Influence of Mercury Exposure During Pregnancy to Neurodevelopmental Disorder: A Systematic Review Protocol

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Abstract

Background: The general population might expose to Hg through various pathways. Prenatal or postnatal exposure to mercury might affect the fetus's neurodevelopment and then further affect the growth and development of the children. There are many reports on mercury exposure, but systematic reviews to conclude the result are still limited, particularly concerning pregnancy. Previous studies focus on one exposure path to Hg and biomarker. The objective is to systematically summarize the relevant records from systematic studies on the relationship between the exposure pattern during pregnancy to pregnant women's Hg concentration and neurodevelopmental disorder that occurred in the children.

Method: We will search online databases (Google Schoolar, PUBMED, Sciencedirect, Proquest, Web of Science, Springerlink, DOAJ (Directory of Open Access Journals) and EBSCO MEDLINE) and reference lists of included articles. Two reviewers will independently screen the titles and abstracts and select the research involving pregnant women with mercury exposure and neurodevelopmental disorder fetus or children. These reviewers will also independently extract and manage the obtained data using a data extraction form that will cover information on characteristic, exposure, and outcomes. Meta-analysis will also be applied when homogeneous group of studies found.

Discussion: This study will describe the available epidemiological evidence and summarise prevalence and incidence rates of mercury exposure and neurodevelopmental disorder. Mean difference of mercury level will be also presented. A better understanding of the relationship between mercury exposure and any neurodevelopmental disorder form will be helpful in the development of guidelines for mercury exposure management.

Systematic review registration: It has been submitted to PROSPERO on February, 10th 2021.

Background

Mercury (Hg) is a global pollutant which is included as one of the most toxic elements that affect environmental and human health. Hg comes in three various forms, including elemental mercury (Hg0), inorganic mercury (mercury salts), and organic mercury/methyl mercury (MeHg).

Hg is present in the environment through natural events, so its long journey causes Hg to be ubiquitous and found in water, air, and soil. Inorganics Hg is released into the atmosphere from various industrial activities, then deposited into aquatic and marine ecosystems through rainfall and dry deposition [1]. Hg is commonly found in consumer goods (including some pharmaceuticals) and food products that expose people to Hg through digestion, skin, and respiration [2]. Higher inorganic Hg exposure was discovered among mercury miners, gold miners, dentists and dental amalgam patients [3].

The general population might expose to Hg through various pathways, such as organic Hg from consumption of seafood (mainly as monomethyl-Hg), dental amalgam filling vapor and, possibly, CH3Hg+, MeHg), elemental Hg (Hg0 vapor released from inorganic Hg(Hg(II)) of cosmetics and

foodstuffs [4]. Previous studies found total concentrations of Hg and Methylmercury in hair, suggesting that the exposure was mainly from food sources through digestion [5]. One of the MeHg exposure medium through digestion is from fish intake due to transformation of Hg to MeHg in aquatic environments. DHA in fish has been recognized as an essential dietary nutrient for rapid brain growth from the third trimester to 2 years of age and is transported mainly through the placenta to the fetus. However, it was found that fish intake was also considered a significant pathway for MeHg exposure and the level of fish consumption was found to be significantly correlated with Hg concentrations in the blood and hair of pregnant women [5][6]. Coastal and island residents, as well as indigenous populations, often consume high MeHg seafood, including top predators such as marine mammals. Therefore, they tend to have increased exposure [7]. In some areas where Hg contaminates paddy fields, rice also contributes significantly to MeHg exposure [8], [9], [10].

Another exposure pathway of Hg is through the skin. The use of skin lightening creams has become a popular behavior among women as a cosmetic purpose. Hg has been added to creams due to its ability to inhibit the pigment melanin. Assuming that Hg can replace the copper required for tyrosinase activity and thereby deactivate the enzyme, leading to a bleaching reaction.The use of skin lightening creams containing Hg result in systemic absorption and accumulation of Hg which leads to kidney, gastrointestinal, and central nervous system toxicity [11].

Mercury exposure in pregnant women might also occur through dental amalgam. Amalgam is a mixture of several metals, such as silver, lead, zinc, and copper. It has been used as a restorative treatment in dentistry for more than hundreds of years. However, about 43–54% of the main component is Hg. Pregnant women exposed Hg from amalgam through dental amalgam filling before or during pregnancy [12] [4]. Mercury from dental amalgam accumulates in the placenta, but part of it also crosses the placenta and is oxidized in the fetal liver. MeHg can enter foetal circulation through penetration of placental and blood-brain barriers Hg(II) might be accumulated in the placenta and reached the foetus [13]. However, Hg(II) may also transfer the placental barrier in minor quantity in rats [14]. Hg is transported to foetal tissues as reported that meconium total Hg (THg) levels correlated positively with fish consumption during pregnancy [15] as well as with dental amalgams [16].

The Joint FAO/WHO Expert Committee on Food Additives (JECFA) has developed a tolerable intake of 1,6 µg/kg body weight per week for Methylmercury. JECFA clarified that life-stages other than embryos and fetuses might be less sensitive to adverse effects of Methylmercury. Up to twice the tolerable intake per week for adults would not pose a risk of neurotoxicity. However, the available data did not allow firm conclusions to be drawn for children, as they could be more sensitive than adults. Consequently, the tolerable intake established in 2004 also applies to children. WHO estimates the average dietary exposure to total mercury from foods other than fish and shellfish for adults as 1 µg/kg BW per week. For children 4 µg/kg BW per week were at or below the PTWI for inorganic mercury [17].

Hg exposure represents Minamata disease, which is caused by prenatal or postnatal exposure to Methylmercury (MeHg) in adults and children [2]. The potential of MeHg to cross the placenta and the

fetal blood-brain barrier found in a famous disaster in Minamata Bay, Japan. Fetal abnormalities, blindness, and severe physical and developmental retardation were reported in the offspring of pregnant women who consumed highly contaminated locally obtained seafood [18].

When the daily dose of MeHg exposure exceeds the reference dose over a lifetime, this may pose a risk to sensitive subgroups (i.e., fetuses and children). So, the mother's DHA intake through fish consumption has also been considered as a factor which can seriously affect prenatal neurodevelopmental outcomes [6].

Hg exposure is usually estimated by biomarkers assessment. Tissues Hg concentrations, such as in hair, urine, blood, and nails, reflect all Hg exposure from any sources [19]. Human hair is often used as a bioindicator for mercury exposure. Hair is generally preferred for documenting methylHg exposure because it provides a simple, integrative, and noninvasive sample [20], except for inorganic Hg0, as the $Hg2+$ in hair is possibly demethylated from external deposition through MeHg demethylation [21]. Total Hg concentration in blood is recognized as an effective biomarker for both MeHg and total Hg exposure [22] as MeHg was reported to make up 70–85 % of the blood total Hg [23]. Nail is also used for measuring MeHg in the general populations [19]. To measure occupational exposure from dental amalgams, Hg level in urine is the most popular biomarker for inorganic Hg [22].

There are many reports on mercury exposure. However, there are still limited systematic reviews, particularly concerning pregnancy. Previous studies concentrate on one form of exposure to Hg and biomarker. The current systematic review intends to include any possible exposure to Hg during pregnancy and all biomarkers. We formulate research question based on Population, Exposure, Comparator, and Outcome (PECO) formulation [24], as follows:

- What is the prevalence and incidence of Hg exposure on each pathway during pregnancy according to internationally published studies?
- According to internationally published studies, what is the prevalence and incidence of Hg exposure based on each biomarker of pregnant women?
- What is the prevalence and incidence of Neurodevelopment outcome on the children due to prenatal Hg exposure according to internationally published studies?
- What is the relationship of Hg exposure pathways during pregnancy to Hg level of pregnant women?
- What is the relationship of Hg exposure during pregnancy to the neurodevelopmental outcome on the children?

Knowledge regarding the distribution of Hg exposure in pregnant women will be necessary for informing the population and the stakeholders to prevent exposure.

Objectives

Considering the inadequacy of an interconnected body of knowledge on mercury exposure during pregnancy, this systematic review protocol aims to provide a clear framework for the collection of

information on the Hg exposure during pregnancy and its effect on the babies children. Furthermore, the systematic review aims to systematically summarize the relevant records from systematic studies on the relationship between the exposure pattern during pregnancy to pregnant women's Hg concentration and neurodevelopmental disorder outcome.

Methods

Protocol

The method for this systematic review was developed in accordance with the recommendations of the Selected Reporting Items for Systematic Review and the 2015 Meta-Analysis Protocol Statement (PRISMA-P) [25].

Eligibility criteria

We determine the eligibility criteria according to PECO statement as follows:

Population : the population of interest will include pregnant women and their children.

Exposure : - exposure to Hg before or during gestation,

- exposure to environmental Hg exposures measures through biological samples of the mothers during pregnancy

- Exposures measured through environmental monitoring or occupational exposures, such as surveys)

Comparators: mother who were exposed to low level Hg before or during pregnancy and their children

Outcomes : Any adverse child outcome such as premature birth, low birth weight, failure of hearing screening or audiology test, adverse score on intellectual ability or adaptive skills tests, diagnoses (*Diagnostic and Statistical Manual* [DSM] or ICD codes) of intellectual disability, autism spectrum disorder, epilepsy, cerebral palsy, attention deficit hyperactivity disorder (ADHD), (inattention, inattentiveness, sustained-attention, disruptive-behavior, habituation, hyperactivity, overactivity, hyperactive, overactive, impulse, impulsiveness, impulse-control, impulsivity, delay-of-reinforcement, delayed-reinforcement, motor-control, motor-activity, disinhibition, inhibition) mental illness, immune or autoimmune conditions and measured levels of cytokines, and evidence of structural or cell damage in live-born children.

Study Design

Studies will be limited on design and observational studies, cross-sectional studies, cohort studies, case control studies, and case series. Non-research letters and editorials, abstracts, seminar reviews, systematic review, non-human studies, and clinical trial will be excluded. Randomized controlled trials will be excluded due to unsuitability the type of questions to be answered. The searches will be focused to

peer-reviewed full-text articles in English. However, unpublish information sources, such as thesis or dissertation will be included.

Information Sources

We will search the publication systematically from the international journal databases, include Google Schoolar, PUBMED, Sciencedirect, Proquest, Web of Science, Springerlink, DOAJ (Directory of Open Access Journals) and EBSCO MEDLINE. Addition publication also will be found from references of the articles. We will limit the publication years from 2015 to 2021. Contact with the authors for further information will be made when needed.

Search Strategy

We will construct structured electronic search strategies using the thesaurus terms of each database (e.g., MeSH for MEDLINE and PUBMED) and using keywords relevant to the population, exposure, and the outcomes. The strategy will then be applied to all of the databases.

Selection Procedure

First, duplicate publications will be removed. Then, the screening will be applied to the title and abstract of the papers to assess the eligibility. We will review the full texts of publications to find the papers meet the inclusion criteria using a checklist based on PRISMA checklist. We will include study with score of minimum 3. Two reviewers will work independently then compare their results and discuss the findings in the presence of differences. A third reviewer will be involved when a consensus is not feasible. Studies will be selected for retrieval following the procedure illustrated in *Figure 1*.

Data extraction and management

We will extract data on (1) general characteristics of the research include investigator names, study and publication year, objectives, search strategy, number of included studies, number of participants and funding source, (2) characteristics of the research population of that may have age, gestation age, location and ethnicity, (3) the exposure, which can include assessment method, distribution in the study population, the exposure pathway and Hg level, (4) outcomes, include outcome measurement methods, various type of outcomes, (5) comparators (6) methods applied which may consist of statistical analysis and factors adjusted for, and (7) results such as incidence and prevalence, the mean or median level of Hg exposure, measures of association, or stratified analyses, (8) review limitation.

For reference screening, we will use Covidence (https://www.covidence.org). We will apply SRDR (Systematic Review Data Repository; https://srdr.ahrq.gov/home/index) for data extraction and management. The data or results will be presented in summary tables and figures.

Any disputes occurring during the process of data extraction will be resolved by dialogue and consensus between the two reviewers and, if necessary, will include a third reviewer. We will try to contact the review

authors if any data is missing or lacking. When it is difficult to obtain any data, then the study will be reported as an "included review" without data.

Quality and strength of Study Evidence

We will evaluate the evidence quality and strength of the included studies by measuring the risk of bias, rank the quality of the studies, and rank the power of the evidence. Risk of bias will be assessed by means of intrument of The Navigation Guide Systematic Review Methodology [27], [28]. According to the methodology, the risk of bias potentially assigned from, inter alia, recruitment strategy, blinding, exposure assessment, confounding, incomplete outcome data, selective reporting, funding source and conflict of interest. Refer to the instrument, We will classify the risk of bias into "low risk," "probably low risk," "probably high risk," "high risk," or "not applicable". Evidence quality will be assessed with some indicators start from moderate which will be downgrade or upgrade to high and low quality in conformity with some factors. The quality of evidence will be assessed with taking into consideration some factors, include the direction of effect estimates, confidence in effect estimates, other compelling attributes of the data that may influence certainty. It will classify into four groups, include sufficient evidence, limited evidence, inadequate evidence, and evidence of lack of toxicity [27].

Data synthesis

If possible, we will perform a meta-analysis. Meta-analysis of outcome variables will be carried out when the study are sufficiently meet the inclusion criteria and uniform (or clarity) reporting of outcome estimates. Otherwise, we will undertake a statistical analysis based on types of variables, as recommended by Grimshaw et al. [38], i.e., dichotomous or continuous data of Hg exposure and neurodevelopmental disorder outcomes. We will report risk ratios and their corresponding 95 % confidence intervals and p values regarding the dichotomous outcomes, and for continuous outcomes, mean differences will be reported [39]. We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [40] to show the overall process of studies selection.

Abbreviations

PRISMA-P, Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols; GRADE, Grading of Recommendations Assessment, Development and Evaluation; PROSPERO, International Prospective Register of Systematic Reviews

Declarations

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Not applicable.

Competing interests

"The authors declare that they have no competing interests"

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Authors' contributions

HA initiated the protocol, wrote the manuscript and reviewed it for important intellectual content. NKn and MFN conceptualized the research plan for the the proposed systematic review and wrote the manuscript. ABW and SS critically reviewed the methodology and the manuscript for important intellectual content. All authors read and approved the final manuscript.

Consent for publication

Not applicable.

Ethics approval and consent to participate

Not applicable.

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