comparability of the groups and ascertainment of the outcome of interest. Discrepancies will be resolved by consensus, and if needed, disagreements will be settled by a third author.

Inclusion criteria

The following studies will be included: (1) Cohort studies; (2) studies that have reported at least one risk factor related to schizophrenia; (3) studies published as full-length articles in peer-reviewed English journals; and (4) studies in which the diagnosis of schizophrenia should be determined by Diagnostic and Statistical Manual of Mental Disorders (DSM III, III-R, IV, IV-TR or V) or International Statistical Classification of Diseases and Related Health Problems (ICD-10 or ICD-11).

Exclusion criteria

Studies meeting the following criteria will be excluded: (1) Conference abstracts, clinical trials, comments, letters, animal studies, any type of reviews, case reports, case series and in vitro studies; (2) duplicate publications; (3) qualitative studies; (4) reports from organisations; (5) studies assessing the validity and reliability of the questionnaires; (6) studies with insufficient data for calculating the required parameters; and (7) studies conducted on high-risk groups, including people with genetic diseases that may disrupt their ordinary life, such as cancer, severe physical disability, mental retardation. We intend to limit the role of genetic factors in the occurrence of schizophrenia by excluding high-risk groups.

If studies overlap with the participants, reports with larger sample sizes will be included in the present study.

Screening and data extraction

A reviewer will screen the articles based on title and abstract to remove irrelevant articles. In this process, we do not remove the articles with dubious relevance. In the next step, three reviewers independently check the remaining articles from the previous step by reading their full text. They will select the articles that meet all the inclusion criteria and have none of the exclusion criteria. They will discuss with each other to solve the disagreements. After that, two reviewers will extract the data independently, and differences between them will be resolved through consensus. Also, if needed, at each stage, the disagreements will be settled by the third or fourth author. Data extraction checklist will include the name of the first author, publication year, the region of study, the study design, number of patients, mean age, response rate, gender, type of sampling, sample population (general or something else) and risk factors of schizophrenia using the crude and, if available, adjusted reported ratios of association measures with 95% CIs.

If the data of interest are not available in some of the included studies, attempts will be made to contact the first or corresponding author to obtain the missing data. If we do not receive a response after three emails, we will exclude that study.

Strategy for data synthesis

In this study, the effect size of each risk factor will be reported with 95% CI. If the number of studies is sufficient (≥ 4) for synthesis, we will report the pooled effect size. Heterogeneity of studies are calculated using an index (I^2) and Q Cochran test. We will use the random model and otherwise the fixed model effect if I^2 index indicates the heterogeneity of studies ($p < 0.05$, $I^2 > 50\%$). Subgroup analysis, meta-regression or sensitivity analysis will be our solution to deal with heterogeneity between studies. We will use a funnel diagram as well as Begg and Egger tests to check for possible publication bias. Data will be analysed using Stata V.16 software.

DISCUSSION

The purpose of this study is to present a protocol for systematic review and meta-analysis of global environmental risk factors for schizophrenia. So far, many studies have been conducted on environmental risk factors related to schizophrenia. Some environmental risk factors have also been identified, including cannabis use in adolescence,¹⁰ migration,¹² low socioeconomic status,¹⁴ etc. In this study, we intend to systematically examine the environmental risk factors of schizophrenia worldwide. By systematically examining the environmental risk factors related to schizophrenia, this research can present a comprehensive understanding of the ways in which this disorder arises. Also, by clarifying all the environmental risk factors of schizophrenia, including the social context, ecological and cultural factors, we can represent a better perspective of this disease to better control those factors.

By controlling environmental risk factors, we may be able to prevent further occurrence of this disease.

This study will provide a clear view of environmental risk factors for schizophrenia. This will be the first step to control these environmental risk factors.

The findings of this study can be useful for the treatment staff, health policymakers and, most importantly, for the general public.

ETHICS AND DISSEMINATION

Ethical approval is not required because there will be no primary data collected nor human involvement. The results of this study will be published in an international peer-reviewed journal.

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Contributors SMMM conceived the idea and prepared the draft. AM wrote Strategy for data synthesis and helped in developing the data extraction form. SF reviewed and revised the protocol. All authors reviewed and approved the final manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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