INPLASY PROTOCOL

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Maternal exposure to pesticides during pregnancy and risk for attention deficit hyperactivity disorder in offspring: a protocol for systematic review and meta-analysis

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Review question / Objective: To explore whether there is an association between maternal exposure to pesticides during pregnancy and risk for attention deficit hyperactivity disorder in offspring.

Condition being studied: Several studies have explored the effects of maternal exposure to pesticides during pregnancy and ADHD risk in offspring, but obtained inconclusive results. There is no existing systematic review and meta-analysis that has assessed the association of maternal exposure to pesticides during pregnancy with ADHD risk in offspring.

Information sources: Relevant studies will be identified by searching PubMed, Embase, Web of Science, Cochrane Library, and the PsycINFO. All the Database will be searched from inception to May 2021.

INTRODUCTION

Review question / Objective: To explore whether there is an association between maternal exposure to pesticides during pregnancy and risk for attention deficit hyperactivity disorder in offspring

Rationale: Attention deficit hyperactivity disorder (ADHD) is the most common psychiatric disorder in childhood, which often persists into adulthood and is estimated to affect around 5% of children under 18 years old and 2·5% of adults worldwide. ADHD are associated with a

wide range of other mental health problems, including affective disorders, defiant, antisocial personality disorder, self-harm, substance misuse. In addition, ADHD may seriously disrupt one's social life, leading to a series of negative outcomes such as educational underachievement, unemployment, and criminality. Although short term medication-based treatment for ADHD have proven to be efficacious and cost-effective, the long-term effectiveness of these treatments on key educational, vocational, and social outcomes remains uncertain. Moreover, the effectiveness of non-pharmacological approaches to treatment have proven to be lower than expected. Therefore, primary prevention targeting at risk factors for ADHD is of great importance to the prevention and management of ADHD from a public health perspective. Although the explicit etiology remains unknown, ADHD is suggested to be a highly heritable disorder, with an estimated heritability of 70% to 80%. Environmental factors may also contribute to the increase of the ADHD prevalence during the last decades. Numerous environmental exposures have also been identified to be risk factors for ADHD. Among those, many prenatal and perinatal risk factors, such as prematurity, low birthweight, intrauterine exposure to tobacco, and maternal stress and obesity during pregnancy. Pesticides are a group of complex chemicals that protect crops and stored products, partially by exterminating harmful insects. Exposure to pesticides during critical perinatal developmental periods can alter reproductive and central nervous system function that causes functional alterations in later life. Maternal exposure to pesticides during pregnancy has been show to be associated with an increased risk of adverse reproductive outcomes and neurodevelopmental disorders in offspring. Several studies have explored the effects of maternal exposure to pesticides during pregnancy and ADHD risk in offspring, but obtained inconclusive results. There is a necessity to conduct a systematic review and meta-analysis to assess the association of maternal exposure to pesticides during pregnancy with ADHD risk in offspring.

Condition being studied: Several studies have explored the effects of maternal exposure to pesticides during pregnancy and ADHD risk in offspring, but obtained inconclusive results. There is no existing systematic review and meta-analysis that has assessed the association of maternal exposure to pesticides during pregnancy with ADHD risk in offspring.

METHODS

Search strategy: Relevant studies will be identified by searching PubMed, Embase, Web of Science, Cochrane Library, and the PsycINFO. Search strategy Main search terms will include "pregnancy", "pesticide", "organochlorines", "organophosphates", "herbicides", "insecticides", "fungicides", "bactericides", "rodenticides", "fumigants", "attention deficit hyperactivity disorder", and "ADHD".

Participant or population: Pregnant women and their offspring will be included.

Intervention: This study will only include observational studies. The exposure group will be children whose mother were exposure to pesticides during pregnancy".

Comparator: Offspring participants whose mother were not exposed or only exposed to relatively low dose of pesticides during pregnancy will be used as the control group.

Study designs to be included: Observational studies, including cohort, case–control, and cross-sectional studies.

Eligibility criteria: Observational studies which reported the association between maternal exposure to pesticides and ADHD risk in offspring were eligible for inclusion. To be included, the association had to have been presented as an odds ratio (OR) with a corresponding 95% confidence interval (CI). When an OR was not provided, data sufficient to calculate it were required to be available in the original publication. Non-

human studies, case reports, conference abstracts, and reviews were excluded.

Information sources: Relevant studies will be identified by searching PubMed, Embase, Web of Science, Cochrane Library, and the PsycINFO. All the Database will be searched from inception to May 2021.

Main outcome(s): The association between maternal exposure to pesticide and ADHD risk in offspring will be quantified using odds ratio (OR) values and the corresponding 95% confidence interval (CI).

Data management: The EndNote reference manager will be applied to store and manager tiles and abstracts of all studies identified by the literature search. Two independent researchers will perform the study selection by scanning the titles, abstracts, or full texts of the candidate studies. Any discrepancies will be resolved by discussion with an experienced third researcher. Using a standard data collection form developed prior to data extraction, two researchers will independently collect the following data from the included studies: name of first author, publication year, country, study design, sample size, ascertainment of ADHD, measurement of pesticide exposure, indicators for quality assessment, the most fully adjusted risk estimate and corresponding 95% confidence interval (CI), and confounding factors.

Quality assessment / Risk of bias analysis: The Newcastle-Ottawa Scales (NOS) will be used to assess the methodological quality of cohort and case-control studies. This tool evaluates the selection of study groups (maximum 4 stars), comparability of the study populations (maximum 2 stars) and ascertainment of outcomes (for cohort studies) or exposure (for case-control studies) (maximum 3 stars). A high score indicates a low risk of methodological quality. The scale of the Agency for Healthcare Research and Quality (AHRQ) will be used to assess cross-sectional studies. The Begg's test and Egger's test will be used to detect potential publication bias.

Strategy of data synthesis: The association between maternal exposure to pesticide and ADHD risk in offspring will be quantified using OR values and the corresponding 95% CIs. Between-study heterogeneity will be evaluated by the I2 statistic. The heterogeneity will be considered statistically insignificant if I2≤50%, then the fixed-effect model will be used to calculate pooled OR among studies. Otherwise, the random-effect model will be adopted. STATA version 12.0 (Stata Corporation, College Station, TX) will be used to conduct the meta-analysis.

Subgroup analysis: Subgroup analysis will be carried out according to study design, study location, subtype of pesticides, ascertainment of ADHD, measurement of pesticide exposure, study quality, and adjustment for confounding factors.

Sensitivity analysis: Sensitivity analysis will be performed by omitting the risk estimate of each study in turn to examine the robustness and stability of the pooled results.

Country(ies) involved: China.

Keywords: pesticide; attention deficit hyperactivity disorder; pregnancy; risk factor; meta-analysis.

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