

# Associated complications

## on neurodevelopmental effects in premature to term infants: systematic review

*Complicaciones asociadas a los efectos del neurodesarrollo en bebés prematuros a término: revisión sistemática*

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### Abstract

Complications of prematurity are the main causes of suffering some type of disability until death, this presents with a high health risk at the neurological level in the long term. **Objective:** To analyze the impact on the associated complications on neurodevelopment in preterm infants until reaching the equivalent of term. **Methodology:** As for the process, it will be carried out following the recommendations established in the PRISMA declaration, it will also work with Scopus, Pubmed and Web of Science databases, the period of the publications will be from 2016 to 2021, obtaining 13 articles for their respective analysis. **Results:** In short, this methodology will allow us to obtain an idea about the impact in relation to complications in prematurity at the neurodevelopmental level, however, the challenge of this article is to obtain recent findings related to neurological changes associated with prematurity and its impact on possible disabilities. **Conclusion:** This is an area that deserves a stronger research approach to identify the modifiable factors that shape the development of these very vulnerable preterm infants.

**Keywords:** Prematurity, neurodevelopment, neurological, disability.

### Resumen

Las complicaciones de la prematuridad son las principales causas de sufrir algún tipo de discapacidad hasta la muerte, esto presenta un alto riesgo sanitario a nivel neurológico a largo plazo. **Objetivo:** Analizar el impacto sobre las complicaciones asociadas en el neurodesarrollo de los niños prematuros hasta alcanzar el equivalente a término. **Metodología:** En cuanto al proceso, se llevará a cabo siguiendo las recomendaciones establecidas en la declaración PRISMA, además se trabajará con las bases de datos Scopus, Pubmed y Web of Science, el periodo de las publicaciones será de 2016 a 2021, obteniendo 13 artículos para su respectivo análisis. **Resultados:** En definitiva, esta metodología nos permitirá obtener una idea sobre el impacto en relación con las complicaciones en la prematuridad a nivel del neurodesarrollo, sin embargo, el reto de este artículo es obtener hallazgos recientes relacionados con los cambios neurológicos asociados a la prematuridad y su impacto en posibles discapacidades. **Conclusión:** Esta es un área que merece un mayor enfoque de investigación para identificar los factores modificables que conforman el desarrollo de estos prematuros tan vulnerables.

**Palabras clave:** Prematuridad, neurodesarrollo, neurológico, discapacidad.



## Introduction

According to the study by Pelayo et al.<sup>1</sup> intervention programs for premature infants are frequent in our environment, the health professionals in charge of the follow-up of these children should be aware of their vulnerability, the problems they present, their early approach, coordinating and supporting the families of premature infants. For Cheong et al.,<sup>2</sup> for many years, preterm infants have been managed as if they were term newborns, placing a heavy burden on interventions and health care, leading to limited knowledge of their medium- and long-term outcome.

On the other hand, Mohammadi et al.<sup>3</sup> according to his study shows that every year 2.5 million premature infants die, of which the vast majority occur in low- and middle-income countries, representing 47% of deaths, coexisting a higher risk of neonatal mortality, suffering health problems. The kangaroo mother plan is a complementary method for stable low birth weight and premature newborns, contributing to improve the quality of care, and is one of the recommendations of the World Health Organization (WHO) for the care of newborns. Evidence-based studies have demonstrated the efficacy of the PMC (Mother Kangaroo Program) in reducing neonatal mortality and morbidity, improving maternal-infant attachment and increasing exclusive breastfeeding.

Undoubtedly, for Favrais et al.<sup>4</sup> determines that, in the findings and longitudinal follow-up of preterm infants, help to a better understanding of the circumstances associated with neurological impairment that favors recent findings such as alterations referred to motor or sensory functions, as well as emotional, behavioral and cognitive skills, their neonatal morbidity that is related to a higher rate of hospital reindications and brain immaturity that may be the main cause of the deficits observed in the long-term neurodevelopment of this population.

On the other hand, for Belfort et al.<sup>5-8</sup> the contradictory effects adjacent to neutrality suggest a probable moderate neurodevelopmental delay with difficulties in each of the domains of cognition, such as executive function, language, learning and memory, complex attention, perceptual-motor function and social cognition, compared to children born at term, although the deficits are not always severe and may even be mildly delayed. Also the investigation of Lea et al.<sup>9-11</sup> improvements in survival patterns have not yet been accompanied by clear evidence of reduced rates of neurodevelopmental disabilities, however, longitudinal studies with follow-up into adulthood are needed to determine the impact in relation to contemporary care and to identify whether ongoing improvements in neonatal medicine have translated into improved outcomes across the lifespan, this analysis manifests the outcomes of this population as a function of multiple perinatal factors. Therefore, the current challenge is to develop efficient screening skills to establish which infants require specific follow-up that results in consequences ranging from difficulties in school to the inability to lead an independent adult life.

After making this absolute introduction, the main objective is to examine in the scientific literature about the complications

associated with the effects on neurodevelopment in premature babies up to term age, in relation to the main objective proposed we have our specific objectives to identify the medium-term complications related to neurodevelopmental effects in premature babies, however, we attach that should be verified in the scientific literature on the effects on cognitive neurodevelopment in premature infants.

## Methodology

### Type of research

A systematic literature review documentary study will be carried out. The process will be carried out following the recommendations established in the PRISMA statement<sup>12</sup>.

### Search strategies

The research was conducted as of November 26, 2021. The following databases were used as search tools for the research: Scopus, PubMed, and Web of Science. The following keywords taken from the DeCs thesaurus were used: prematurity, neurodevelopment, neurological, disability. We also worked with the combination of keywords and Boolean operators AND and OR.

For the data collection process, an information organization matrix was prepared, and a document outline was drawn up to analyze the consistency and correspondence of each of the articles according to their relevance.

### Inclusion criterion

The following are considered

Type of languages: Spanish and English.

Publication period: 2016 to 2021

Original research, systematization, or review article.

Quality of the articles

### Exclusion criteria

Gray literature and studies related to undergraduate work.

Articles not available in full text

That they are not published within the established period

### Evaluation of the quality of the study

The guidelines of the Consolidated Standards for Reporting Trials (CONSORT-2010)<sup>13</sup> were used to assess the quality of the studies. This checklist is used worldwide to improve reported randomized controlled clinical trials using a list of 25 items to assess title (including design type), abstract (structured and complete), background and explanation of rationale, definition of objectives and hypotheses, description of trial design (including major changes in methods after trial

initiation and reasons), eligibility criteria of participants, setting and location where data were collected, description of intervention (with sufficient detail to allow replication), outcome measures (with sufficient detail to allow replication), description of intervention (with sufficient detail to allow replication), outcome measures (with sufficient detail to allow replication), and description of intervention (with sufficient detail to allow replication), the eligibility criteria for participants, the setting and location where data were collected, description of the intervention (with sufficient detail to allow for replication), fully defined outcome measures, sample size calculation (or power analysis), the method used to generate the sample data. The method used to generate the randomization sequence (including type of randomization), use of blinding methods, statistical procedures used for analyses, description of results (including comparison at baseline), discussion of results (including limitations and generalization), and other information (registry, protocol, and funding).

### Processing

In the first stage, the topic and the formulation of the research question were identified through the PO population and observation scale strategy. Having as a question What are the associated complications of neurodevelopmental effects in premature infants up to term age, in the second stage, we proceeded to apply the inclusion criteria in which the articles in English and Spanish language from the years of publication 2016 to 2021 were included. Primary studies, qualitative, quantitative, systematic reviews and research reports. Applying the exclusion criterion to articles other than English and Spanish, publications less than 2017, studies with unexplained methodologies and articles repeated from a previous search. In the third stage, the relevant articles

were selected through a previous analysis of their content. In the fourth stage, the studies were classified in a matrix in which the most important characteristics and results of each of them were recorded. Finally, each result was analyzed by comparing similarities, complementarities and discrepancies between authors of the different publications.

### Results

Once the necessary information on the complications associated with the effects on neurodevelopment in premature infants up to term age had been researched, 79 publications were identified, of which 26 were from the Pubmed, 33 from Web of Science and 20 from Scopus databases. Subsequently, articles that did not address the topic were excluded, leaving a total of 66.

Then, the articles that did not correspond to the study were excluded by reading the abstracts, obtaining 54 publications. Subsequently, when applying the eligibility criteria for complete reading, 41 documents were found. Upon analysis, 21 were excluded, of which 3 were literature reviews, 8 were duplicates and 10 had another objective. After that, the complete studies evaluated for eligibility were 20, excluding 5 studies, to obtain a total of 13 articles for the final sample of the corresponding analysis.

The results are presented according to the inclusion and exclusion criteria established in the methodology, in accordance with the phases of the PRISMA procedure, which are summarized in

Figure 1. Flow chart of article search.

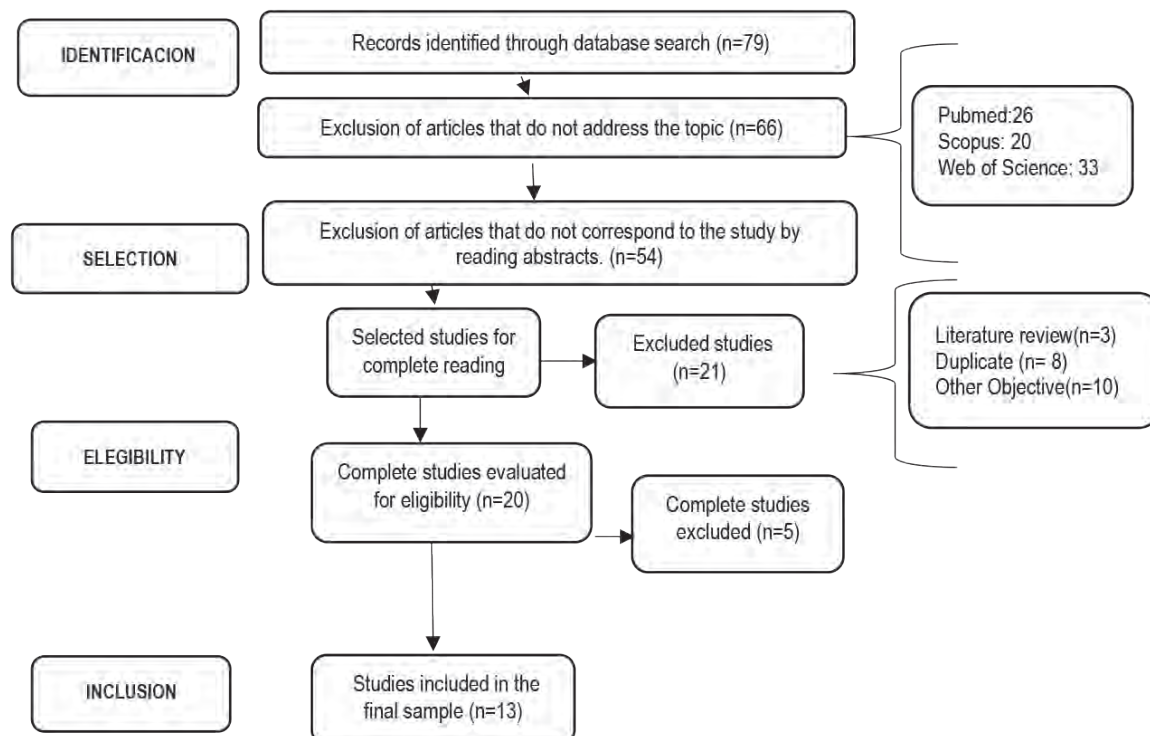


Table 1. Selected articles

	Base	Magazine	Author	Year	Title	Country	medium-term complications	Effects/ neurodevelopment
1	PubMed	Journal Article	Pelayo et al <sup>(1)</sup>	2016	Neurodevelopmental Effects of an Intervention Program in Premature Infants	Mexico	Alterations in muscle tone, absence of righting reactions, balance and lack of orientation response to sensory stimuli, may induce alterations at the cognitive, anatomical and functional levels.	Intervention program, focused on the effects on the stability of bioelectrical activity in the infant's brain.
2	Scopus	Springer- Verlag GmbH	Cheong et al <sup>(2)</sup>	2019	Early environment and long-term outcomes of preterm infants.	Germany	Premature birth has the potential to disrupt the maturation processes of the gray and white matter lesion pattern.	Developmental disruptions can cause global and catastrophic anomalies
3	Scopus	International Breastfeeding Journal	Mohammadi et al <sup>(3)</sup>	2021	Implementation and effectiveness of continuous care of the kangaroo mother: a participatory action research	United Kingdom	Premature infants have an increased risk of neonatal mortality, suffering from long-term health problems, as well as lifelong physical and mental disabilities.	Improves neonatal development and reduces the risk of growth retardation in the first 24 months.
4	Pub Med	Elsevier Masson SAS	Favrais et al <sup>(4)</sup>	2019	Neurodevelopmental outcome of late preterm infants: literature review	France	Describes neurodevelopmental disturbances (emotional, behavioral and cognitive) in children before 32 weeks of age	Shows delayed brain size and maturation compared to full-term infants. Delayed cortical folding
5	PubMed	Elsevier Masson SAS	Belfort et al <sup>(5)</sup>	2016	Neurodevelopmental outcomes and nutritional strategies in very young infants low birth weight	United States	Processes may be more or less vulnerable as certain aspects of brain development may be permanently altered by limited exposure during a critical period.	Low weight gain remains a particular cause of morbidity, which explains the link between neurodevelopmental impairment and nutrition.
6	PubMed	Rev Cubana Salud Pública	Luna et al <sup>(6)</sup>	2018	Nutritional Status and Neurodevelopment in Early Childhood	Bogota- Colombia	The approach to child neurodevelopment is to achieve a better classification of diseases, more accurate diagnoses, effective and preventive treatment and, in general, to choose to provide better guarantees for development.	The acquisition of neurological functions such as attention, memory, language, motor skills, among others, takes place.
7	PubMed	Elsevier Inc.	Novak et al <sup>(7)</sup>	2018	Perinatal brain injury Mechanisms, prevention and outcomes	United States	Improving care, preventive strategies aimed at reducing risk and severity have resulted in a greater number of affected preterm infants.	Brain injury can lead to significant neurodevelopmental impairment
8	Scopus	Arch Dis Child	Johnson et al <sup>(10)</sup>	2017	Early and long-term outcome of infants born extremely preterm.	United Kingdom	Significant range of basic cognitive processes including memory, speed of processing, among others.	Changes in the prevalence of developmental impairment over time are more difficult to assess.
9	Scopus	Arch Dis Child Fetal Neonatal	Lea et al <sup>(9)</sup>	2016	Protecting the Premature Brain: Current Strategies Based on in evidence to minimize perinatal brain injury in infants premature	United Kingdom	Normal brain growth and neurological development is an important consequence resulting in physical and cognitive impairment.	The number of children with neurodisabilities is increasing.
10	PubMed	Journal of Neurodevelopmental Disorders	Rogers et al <sup>(11)</sup>	2018	Structural and functional connectivity aberrant and neurodevelopment in premature infants	United States	In premature birth, neurological disability is still a problem.	Prematurity-associated changes in structural and functional brain connectivity
11	Scopus	Elsevier Inc.	Da Fonseca et al <sup>(12)</sup>	2020	Prevention of preterm births	Brasil	Symptomatic treatment of pregnancies that occur during preterm labor with corticosteroids and antibiotics does not reduce the incidence of preterm labor.	Prophylactic administration of progesterone should be offered for the prevention of preterm delivery.
12	PubMed	Springer Nature	Pineda et al <sup>(13)</sup> timing and frequency of sensory-based interventions that optimize outcomes can inform environmental modifications. The objective of this study was to conduct an integrative review on sensory-based interventions used with very preterm infants in the NICU to improve infant and parent outcomes. Study design: The data sources include MEDLINE, CINAHL, Cochrane Library and Google Scholar. Studies were identified that used sensory-based interventions in the NICU with preterm infants born <32 weeks gestation, were published in a peer-reviewed journal between 1996 and 2015, and measured outcomes related to infant and parent outcomes. Studies were extracted from electronic databases and hand-searched from identified reference lists. Results: Eighty-eight articles were identified (31 tactile, 12 auditory, 3 visual, 2 kinesthetic, 2 gustatory/olfactory and 37 multimodal)	2016	Improving sensory experiences for very premature babies in the NICU: an integrative review	United States	High incidence of morbidity, which does not explain the clinical course or the presence of brain lesions and influences the neural development of infants	Experiences alterations in sensory experiences
13	PunMed	American Journal of Epidemiology	Louise et al <sup>(14)</sup>	2017	Risk Factor Models for Neurodevelopmental Outcomes in Children Born very premature or with very low birth weight: a systematic review of the methodology and reports	Oxford, United Kingdom	Early identification of factors is necessary to guide clinical management to provide information and aid neurodevelopment in premature infants.	Generalized effect leading to a range of conditions including impairment of motor and cognitive functions



Thirteen empirical articles with scientific evidence on complications associated with neurodevelopment in premature to term infants were selected. The following is a description of the confirmations or adjustments:

We could summarize below that for Pelayo et al, motor activity is a process that precedes functions such as language, perception, attention among others, so it is important to identify early on the mechanisms for proper development, with this work we can identify abnormal motor reaction, thanks to the (Vojta system) being this a scale that helps determine the central nervous system level an important influence of postural control. In this way the effect of this intervention is estimated both in the medium and long term, considering a possible indicator of stability, although it remains to be discussed if the electroencephalographic pattern changes results, it is possible to consider then that the motor action is formed of stereotype that organizes functional systems that lead to the mediation of psychological processes that depend on such actions.

In effect the Cheong et al criteria, developmental care was originally a framework designed to support infant development in the NICU, the challenge is to examine the evidence for early neurodevelopmental intervention, consequently, not all interventions had the same effect on developmental outcomes, from a meta-analysis of 25 trials, the evidence supports better cognitive outcomes, Thus all preterm infants have the potential to benefit from developmental interventions, however, it is important to target interventions to the needs of the individual infant, it has been verified in a randomized controlled trial of an early developmental intervention program for infants born at <30 weeks gestation, greater cognitive benefits were observed in infants from higher social risk families who received intervention than in those at lower social risk. Similarly, infants diagnosed with neurodevelopmental impairment, such as cerebral palsy, are more likely to benefit from specific cerebral palsy. In any case, it is suggested that early environmental exposures may affect long-term development in premature infants.

It can be noted with the recommendations of Mohammadi et al, that a newborn should receive the highest quality care, certain studies have shown that the NICU area faces a number of care challenges ranging from nursing care to family-centered care involving parents in the care of preterm newborns considering that the kangaroo method is part of family-centered care for sick infants. The kangaroo method is a relevant component for neonatal development due to its multiple benefits, reducing crying, improving physiological conditions, stabilizing the cardiac and vascular status of the newborn, and even improving neonatal development and reducing the risk of growth retardation in the first 24 months. Its benefits can be observed even in adolescence and adulthood, the longer the duration of care, the greater the benefits obtained.

It should be noted that for Fravrais et al, neurodevelopmental outcomes have generated much controversy, namely that preterm infants experience brain immaturity, with emerging

data showing that each week up to 39 weeks of gestation contributed to a reduction in neonatal morbidities and improvement in neurodevelopment. In any case, for<sup>15</sup> birth term may be a crucial factor in predicting neurological outcome to a greater extent than maturational subgroups, lacking rigorous and homogeneous methodology with respect to birth term, judgment criteria and assessment tools makes the findings inconclusive. However, contradictory or nearly neutral findings suggest a moderate risk of neurodevelopment in preterm infants, i.e., preterm infants account for nearly 70% of preterm deliveries. This new influx of patients may represent a sudden burden on follow-up networks and could potentially be detrimental to patients with identified neurological impairment.

Therefore, systematic long-term follow-up of premature infants is unrealistic. As written by<sup>16</sup> screening may be a safe strategy to detect infants at risk for neurological deterioration. Selection criteria may be based on perinatal factors, the neonatal period or validated neurological examinations at term equivalent age. In general, neurodevelopmental impacts currently remain elusive. The low methodological quality of epidemiological studies and the heterogeneity of the neonatal course interfere with insightful determinations of neurological prognoses. In other words, the current challenge is to determine effective screening strategies to select those requiring neurological follow-up.

Fundamentally, in their study by Belfort et al, called neurodevelopmental outcomes and nutritional strategies in very low birth weight infants, it should be noted that the preterm brain is very sensitive to the nutritional environment. It can be noted that nutritional care strategies are critical to improving neurodevelopmental outcomes in VLBW infants. Providing a nutrient-rich diet during NICU hospitalization is effective in improving early growth and long-term neurodevelopmental outcomes.

The period of time after discharge from the NICU provides an opportunity to make up for deficits that accumulated during the stay and continuing to provide a nutrient-enriched diet during this time may be beneficial. More work is needed to elucidate the composition of preterm formula and breast milk fortifier that supports optimal growth and brain development. More research is also needed to determine optimal feeding strategies after discharge.

According to Johnson et al, neonatal survival is continuously evolving, particularly at extremely low gestational ages. Survival at lower gestational ages (23-24 weeks) varies in population-based reports, mainly because different countries and hospitals take contrasting positions on the provision of active care, determining, the improvement in survival rates of PD deliveries in recent decades has not yet been accompanied by clear evidence of a reduction in neurodevelopmental disability rates.

A high prevalence of intellectual disabilities, behavioral, social and emotional problems, and learning difficulties continues to dominate the literature related to childhood outcomes, and recent reports have confirmed that these difficulties persist into adulthood. Neuropsychological deficits appear to mediate

the relationship between birth PD and long-term outcomes and may represent potential targets for intervention, although evidence for the long-term efficacy of early intervention efforts remains limited. Longitudinal studies with follow-up into adulthood are needed to determine the impact of PD delivery relative to contemporary care and to identify whether ongoing improvements in neonatal medicine have translated into improved outcomes across the lifespan. Although a substantial proportion of PD survivors are likely to need intervention to facilitate their performance in school and to support<sup>17</sup>.

Indeed for Rogers et al, there is no doubt that advances in prenatal and neonatal care, preterm birth remains one of the leading causes of neurological disabilities in children. Infants born prematurely, particularly those born at the earliest gestational ages, commonly demonstrate higher rates of impairment in multiple neurodevelopmental domains. More than 50% of children diagnosed with cerebral palsy are born preterm, with the greatest likelihood among those born at the earliest gestational ages. An even higher proportion of preterm infants experience other, more subtle fine and gross motor problems, with approximately 40% showing mild to moderate motor problems. Similarly, 15-20% of intellectual disabilities and 10-15% of other learning disabilities are attributable to preterm birth.

Regarding this topic of study, in their statement Fonseca et al. give, each year, about one million babies die prematurely and many survivors are disabled. Worldwide, 15 million babies are born preterm, with two decades of increasing rates in almost all countries with reliable data and with a global preterm birth rate of 11%.

Survival and neurological prognosis improve with advancing gestational age. Infants born at 25 weeks have a 40% risk of death before hospital discharge, and about 45% of survivors are expected to have moderate to severe disability, whereas those born at 32 weeks have a 98% chance of survival, only 4% risk of cerebral palsy by age 2 years, and 8% risk of neurodevelopmental delay. Thus, the economic burden of prematurity is related not only to the initial neonatal intensive care unit, but also to the increased long-term use of specialized medical, social, and educational services, as well as to the loss of economic productivity.

In closing, we discuss certain risk factors for neurodevelopmental outcomes in children born very preterm. From the perspective of Linsel et al, early identification of factors that mediate long-term outcomes is necessary to guide clinical management of children born preterm, provide information to parents, and help develop, target, and evaluate interventions.

## Conclusión

This systematic review of 13 published articles reporting on interventions, outcome, effects, and multivariable risk factor models for neurodevelopmental outcomes in preterm infants has revealed some shortcomings in methodology and reporting that could be improved in future studies and has confirmed that there is a paucity of well-designed material and well-conducted prognostic model studies in this field.

It would be feasible to model long-term outcomes in such a heterogeneous population being a challenge, often with the existence of multiple impairments within the same individual and with multiple risk factors acting sequentially over time.

In the published reviews of risk factors for cognitive and motor impairment and behavioral problems that were based on these studies, the evidence for most of the risk factors was mixed or nuclear. This may be due to the difficulty of modeling prognosis in this population but may also be due to differences in study design, study population, methodological quality, and lack of standardization of measures. The findings and recommendations of this critical review should be used as a basis for the design and analysis of future studies seeking to develop multivariate risk factors or prognostic models in this population. It is important to have more research related to the comorbidity of patients from the nursing staff's point of view, in order to have more scientific data that will allow further conclusive analysis of studies similar to the current one. It is necessary to develop empirical research in comorbidity, based on evidence from the Ecuadorian health system, with the intention of becoming a reference in scientific databases.}

On the other hand, it would be interesting to conduct empirical studies on the fear of COVID-19 in the face of the health emergency due to the COVID-19 pandemic in both the confinement, distancing, and vaccination stage in various populations<sup>18-20</sup> related to emotional<sup>21,22</sup> and educational aspects<sup>23-31</sup>.

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