

# **Environmental Exposures and Craniofacial Birth Defects: A Scoping Review Protocol.**

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## **Abstract**

Introduction: birth defects and congenital anomalies include a variety of pathologies that affect 2-3% of all newborns, with craniofacial birth defects (CFBD) such as neural tube defects (NTD) and orofacial clefts (OFC), being some of the most prevalent congenital anomalies in children. Since an individual may be exposed to pollutants present in the workplace, and at the same time, the population may be exposed to multiple sources of environmental contamination (for example water, soil and air) and socioeconomic deprivation, assess the possible association between environmental exposures, both at the individual and area level, it could improve the understanding of how these variables would affect pregnant women and the developing fetus. To provide an overview about updated information related to those factors and its association with NTD and OFC, we consider performing a scoping review. The aim of this publication is to present a scoping review protocol about the relationship between environmental exposures and the etiology of CFBD. Methods and analysis: the identification of the papers for this review was done through a search strategy using MeSH vocabulary, in the electronic database PUBMED MEDLINE and SCIELO. Additionally, we performed a gray literature search using Google Scholar. All the selected studies for the review were subjected to methodological quality assessment, according to the Joanna Briggs Institute protocol for scoping reviews. Ethics and dissemination: a paper summarizing the findings from this review will be published in a peer-reviewed journal. Ethical approval is not required.

**Keywords:** congenital craniofacial birth defects, neural tube defects, orofacial cleft, risk factors, environmental factors, epidemiological evidence

### **Strengths and limitations of the study**

Results from this scoping review will contribute to a broader perspective of the environmental and socioeconomic factors that could influence on CFBD.

A potential limitation could be the small number of eligible articles in the literature.

As this is a scoping review, the quality of the evidence will not be assessed.

## **Introduction**

According to the World Health Organization (WHO), congenital abnormalities or birth defects (BD) are structural, functional and/or biochemical-molecular abnormalities present at birth, which can be detected or not, at that time (1). It is estimated that of all newborns, 2-3% are born with some type of BD (2), and at least, one third have anomalies in the head and face (3). Since craniofacial birth defects (CFBD) such neural tube defects (NTD) and orofacial clefts (OFC), are among the most common malformations in humans (4), the research on how factors like environmental exposures and socioeconomic characteristics may play a significant role in the etiology of these diseases is interesting, and also, could represent a key element for understand and prevent these anomalies.

In order to obtain updated information on the relationship between environmental exposures with NTD and OFC, a scoping review was conducted. The scoping study (or scoping review), aims to map the main concepts that support a certain area of knowledge, examine the extent, scope and nature of the investigation; summarize and disseminate research data, and identify existing research gaps (5).

Reporting guidelines that provide information about how a research should be conducted, and how the quality analysis assessment should be performed, is already usual, especially for clinical trials or systematical reviews. However, since scoping reviews are a relatively new research approach, there is not yet a universal study definition or definitive procedure (5–9) for conduct these studies. To provide researchers with a methodologic protocol, the Joanna Briggs Institute and collaborators, developed a guideline for scoping review protocols (10). Following these guidelines, this document presents a protocol of a scoping review on selected craniofacial birth defects and environmental exposures.

## **Research question, objectives and context**

Considering that the topic of interest on this research is environmental exposures and CFBD, the research question is: *What socioeconomic and environmental factors are related with the occurrence of specific craniofacial birth defects?* The question encompasses the two CFBD of interest for the review, this is, NTD and OFC; as well

as the environmental exposures related with these anomalies, both at the area and at the individual level.

The aims are, (1) to map the recent literature about environmental exposures, NTD and OFC; (2) to describe the environmental factors that could be influencing the occurrence of these pathologies, both, at the area level as well at the individual level, and (3), to identify the gaps in literature related to this knowledge field.

### **Inclusion Criteria**

Were included studies about NTD and/or OFC and environmental exposures, publications in English, Spanish or Portuguese language; epidemiological studies, including meta-analyses, case-control studies, prospective and retrospective cohorts, and papers published between 2014 and 2019.

### **Exclusion Criteria**

Studies that did not specifically include NTD and/or OFC in their analysis, were excluded, as well as in vitro and animal studies, or syndromic presentations of OFC. In addition, papers published in languages other than English, Spanish or Portuguese, as well as those published before 2014, were also excluded. For the purposes of this review, studies that evaluated or described the teratogenic effect of drugs and/or psychoactive substances were not considered.

### **Research and study selection**

This scoping review followed the five steps proposed by Ashley and O'Malley: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) collecting data, (5) mapping, summarizing and describing the results (5). In order to build the search strategy, an adapted version of the PECO methodology was adopted (P: patient, E: exposure, C: comparison, O: outcomes), turning it into EO, in which "E" means the phenomenon of interest (exposure to environmental pollutants and socioeconomic factors), and "O", the outcomes associated with the studied phenomenon (birth defects). Following the adapted PECO methodology mentioned above, the descriptors and their combinations used to build the search strategies were:

*For area level environmental exposure:* [(‘residence’ OR ‘municipality’ OR ‘mines’ OR ‘industry’ OR ‘facilities’ OR ‘estates’ OR ‘landfill’ OR ‘incinerator’ OR ‘waste’ OR ‘natural gas’ OR ‘shale gas’ OR ‘chemical’ OR ‘harbor’ OR ‘asbestos’ OR ‘pesticides’ OR ‘agrochemical’ OR ‘power plant’ OR ‘air pollution’ OR ‘air pollutants’ OR ‘particulate matter’ OR ‘gases’ OR ‘urban pollution’) AND (‘congenital abnormalities’ OR ‘neural tube defects’ OR ‘cleft lip’ OR ‘cleft palate’ OR ‘birth defects’ OR ‘congenital anomalies’ OR ‘congenital malformations’)]

*For individual level environmental exposure:* [(‘occupational diseases’ OR ‘occupations’ OR ‘job’ OR ‘workplace’ OR ‘work place’ OR ‘work location’ OR ‘worksite’ OR ‘work site’ OR ‘jobsite’ OR ‘job site’ OR ‘socioeconomic factors’ OR ‘health status disparities’ OR ‘standard of living’ OR ‘living standard’ OR ‘inequality’ OR ‘inequalities’ OR ‘diabetes mellitus’ OR ‘diabetes’ OR ‘hyperglycemia’ OR ‘obesity’ OR ‘overweight’ OR ‘metabolic diseases’ OR ‘communicable diseases’ or ‘infectious disease’) AND (‘congenital abnormalities’ OR ‘neural tube defects’ OR ‘cleft lip’ OR ‘cleft palate’ OR ‘birth defects’ OR ‘congenital anomalies’ OR ‘congenital malformations’)]

The identification and selection of publications potentially eligible for the study, was permed according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) methodology (11). Titles and abstracts were read and analyzed for all the team members, and the selected studies were fully read by two independent reviewers (MAM, JVL), when relevant, data was extracted. For screening and data extraction, a reference management software was used.

### **Extracting and charting results**

The data extraction was performed in Excel files. Data about the author, year of publication, journal, exposure assessment, NTD and OFC association, objectives, methodology (design, population/sample, duration, outcome and confounding variables) and main results were collected.

For the review of selected articles, the environmental exposure was divided into two broad categories:

- 1) Environmental exposure at the area level, and
- 2) Exposure at the individual level.

According to the SENTIERI methodology (12), the environmental sources of exposure at the area level, were subdivided into four groups:

- Industries (refineries, petrochemicals and metals)
- Sanitary landfills,
- Incinerators and
- Environmental pollutants (fine particles in the air, noise, etc.) (not included in the SENTIERI methodology)

The individual exposures considered were:

- Socioeconomic status (SES)
- Professional / occupational exposure and
- Health conditions (infectious and metabolic)

For the purposes of this review, the health conditions included were limited only to those that have already been shown to be teratogenic in the craniofacial region within this category (except for arterial hypertension), according to Mazzu *et al.* (2017) (13).

## **Synthesis and reporting of results**

The general characteristics of included studies was summarized. According to the SENTIERI methodology (12), the data of the selected studies was organized as environmental exposure at the area and individual level, and gaps in the epidemiological assessment for craniofacial birth defects studies were commented. A paper summarizing the findings from this review will be published in a peer-reviewed journal. The PRISMA extension for Scoping Reviews (PRISMA-ScR) (14) was used to report this review.

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### **Authors' contributions**

All authors contributed to conceptualizing and designing the study. MAM drafted the protocol, whereas JVM and SAA made major revisions. All authors read and approved the final version of the protocol. The same process was used to write the final manuscript.

### **Competing interests**

None.

### **Ethics approval**

Not required.

### **Conclusion and implications for research and practice**

This research attempted to synthesize the most recent epidemiological evidence on environmental exposures and their possible correlation with the occurrence of specific CFBD, such as NTD and OFC. It is expected that the results of this scoping review can help managers, professionals, and researchers in the public health area to understand better the environmental etiology of this pathologies and prevent its occurrence in the population.

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Associations Between Disinfection By-Product Exposures and Craniofacial Birth Defects. October 2017. Journal of Occupational and Environmental Medicine 60(2):1. Objective: Examine associations between craniofacial birth defects (CFDs) and disinfection by-product (DBP) exposures, including the sum of four trihalomethanes (THM4) and five haloacetic acids (HAA5) (i.e., DBP9). Methods: We calculated first trimester adjusted odds ratios (aORs) for different DBPs in a matched case-control study of 366 CFD cases in Massachusetts towns with complete 1999-2004 THM and HAA data. Demonstration Project on Selected Birth Defects and Environmental Factors in New Jersey. Program 03074, Environmental and Health Effects Tracking Cooperative Agreement Number: U50/CCU223289 National Center for Environmental Health Centers for Disease Control and Prevention (CDC). Through the development of birth defect selection criteria, protocol, and data analyses, the various agency representatives had input into the kinds of questions asked of the data, and the methods of analysis. Birth defects are a significant public health concern in the United States, affecting approximately 3 to 5% of all live births in the United States, 20% of all infant deaths, and a significant but unknown proportion of pregnancy terminations. They are a leading cause of infant mortality. Introduction: birth defects and congenital anomalies include a variety of pathologies that affect 2-3% of all newborns, with craniofacial birth defects (CFBD) such as neural tube defects (NTD) and orofacial clefts (OFC), being some of the most prevalent congenital anomalies in children. The aim of this publication is to present a scoping review protocol about the relationship between environmental exposures and the etiology of CFBD. Methods and analysis: the identification of the papers for this review was done through a search strategy using MeSH vocabulary, in the electronic database PUBMED MEDLINE and SCIELO. Additionally, we performed a gray literature search using Google Scholar. defects, and gastrointestinal malformations. Alcohol: three systematic reviews with metanalysis, two metanalyses, one multicentre study, and four single studies were collected for the period under review. The acquired literature has provided limited epidemiological evidence for associations between alcohol consumption and CAs in the nervous system, particularly for anencephaly and spina bifida. Occupational exposure: the literature search collected one metanalysis, eight multicentre studies, and five single studies. The epidemiological evidence for associations between paternal occupational exposure to solvents and neural tube defects and between maternal pesticide exposure and gold-facial clefts were judged limited. Manuscript Review and Publication. Criteria for Publication. Editorial and Peer Review Process. Our work is the first to show that ECIG use could pose a potential hazard to the developing embryo and cause craniofacial birth defects. This emphasizes the need for more testing and regulation of this new popular product. Embryos exposed to e-cigAM A-D exhibited only subtle orofacial defects, and largely resembled untreated controls and embryos treated with the Lab grade e-cigAMs (Fig 3A-3E). On the other hand, e-cigAMs E and F resulted in a much more distinct craniofacial phenotype, in which the lenses were protruding and the face appeared narrower, particularly the midface (Fig 3F and 3G).