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Review article

Maternal respiratory viral infections during pregnancy and offspring's neurodevelopmental outcomes: A systematic review

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ABSTRACT

Maternal infections during pregnancy, as cytomegalovirus and zika, have been consistently associated with severe newborn neurodevelopmental conditions, mainly related to vertical transmission and congenital infection. However, little is known about the neurodevelopmental consequences of maternal respiratory viral infections, which are the most prevalent infections during pregnancy. The recent COVID-19 pandemic has increased the interest in understanding the consequences of infections in offspring's development. This systematic review explores whether maternal gestational viral respiratory infections are associated with neurodevelopmental deviations in children below 10 years-old. The search was conducted in Pubmed, PsychInfo and Web of Science databases. 13 articles were revised, including information about maternal infection (Influenza, SARS-CoV-2 and unspecified respiratory infections) and offspring's neurodevelopment (global development, specific functions, temperament and behavioral/emotional aspects). Controversial results were reported regarding maternal respiratory infections during pregnancy and infants' neurodevelopment. Maternal infections seem to be associated with subtle alterations in some offspring's developmental subdomains, as early motor development, and attentional, behavioral/emotional minor problems. Further studies are needed to determine the impact of other psychosocial confounding factors.

1. Introduction

Essential processes for the formation of the human central nervous system (CNS) occur during the prenatal period. Massive neurogenesis, neuronal migration to the cortex and synaptogenesis, among others, are crucial processes for a future brain healthy function (Davis and Narayan, 2020). Due to the complexity of these events, the fetus is particularly vulnerable to the prenatal environmental conditions, mainly related with maternal health, that can modify the cellular homeostasis and produce changes on the epigenetic program of the fetus (Tobi et al., 2015; Palma-Gudiel et al., 2019). In fact, there is a long history in the scientific literature indicating that prenatal environmental risk factors might have both proximal and long-term effects on human health and disease (Newnham and Ross, 2009).

A factor that has been consistently associated with lifetime neurodevelopmental and neuropsychiatric alterations is the exposure to maternal infections in utero, including zika, rubella, herpes simplex virus, influenza and coronaviruses, among others (Zimmer et al., 2021). In that sense, epidemiologic and birth cohort studies led to the formulation of the "Viral Hypothesis of Schizophrenia", claiming that prenatal viral infections produce long-lasting brain alterations which later contribute to the etiology of this complex disorder (Torrey and Peterson, 1976), especially in children exposed during the second trimester of pregnancy (Al-Haddad et al., 2019). Although it is difficult to establish

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such distal associations due to the postnatal confounders that exist between pregnancy and the juvenile onset of psychotic disorders (Zimmer et al., 2021), a number of indicators of neurodevelopmental disruption (e.g.: neurointegrative defects and motor-related traits) seem to indicate preexistent alterations in children who later develop schizophrenia (Jones et al., 1994; Fish, 1977). Additionally, neurodevelopmental disorders as autism spectrum disorders (ASD) (Jiang et al., 2016) and Attention-Deficit/Hyperactivity Disorder (ADHD) (Zhu et al., 2022) have been also identified as proximal consequences of exposure to gestational maternal infections.

Previous reports in the literature indicate that the consequences on the fetus depend on the specific type of maternal infection. For instance, it has been clearly demonstrated that infections by neurotropic viruses that cross the placental barrier can cause severe consequences on brain development which may even compromise fetal viability (Gordon-Lipkin et al., 2021). In that sense, it is well known that congenital zika leads to defects in offspring's brain formation as microcephaly, developmental delays, epilepsy and sensorial impairments (Cranston et al., 2020; Melo et al., 2016). Additionally, cytomegalovirus infection has been associated with alterations on CNS formation, neurological damage and sensorineural hearing impairments (Leruez-Ville et al., 2020; Singh and Gaidhane, 2022).

Respiratory viral infections deserve especial attention since they are the most frequently reported infections during pregnancy, although they do not show a special affinity for nervous tissues and generally do not cross the placental barrier (Collier et al., 2009). In fact, those pathogens have been a source of concern for the health-care community since they have caused several and serious pandemics due to the high rate of person-to-person transmission, including the Influenza H1N1/09 pandemic in 2009 (World Health Organization, 2022a); the Middle East Respiratory Syndrome pandemic in 2012 (World Health Organization, 2019); and the current Severe Acute Respiratory Syndrome-Coronavirus-2 (SARS-CoV-2) pandemic (World Health Organization, 2022b).

There are several viral pathogens that cause respiratory viral infections, being the most common: influenza, parainfluenza, rhinovirus, adenovirus, coronavirus, metapneumovirus, bocavirus and respiratory syncytial virus (Boncristiani et al., 2009). Although prenatal exposure to maternal respiratory viruses, specially influenza, has been related to an increased risk of schizophrenia, (Brown et al., 2004), ASD (Atladóttir et al., 2010) and ADHD (Silva et al., 2014), little is known about the impact of these infections in the different domains of early childhood normative neurodevelopment before the onset of these diseases.

The biological mechanisms that underlie the abovementioned developmental alterations have not been fully identified. However, recent studies indicate that maternal immune and endocrinological responses to the infection may play a key role on this association (Knuesel et al., 2014; Vlenterie et al., 2022), both by dysregulating maternal and infant neuroendocrine and immune responses or by a direct effect of the maternal antibodies and/or proinflammatory molecules on the developing brain (Khandaker et al., 2013). One of the most supported hypotheses claims that maternal immune activation (MIA) in front of infections can directly alter the fetus brain development, but also produce epigenetic changes that make the brain more vulnerable in front of future adverse conditions (Estes and McAllister, 2016; Lins, 2021). Furthermore, structural and immunological abnormalities have been identified in placental tissues of mothers infected by respiratory viruses, suggesting a potential mechanism for fetal brain damage (Brien et al., 2021).

To the best of our knowledge, no previous systematic reviews have addressed the link between maternal respiratory infections and childhood normative developmental outcomes, although studies with other families of viruses have identified possible alterations in prenatally exposed children, including a worse cognitive, motor and emotional performance (Kwok et al., 2022; Green et al., 2018). Noticeably, since humans are born with a significant neurological immaturity at birth, childhood is an extraordinary prolonged period of life in which neurodevelopment continues and different developmental milestones are achieved (Hasset, 2022). Due to its complexity, this distinguished and unique period of life is often divided in infancy (birth to 1 year), early childhood (1–5 years), middle childhood (5–11 years) and adolescence (11–21 years) (American Academy of Pediatrics, 2022). An overview of normative neurodevelopment across childhood can be observed in Fig. 1. For that reason, the putative neurodevelopmental consequences of prenatal adverse environments could be observed early across the stages of childhood and could be recognized when the expected progresses on cognitive, linguistic, motor and social-emotional domains are not achieved (Sameroff, 2009).

The early identification of subtle developmental alterations may provide a framework for studying the impact of prenatal exposure to infections on neurodevelopment, identifying the underlying biological mechanisms and designing epidemiological preventive strategies to avoid future severe disorders in affected children. Considering the current Coronavirus Disease (COVID-19) pandemic, it is of vital importance to identify possible early unspecific neurodevelopmental signs in children born to infected mothers and the need of further monitoring.

Therefore, the aim of this systematic review is to examine the existing literature linking maternal viral respiratory infections during pregnancy and possible consequences on the development of the offspring during early and middle childhood. We hypothesize that the exposure to maternal viral respiratory pathogens during pregnancy will be associated with greater difficulties in different neurodevelopmental domains.

2. Materials and methods

2.1. Eligibility criteria

The present review was elaborated in accordance to 2020 PRISMA guidelines for reporting systematic reviews and meta-analysis (Page et al., 2020).

For studies selection, the following inclusion criteria were considered: 1) human studies; 2) articles containing information about maternal viral respiratory infections during pregnancy (influenza, parainfluenza, rhinovirus, adenovirus, coronavirus, metapneumovirus, bocavirus and respiratory syncytial virus), defined by self-reported symptoms, medical diagnosis or biological confirmation; 3) articles containing standardized and validated evaluations of offspring's neurodevelopment before 10 years old; 4) articles employing instruments addressed to evaluate normative milestones achieved through neurodevelopment on different subdomains (global development, specific neuropsychological functions, temperament, and social-emotional); and 5) studies which explore the relationship between maternal viral respiratory infections during pregnancy and offspring's neurodevelopmental outcomes in mother-infant dyads. Only scientific articles were selected, while abstracts, congresses publications, book chapters and letters to editors were not included. Additionally, studies evaluating the impact of bacterial or non-respiratory viral infections were rejected. Articles written in languages different from English and Spanish were also excluded. Noticeably, since the aim of this review is to explore subtle deviations on early neurodevelopmental profiles in infants born to infected mothers, articles which exclusively included information about clinical diagnoses of neurodevelopmental or psychiatric disorders were excluded. For that reason, articles including only diagnosis from the "Diagnostic and Statistical Manual of Mental Disorders" (DSM) or the "International Statistical Classification of Diseases and Related Health Problems" (ICD), but not evaluations of developmental milestones, were not included. There were no limitations with regard to publication time. For further information regarding eligibility criteria, see Appendix A, section 1.3.

Subsequently, to synthesize the main findings of the reviewed articles, the following developmental dimensions were considered: general

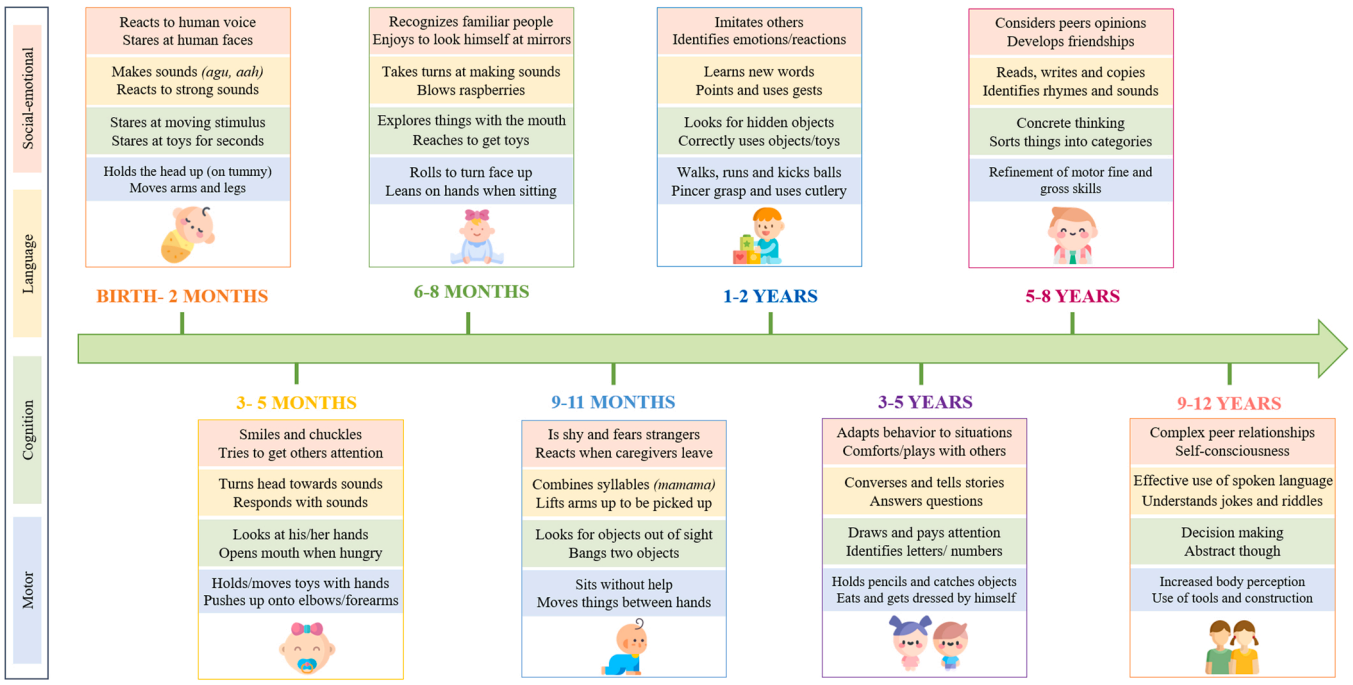

Fig. 1. Normative neurodevelopmental profiles across infancy, early and middle childhood. Representation of the normative neurodevelopmental milestones that children achieve through the different stages of childhood, including the progresses on the global developmental domains: motor, cognitive, language and social-emotional development.

neurodevelopment, specific functions, temperament and behavioral and emotional development.

2.2. Information sources and search strategy

The systematic research was conducted on 24th of November 2022 in Pubmed, PsycInfo and Web of Science Core Collection databases by two independent authors (N.SM-G and A.C-Q). The following terms were used: ("Respiratory virus" OR (influenza OR flu) OR "respiratory syncytial virus" OR parainfluenza OR metapneumovirus OR rhinovirus OR coronavirus OR adenovirus OR bocavirus OR cold) AND (prenatal OR antenatal OR pregnan* OR matern*) AND ((newborn OR child* OR infant OR offspring OR prescholar OR baby) AND (neurodevelopment* OR development* OR cogniti* OR emoti* OR behavior* OR motor OR social OR psychologic* OR temperament*)). No additional filters or limits were applied. See Appendix B for full information about the literature search strategy.

In addition to the systematic search in databases, the following sources were consulted: 1) references of the identified articles; 2) scientific journals; 3) doctoral theses repositories; 4) systematic and non-systematic reviews analyzing similar topics.

2.3. Selection process

The studies identified in the different databases were listed considering information relative to title, authors and year of publication. EndNote X9 citation manager was employed to identify and eliminate duplicated studies. For the eligibility process, two reviewers (N.SM-G and A.C-Q) independently screened for title, abstract and full text of the identified articles. In case of disagreement, a third author (L.M.F) helped to reach consensus.

2.4. Data collection process

Data was collected from the selected studies by N.SM-G and afterwards revised by A.C-Q. Extracted data refers to first author, year of publication, country in which study was conducted, design of the study, sample size, maternal information (mean age, type of respiratory virus and procedures for infection detection), children information (mean age at evaluation, sex, instruments used for neuropsychological evaluation and type of report), statistical analysis, and main findings.

2.5. Risk of bias assessment

The risk of bias of all included studies was evaluated independently by N.SM-G and A.C-Q, following the "Newcastle - Ottawa Scale" (NOS) for quality assessment of cohort studies and case-control studies (Wells et al., 2009). Discrepancies were resolved by discussion between the two assessors and a third author (L.M.F) helped to reach agreement if necessary. Adaptations of NOS were made considering the methodological design of the studies, in order to better assess the quality of the information that was relevant for this review. To that aim, 7 items were considered: (1) Adequate case definition (measures of maternal infection; see section 2.6); (2) Definition of control group (false negative control); (3) Sample size; (4) Control for covariates; (5) Quality of neurodevelopmental assessments (type of report); (6) Adjustment to infant's age range; (7) Lost to follow-up sample bias. Each item was scored on a three-point scale, being 0 the lowest punctuation and 2 the highest one. For further information regarding each item's punctuation, see Table S1 of the Supplementary material. Then, an overall score was calculated for each study by summing the scores of each criterion and expressing it as a percentage, being 100% the best possible score. Articles with a final score above 70% were considered as high-quality, articles with scores between 40% and 69% were considered as mid-quality and articles with final scores above 39% were considered as low quality.

3. Results

3.1. Studies selection

The process of studies selection is represented in Fig. 2. In the first systematic search, a total of 6458 articles were identified in the selected databases. After removing duplicates and screening for title and abstract, 66 articles were selected for full-text evaluation and a total of 12

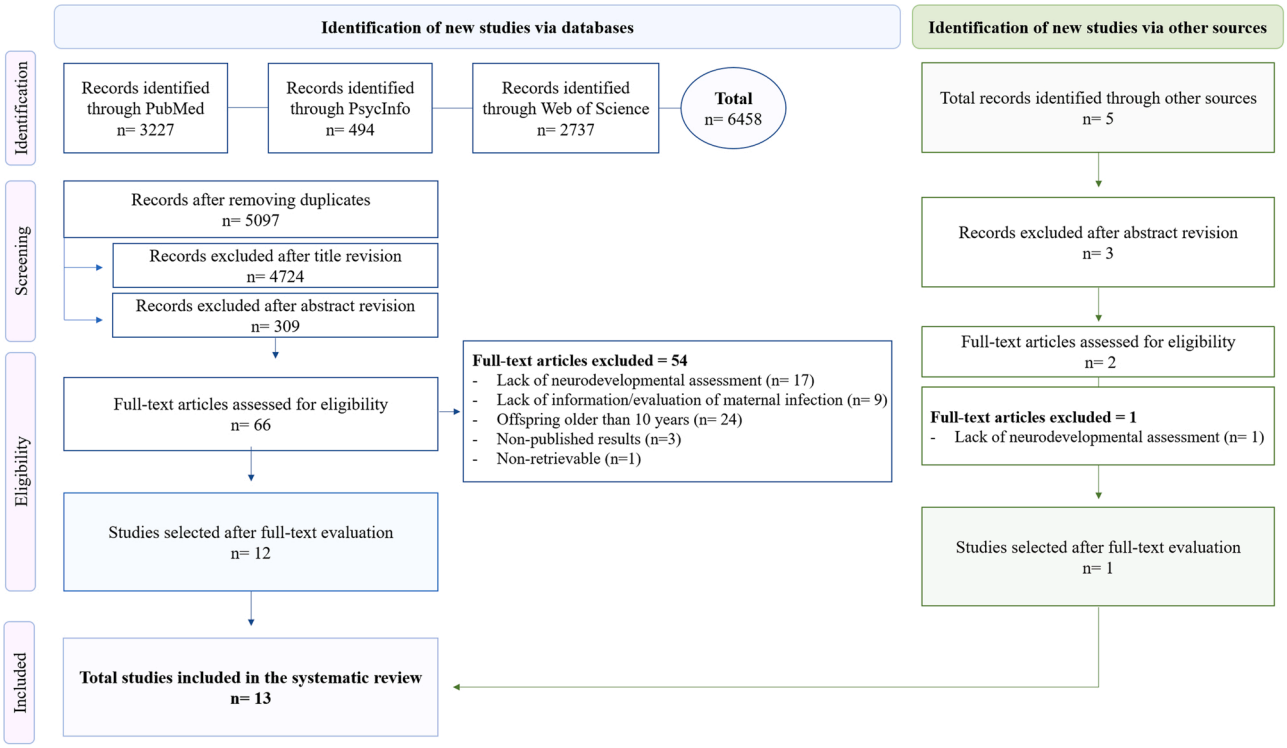

Fig. 2. PRISMA Flowchart of the selection process.

articles met the inclusion criteria. Moreover, only one out of the 5 studies identified by other sources met the inclusion criteria. Thus, a total of 13 articles were included in the systematic review.

3.2. Studies characteristics

Main information about selected articles can be found in Table 1. Regarding the type of studies, 7 out of the 13 studies were longitudinal and 6 employed a cross-sectional design.

3.3. Maternal characteristics and infection report

Maternal mean age ranged from 18 to 46 years. Only 6 studies provided information about maternal ethnicity (Azziz-Baumgartner et al., 2022; Ellman et al., 2009; Freedman et al., 2020; Mulkey et al., 2022; Parker et al., 2016; and Shuffrey et al., 2022); including mainly White (Freedman et al., 2020; Mulkey et al., 2022; Parker et al., 2016; Shuffrey et al., 2022) and Mestizo or African/American (Azziz-Baumgartner et al., 2022; Ellman et al., 2009) participants.

Selected studies employed different measures of maternal infection during pregnancy. Out of the 13 articles revised, 10 articles confirmed maternal respiratory infections employing laboratory procedures such as polymerase chain reaction (PCR), reverse transcription polymerase chain reaction (RT-PCR) and serological testing for antibodies of both SARS-CoV-2 and Influenza viruses. Nasopharyngeal samples and blood samples were obtained for that aim. Specifically, 4 studies employed PCR testing during pregnancy (Influenza: Azziz-Baumgartner et al., 2022; SARS-CoV-2: Ayed et al., 2022; Cheng et al., 2021; and Wu et al., 2021), 4 articles employed both symptom-based SARS-Cov-2 PCR and antibody assays during pregnancy (Aldrete-Cortez et al., 2022; Liu et al., 2022; Mulkey et al., 2022; and Shuffrey et al., 2022) and universal SARS-Cov-2 testing at delivery (Shuffrey et al., 2022), and 2 studies collected Influenza antibodies samples at delivery (Borren et al., 2018; and Ellman et al., 2009). Moreover, one study included C-Reactive-Protein (CRP) measures, whose levels increment during unspecific inflammatory responses (Freedman et al., 2020).

Additionally, 3 studies defined infection only by maternal retrospective self-report or hospital records of respiratory infection-related symptoms (Freedman et al., 2020; Hall et al., 2021; and Parker et al., 2016). In those cases, mothers were asked if they had experienced confirmed infections, or they were screened for the presence of infection-like symptoms during pregnancy. Moreover, clinical diagnoses were extracted from hospital medical records and information was compared to maternal reports.

Regarding the type of maternal infections, 3 studies included Influenza virus (Azziz-Baumgartner et al., 2022; Borren et al., 2018; and Ellman et al., 2009), 7 included SARS-CoV-2 (Aldrete-Cortez et al., 2022; Ayed et al., 2022; Cheng et al., 2021; Liu et al., 2022; Mulkey et al., 2022; Shuffrey et al., 2022 and Wu et al., 2021), and 3 studies included unspecified respiratory infections (Freedman et al., 2020; Hall et al., 2021; and Parker et al., 2016).

3.4. Offspring's characteristics

The number of children evaluated in selected studies ranged from 18 to 14021 participants. All studies included both male and female children. The study by Ellman and colleagues (2009) is the only one which includes children who later developed a psychotic disorder.

Regarding infant's age, it ranged from 3 months to 10 years. Five studies evaluated infants up to 7 months of age (Aldrete-Cortez et al., 2022; Borren et al., 2018; Freedman et al., 2020; Shuffrey et al., 2022; Wu et al., 2021); 2 studies evaluated infants between 8 and 12 months old (Ayed et al., 2022; Cheng et al., 2021), one study performed different evaluations until 13 months of age (Liu et al., 2022); one study performed three evaluations until 15 months of age (Mulkey et al., 2022); one study evaluated infants in two different occasions, at 1 and 2 years of age (Azziz-Baumgartner et al., 2022); one study evaluated toddlers at 3 years (Hall et al., 2021); and 2 studies evaluated children about 7 years of age (Parker et al., 2016; Ellman et al., 2009).

Table 1
Overview of the characteristics of the included studies.

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
Aldrete-Cortez et al. (2022) Mexico	Cross sectional study Pregnancy follow-up: Clinical, demographic data and confirmed diagnosis were obtained from medical records. Postpartum follow-up: Parents were asked to film their newborns' spontaneous movements at 3–5 months of age and those videos were evaluated by 2 experts. Date of data collection: 2020–2021	Initial sample: 81 Follow-up: 56	Infected 29.8 (5.6) Non-infected 29–9 (5.3)	SARS-CoV-2	- In the presence of symptoms, laboratory RT-PCR test during pregnancy was performed to confirm infection	Exposed[c]: 15.87 weeks (2.14) Non-exposed: 14.74 (1.92)	Infected 46% Non-infected 61%	MOTOR DEVELOPMENT Prechtl's method: *-Fidgety movements -Movement patterns -Age adequacy of movement repertoire -Postural patterns -Movement character -Total MOS score*	Professional report	CHI-SQUARE, T-TEST AND MANN-WHITNEY U TEST GENERALIZED LINEAR MODEL COVARIATES Not specified	"Total MOS" score was significantly lower in children born to infected mothers ($p = .002$). Among infants born to infected mothers, there is a tendency to alterations on fidgety movements ($p = .057$). In the exposed group, 11% of infants did not present fidgety movements and 11% presented abnormal fidgety movements. In the non-exposed group, 3.5% of infants showed abnormal fidgety movements. Regarding movements and postures, age-adequacy ($p = .011$), postural patterns ($p = .025$) and movement character subdomains differed between groups ($p = .037$). Specifically, atypical body symmetry item consistently differed between groups ($p = .009$).
Ayed et al. (2022) Kuwait	Cross-sectional study Pregnancy follow-up: Clinical data and confirmed diagnosis were obtained from medical records. Postpartum follow-up: Parental self-administered questionnaire completed at 10–12 months. Then,	Initial sample: 445 Follow-up: 298	31 (25–37)	SARS-CoV-2	- Laboratory confirmed PCR test during pregnancy	10.3 months (10–12.7)	56%	GLOBAL DEVELOPMENT ASQ-3: *- Gross motor (GM) - Fine motor (FM) - Problem solving (PRS) -Personal/social (PS) - Communication (CO)*	Parental report	MULTIVARIATE LOGISTIC REGRESSION ANALYSIS COVARIATES Birth weight, sex, parental education and type of feeding in the first 6 months	10% of the assessed infants presented developmental delays in some ASQ-3 subdomain, being especially common on *FM* subdomain (40%). Developmental delays were more common in children born to mothers infected in the first ($p = .039$) and second ($p = .001$)

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
	parents reviewed the scale with a researcher by telephone. Date of data collection: 2020–2021										trimesters. Developmental delays were more common in children born before 31 weeks of gestation ($p = .032$).
Azziz-Baumgartner et al. (2022) Panama & El Salvador	Longitudinal study Pregnancy follow-up: Telephonic screening of symptoms once a week. Postpartum follow-up: Telephonic screening of infant's infection once a week and administration of BSID-III at 12 and 24 months. Date of data collection: 2014–2017	Initial sample: 1567 Follow-up: 1st: 1062 2nd: 623	NA (19–28)	Influenza	-Self-reported symptoms during pregnancy - In the presence of symptoms, laboratory PCR test was performed to confirm infection	1st follow up: 12,3 months (12.1–12.11) 2nd follow-up: 24,3 months (24–24.9)	53.80%	GLOBAL DEVELOPMENT BSID-III - *Cognition* - *Language* - *Fine and gross motor* *-Social-emotional* - *Adaptative behaviour*	Professional report	MULTILEVEL MIXED EFFECTS REGRESSION MODELS COVARIATES Maternal Zika or respiratory illness; Infant Influenza vaccination; Number of household members; children and children aged < 5 years.	No association was found between maternal Influenza infection and scores on Bayley subdomains at 1 nor at 2 years. Children's influenza at any point was associated with lower BSID-III scores at 2 years ($p = .04$).
Borren et al. (2018) Norway	Longitudinal study Pregnancy follow-up: Self-administered questionnaires during pregnancy and information extracted from national registers. Postpartum follow-up: Parental self-administered questionnaire completed at 6 months. Date of data collection: 2009–2010	Initial sample: 3203 Follow-up: 609	< 19–24: 4.1% 25–34: 64.0% > 35: 29.4% Missing: 2.5%	Influenza	-Self-reported symptoms during pregnancy and laboratory confirmed antibodies test at delivery - 4 groups: seropositive with symptoms, seropositive without symptoms, seronegative with symptoms and seronegative without symptoms	7.0 months (.8)	NA	TEMPERAMENT ICQ- Fussy Baby Subscale: - *Fussy/Difficult* - *Unadaptable* - *Dull* - *Unpredictable* GLOBAL DEVELOPMENT ASQ: - *Gross motor (GM)* - *Fine motor (FM)* - *Problem solving (PRS)* *-Personal/social (PS)* - *Communication (CO)*	Parental report (both instruments)	LINEAR MULTIVARIATE MODEL COVARIATES Maternal age; Parental education; Marital status; Parity; Pregnancy length; Preeclampsia; Maternal smoking and alcohol use during pregnancy; Several maternal somatic conditions. Sensitivity analyses Gestational length; Maternal psychological distress (6 months); Native language; Child's age.	An overall association was found between maternal infection and global psychomotor development ($p = .03$). Early pregnancy exposure (GW: <0–8) is associated with lower *FM* scores ($p = .03$). Late pregnancy exposure (GW:9–40) is associated to poorer scores on *CO* subdomain ($p = .02$). No significant associations were found between prenatal influenza and temperament ($p = .10$).
Cheng et al. (2021) China	Cross-sectional study Pregnancy follow-up: Sociodemographic information, blood samples and COVID-19	Initial sample: 60 Follow-up: 18	Infected 31.8 (4.6) Non-infected 31.0 (4.9)	SARS-CoV-2	- Laboratory confirmed PCR test during pregnancy	NA (8–10 months)	38.89%	GLOBAL DEVELOPMENT ASQ-3: - *Gross motor (GM)* - *Fine motor (FM)* - *Problem solving*	Parental report	STUDENT'S T TEST, MANN-WHITNEY'S U-TEST OR CHI-SQUARE TEST COVARIATES Not specified	Neonates born to SARS-CoV-2 infected mothers showed lower scores in all ASQ-3 domains, although they did not reach significance.

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
	diagnosis were obtained upon admission. Data were extracted from medical records. Postpartum follow-up: Telephonic contact. Online parental self-administered questionnaire completed at 8–10 months. Date of data collection: 2020							*(PRS)* *-Personal/social (PS)* - *Communication (CO)*			Only differences on *FM* scores were statistically significant (p = .03).
Ellman et al. (2009) USA	Longitudinal study Pregnancy follow-up: Not specified. Maternal blood samples were collected at delivery. Postpartum follow-up: Infant's went through different evaluations until the age of 7. Psychiatric adult diagnoses (cases) were obtained in the database of the study. Date of data collection: 1959–1966	Initial sample: 444 Follow-up: 370	24.2 (~ 6.90)	Influenza	-Laboratory confirmed IgG test at birth	WISC: 7.54 years (1.46) Psychiatric adult diagnoses: 30–37 years	69.19%	SPECIFIC FUNCTIONS WISC: VIQ subscale: *-Information* *-Vocabulary* *-Comprehension* *-Digit span* PIQ subscale: *-Picture completion* *-Block design* *-Coding* FIQ Psychiatric diagnosis: DSM-IV	Professional report	ANALYSES OF COVARIANCE (ANCOVA) COVARIATES Maternal social status; Infant sex; Child's race	No significant differences between controls prenatally exposed and non-exposed to maternal influenza B were found on any of the WISC subscales (FIQ: p = .213; VIQ: p = .199; PIQ: p = .644). ANCOVA revealed a significant interaction between case status and maternal Influenza for VIQ scores (p = .01) Post-hoc analyses indicated decreased IQ scores on cases exposed to prenatal influenza B, although these differences only reached significance for VIQ scores (p = .024). With regard to WISC subtests, there was a significant interaction between case status and maternal Influenza B for the "Information" (p = .005) and "Digit Span" tests (p = .026). Post-hoc analyses indicated that exposed cases presented worse

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
											scores on "Information" subtest when compared to non-exposed cases ($p = .04$).
Freedman et al. (2020) USA	Cross-sectional study Pregnancy follow-up: Retrospective maternal self-report of illnesses at 16, 22, 28, 34 and 40 weeks of pregnancy. Postpartum follow-up: Parental self-administered questionnaire completed at 3 months. Date of data collection: NA	Initial sample: 96 Follow-up: 84	Infected 28.8 (5.9) Non-infected 31.6 (5.5)	Unspecified respiratory infection	-Retrospective self-reported symptoms -CRP and choline levels during pregnancy were obtained as indicators of immune activation (not to confirm the diagnosis)	NA (~3 months)	52.08%	TEMPERAMENT IBQ-R-SF: *-Orienting/ Regulation (Regulation)* *-Negative Affectivity (negativity)* *-Surgency/ Extraversion (Surgency)*	Parental report	MULTIVARIATE GENERAL LINEAR MODELS COVARIATES Infant Sex; Maternal age; Maternal Obesity; Maternal Depression	Infants of infected mothers with choline levels ≥ 7.5 μM had significantly higher IBQ-R scores on the regulation dimension and attention subscale compared to infants born from infected mothers with choline levels < 7.5 μM ($p < .001$). Infants born to infected mothers with choline levels ≤ 7.5 μM showed no effects of infection on regulation and attention, compared with children from non-infected mothers ($p = .48$).
Hall et al. (2021) UK	Cross-sectional study Pregnancy follow-up: Retrospective maternal report of infection collected by an interview at 9 months postpartum. Postpartum follow-up: Infants were followed-up at 9 months, 3,5,7,11,14 and 17 years. Parental self-administered questionnaire completed at 3 years. Date of enrollment: 2000–2002	Initial sample: 19518 Follow-up: 14021	28.7 (5.9)	Unspecified respiratory infection	-Retrospective self-reported symptoms	37.68 months (2.47)	50.99%	BEHAVIORAL-EMOTIONAL SDQ: *- Emotional symptoms* *- Conduct problems* *- Hyperactivity/ inattention* *- Peer relationship problems* *- Prosocial behavior.*	Parental report	LINEAR REGRESSION MODEL COVARIATES Adjusted model: Maternal age at birth; Maternal education; Area-based deprivation. Additionally adjusted model: Child's sex; Child's age at assessment; Maternal prenatal smoking; Harsh parenting; Maternal psychiatric illness; Maternal postnatal psychological distress. Sensitivity analysis: paternal age; education; history of psychiatric illness and postnatal psychological distress;	*Maternal-reported infections*: significant associations between infection and total difficulties ($p = .008$) and emotional symptoms ($p = .007$). *Hospital-recorded infections*: maternal infections were associated with higher scores on total difficulties ($p = .029$), emotional symptoms ($p = .043$) and peer relationship problems ($p = .025$) only in unadjusted model. No significant associations were found when adjusting for possible

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
										gestational age and birth weight.	confounders. *Combined hospital and recorded infections*: maternal infections were related to worse scores on total difficulties (p = .01) and emotional symptoms (p = .002). Sensitive analysis showed significant relationships between maternal-reported infections and emotional symptoms (p = .007).
Liu et al. (2022) China	Longitudinal study Pregnancy follow-up: Demographic and clinical data were obtained from medical records. Postpartum follow-up: Children were followed at different times after delivery and DDST evaluation was performed. Date of data collection: 2020–2021	Initial sample: 100 Follow-up: 1st: 76 Follow-up: 2nd: 127	Infected 30.5 (3.4) Non-infected 31.7 (4.6)	SARS-CoV-2	-Laboratory confirmed PCR test during pregnancy - Laboratory confirmed antibodies test	NA (1–13 months)	58%	GLOBAL DEVELOPMENT DDST: - *Personal-social* - *Fine motor-adaptive* - *Gross motor* - *Language.*	Professional report	LINEAR MIXED-EFFECT MODELS COVARIATES: age and sex	Fine motor abnormalities at 1–2 months were significantly higher in infants born of infected mothers (p = .02). Fine motor developmental delays were corrected at 13 months of age in all affected infants.
Mulkey et al. (2022) USA	Longitudinal study Pregnancy follow-up: Demographic and clinical data were obtained from medical records. Postpartum follow-up: Newborns born to infected mothers were enrolled in the "Congenital Infection Program" and followed-up to 3 times with the ASQ-3. Date of data collection: 2020–2021	Initial sample: 34 Follow-up 1st: 34 Follow-up 2nd: 18 Follow-up 3rd: 4	30.8 (6.4)	SARS-CoV-2	-Laboratory confirmed PCR test during pregnancy - Laboratory confirmed antibodies test	1st Follow-up: 111.6 days (24.2 days) 2nd Follow-up: 316 days (87.7 days) 3rd Follow-up: 439.5 days (63.8 days)	41%	GLOBAL DEVELOPMENT ASQ-3: - *Gross motor (GM)* - *Fine motor (FM)* - *Problem solving (PRS)* -*Personal/social (PS)* - *Communication (CO)*	Parental report	TWO SAMPLE T TEST AND CHI SQUARE TEST	There was a greater proportion of infants with scores close or below the ASQ cut-off values among infants born to symptomatic mothers when compared to infants from asymptomatic mothers and infants with neonatal infection. Infants born to asymptomatic mothers had the lowest rate of scores below the ASQ cut-off. Children born to symptomatic mothers

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
											had a greater tendency to present scores below the cut-off values in all ASQ-3 subdomains when compared to infants born to asymptomatic women (p = .04), especially in FM (p = .01) and PS (p = .02) subdomains.
Parker et al. (2016) USA	Cross-sectional study Pregnancy follow-up: Retrospective maternal report of infection collected by telephonic interview one year after delivery. Postpartum follow-up: Neurodevelopmental and behavioral outcomes were evaluated at 5–6 year by professional and parental-reported evaluations. Date of enrollment: 1996–2002	Initial sample: 570 Follow-up: 534	< 25: 21.8% 25–34: 59.2% ≥ 35: 19%	Unspecified URI	-Retrospective self-reported symptoms	6.9 years (1.0)	49.8%	SPECIFIC FUNCTIONS PPVT-III - *Receptive vocabulary* VMI-5 - *Perceptual-motor skills* BEHAVIORAL-EMOTIONAL CBCL // TRF: - *Internalizing problems* - *Externalizing problems* - *Total problems* - *8 syndrome scales*	Professional report Parental // teacher report	ADJUSTED LINEAR REGRESSION MODEL COVARIATES Maternal race; Maternal age; Maternal education; Maternal smoking during pregnancy; Maternal pre-pregnancy BMI.	Maternal URI was not significantly associated with child receptive vocabulary (adjMD: 1.34; 95% CI: −1.16, 3.84) and visual-motor abilities (adjMD: 0.32, 95% CI: −1.65, 2.28). URI exposure is related to increased CBCL and TRF "total behavior problems" scores (CBCL- adjMD: 3.72, 95% CI: 1.91, 5.54; TRF- adjMD: 2.74, 95% CI: 0.97, 4.50); especially for attention problems and aggressive behavior. Associations between prenatal exposure to URIs and behavioral problems were greater when infection occurred during mid pregnancy when compared to early exposure (CBCL total behavioral problems- adjMD: 5.14, 95% CI: 2.75, 7.54; TRF total behavioral problems- adjMD: 4.18, 95% CI: 1.89, 6.47)
Shuffrey et al. (2022) USA	Longitudinal study	Initial sample: 456	Infected 32 (19.0–45.0)	SARS-CoV-2	- Laboratory confirmed PCR and serological	185 days (9.97 days)	51.42%	GLOBAL DEVELOPMENT ASQ-3:	Parental report	ANALYSES OF COVARIANCE COVARIATES	No significant differences were found between infants

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
	Pregnancy follow-up: Mothers in the pandemic cohort were tested for SARS-CoV-2 at delivery or during pregnancy (symptom-based testing). Postpartum follow-up: Parental self-administered questionnaire completed at 6 months. Date of data collection: 2020–2021	Follow-up: 317 Follow-up: 72	Non-infected 32 (18.0–46.0)		antibodies tests during pregnancy			- *Gross motor (GM)* - *Fine motor (FM)* - *Problem solving (PRS)* -*Personal/social (PS)* - *Communication (CO)*		Minimally adjusted: Gestational age at birth; Infant sex; Infant age at assessment. Fully adjusted: Maternal race and ethnicity; Age at delivery; Educational level; Parity; Type of delivery. Sensitivity analysis: Exclusion of infants diagnosed with COVID-19 between delivery and neurodevelopmental evaluation; exclusion of infants in the historical cohort evaluated during the pandemic period.	exposed and non-exposed to maternal SARS-CoV-2 for any of the ASQ-3 subdomains (*GM*: p = .63; *FM*: p = .99; *PRS*: p = .81; *PS*: p = .34; *CO*: p = .89) Infants in the pandemic cohort had significant lower mean scores on *GM* (p < .001), *FM* (p < .001) and PS (p = .01) subdomains when compared to the historical cohort. There was a higher proportion of infants who met the cutoff for delay on *GM* subdomain in the pandemic cohort (p = .01). First trimester of pregnancy in the peak of the pandemic was associated with lower *GM* (p < .05), *FM* (p < .05) and *PS* scores (p < .005).
Wu et al. (2021) China	Longitudinal study Pregnancy follow-up: Information about infection retrieved from medical records. Postpartum follow-up: Follow-up at 1 week, 1 month, and 3 months. Information obtained from telephonic interview and medical records. Date of data collection: 2020 Parental online self-administered	Initial sample: 176 Follow-up: 135	Infected 31.2 (28.3–34.4) Non-infected 29.0 (28.0–31.0)	SARS-CoV-2	- Laboratory confirmed PCR test during pregnancy	NA (3–3.20 months)	48.89%	GLOBAL DEVELOPMENT ASQ-3: - *Gross motor (GM)* - *Fine motor (FM)* - *Problem solving (PRS)* -*Personal/social (PS)* - *Communication (CO)* BEHAVIORAL-EMOTIONAL ASQ:SE-2: - *Self-regulation* - *Compliance* - *Social-communication*	Parental report (both instruments)	MULTIVARIABLE LINEAR REGRESSION MODEL COVARIATES Length of mother-infant separation; Low birthweight; Infant gender; Preterm birth; Admission to neonatal intensive care unit; Breastfeeding after delivery	*FM* (p = .038), *PRS* (p = .002) and *PS* (p = .002) scores were significantly lower in the infection cohort. Maternal SARS-CoV-2 infection was not related to an increased risk of social–emotional delay (p.=617), overall delay (p = .951) nor ASQ-3 and ASQ:SE-2 scores. Length of mother-infant separation negatively correlated with scores on *GM* domain (p = .008).

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Table 1 (*continued*)

Author, year and country	Type of study, procedure and date of data collection	Sample size	Maternal Information			Offspring information				Statistical analysis (models and Covariates)	Main findings[b]
			Age[a] (mean age; SD/range in years)	Type of virus / symptoms	Detection	Age (mean age; SD/range)	Sex (% male)	Neuro-psychological evaluation (evaluated domains)	Parent/ professional report		
	questionnaire completed at 3 months.							- *Adaptive functioning* - *Autonomy* - *Affect* - *Interaction with people*			Infection significantly increased mother–infant separation length ($p < .001$), which significantly affected the scores on the gross motor domain ($p = .01$).

[a]Maternal age is specified as mean (SD) or mean (range). When this information was not available, percentages on each interval of age were employed.

[b]The findings included in this table represent the information of the most adjusted models that authors used.

[c]Infant's age was defined by authors as conceptional age + weeks of life. Mean age at evaluation was calculated by subtracting the age authors provided minus mean gestational age for each group.

Abbreviations: **adjMD:** Adjusted mean difference; **ASQ**: Ages and Stages Questionnaires; **ASQ-3:** Ages and Stages Questionnaires, Third Edition; **ASQ:SE-2:** Ages and Stages Questionnaire: Socio-emotional, Second edition; **BSID-III:** Bayley Scales of Infant and Toddler Development, Third Edition); **CBCL:** Child Behavior Checklist / **TRF**: Teacher reported form; **DDST:** Denver Developmental Screening Tests; **FIQ**: Full Scale Intellectual quotient; **GW**: Gestational week; **IBQ-R-SF**: Infant Behavior Questionnaire- Revised Short Form; **ICQ:** Infant Characteristics Questionnaire; **IgG**: Immunoglobulin G; **IQ**: Intellectual quotient; **MOS**: Motor Optimal Score; **NA**: Not applicable; **PIQ**: Performance Intellectual quotient **PCR**: polymerase chain reaction; **PPVT-III:** Peabody Picture Vocabulary Test; **SARS-CoV-2:** Severe Acute Respiratory Syndrome Coronavirus-2; **SDQ**: Strengths and Difficulties Questionnaire; **URI**: Upper-respiratory infection; **VIQ**: Verbal Intellectual quotient; **VMI-5:** Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition; **WISC**: Wechsler Intelligence Scale for Children.

3.5. Neurodevelopmental assessments

For the purpose of this review, articles were classified according to the neurodevelopmental dimension which they assessed as: measures of global development (cognition, motor, language and personal/social domains), measures of specific functions (vocabulary, visual motor integration and intelligence), measures of temperament and measures of behavioral and emotional development. For a clearer understanding of the purpose and results of this systematic review, an explanation of the evaluated domains and the different instruments employed will be provided below.

3.5.1. Measures of global development

Instruments were classified as measures of global development when they included, at least, one of the most usual key developmental subdomains: cognitive, motor, language and personal/social. Cognitive scales include developmental milestones related to cognitive processing (e.g.: sensorimotor skills, object permanence, memory, exploration or manipulation of objects). Language scales evaluate infant's ability to communicate and they are often divided in receptive and expressive language subscales. Receptive language scales evaluate preverbal behaviors and comprehension development, meanwhile expressive language scale assess preverbal and verbal communicative behaviors. Motor domains include the changes on movements and actions during development and they are often divided into gross and fine motor subscales. Gross motor subscales evaluate abilities that involve the use of large muscles (e.g.: positioning, locomotion, movement or balance), while fine motor subscales assess the ability to make precise movements using small muscles of the hands (e.g.: prehension, perceptual-motor integration, motor planning and motor speed). Personal/social scales are usually employed to monitor healthy and deficient socio-emotional capacities related to self-regulation, relationships, use of emotions and interactions. The different instruments employed to study general development and its subdomains will be explained below.

"**Pearson Bayley Scales of Infant and Toddler Development, Third Edition**" **(BSID-III)** (Bayley, 2006) have been constituted as a reliable tool for evaluating infant's and toddler's developmental functioning and detecting early delays. It can be applied to children aged from 1 to 42 months in order to evaluate their performance in five domains: cognition, motor, language, socio-emotional and adaptative behavior. Cognitive scale is composed of 91 items; language scale of 97 items; motor scale of 138 items; social-emotional scale of 35 items; and adaptative behavior scale of 241 items. This battery is applied by trained professionals, excepting socio-emotional and adaptative behavior domains, which are reported by infant's main caregivers. The starting point is defined by corrected infant's age, items are scored as passed or not passed and the administration of the cognitive, motor and language scales ends when the infant is not able to pass 5 consecutive items. Composite scores are calculated considering infants' age and they can be classified according to percentiles or in a qualitative description (extremely low, borderline, low average, average, high average, superior and very superior).

The "**Ages and Stages Questionnaires**" **(ASQ)** (Squires and Bricker, 2009) are a group of parent-reported questionnaires designed to evaluate global neurodevelopment in children aged from 2 to 60 months. They evaluate five crucial subdomains: fine and gross motor, communication, problem solving (cognition) and personal-social skills. Each scale is composed of 6 items and the entire test includes a total of 30 items, which vary depending on infant's age. This scale is also used as a level-1 screening tool to detect possible developmental deficits and alterations. This evaluation allows to discriminate between children who are typically developing, children who may need further assessments and the ones who must be monitored since they present a higher risk for developmental delays.

"Denver Developmental Screening Tests" (DDST) (Frankenburg et al., 1992) can be administered to children and preschoolers from 2

weeks to 6 years old. This tool does not measure hypothetical constructs (such as intelligence or physical skills), but it defines the ages at which children accomplish specific tasks. It is divided in four subdomains: personal-social, fine motor-adaptive, gross motor and language. The test is administered by trained experts and composed by 125 items. Children development can be classified as "normal", "questionable" and "abnormal".

"Prechtl's Method" (Einspieler et al., 1997) is qualitative evaluation of newborns' general movements which are indicative of CNS integrity and possible brain dysfunctions. For that aim, newborns' spontaneous motor activity is video recorded when they are in a peaceful state and then videos are analyzed by trained experts. Specifically, in the first two months postpartum, researchers can evaluate writhing movements, which are classified as "normal", "cramped--synchronized", "chaotic" or "poor repertoire". The movement pattern changes at 6–9 weeks leading to fidgety movements, which are present until 6 months of age and can be classified as "normal", "absent" (if they do not appear) or "abnormal" (if movements are exaggerated). Besides fidgety movements, the concurrent motor repertoire (movements patterns, age-adequacy, postural patterns and movement character) can be evaluated. Summing all values, professionals calculate a total Motor Optimal Score (MOS), which ranges from 5 (poor) to 28 (optimal) points (Einspieler et al., 2004).

3.5.2. Measures of specific functions

Instruments were classified as measures of specific functions when they were addressed to evaluate specific complex functions as intelligence, vocabulary and visual-motor integration.

"Wechsler Intelligence Scale for Children" (WISC) (Weschler, 1949) is employed to evaluate children's intelligence. WISC can be administered to children from 6 to 16 years old to evaluate their intelligence and their cognitive functioning on different domains. This version of WISC encompassed in 3 intelligence quotient (IQ) scores: Verbal IQ (VIQ), Performance IQ (PIQ), and Full-Scale IQ (FIQ) and their corresponding subscales. Raw scores for each subtest and scaled scores can be obtained and transformed to composite scores by comparing them to general population scores.

"Peabody Picture Vocabulary Test" (PPVT-III) (Dunn and Dunn, 1997) is used to evaluate infant's receptive vocabulary. It is a norm-referenced tool which can be administered to children and adults from 30 months to + 90 years old. In each item, examiners present four simple illustrations and they say a word. Participants are asked to choose which of the images better correspond to the word the examiner said. The test is composed of 204 items, which are presented in order of increasing difficulty. Participants can be classified according to age and grade-based standard scores, percentiles, normal curve equivalents, stanines and Growth Scale Values.

"Beery-Buktenica Developmental Test of Visual-Motor Integration, Fifth Edition" (VMI-5) (Beery and Beery, 2004) is employed to evaluate visual-motor integration abilities. This norm-referenced tool is designed to be applied to people between 2 and 99 years. Participants are asked to copy 24 drawings containing geometric forms, presented in order of increasing difficulty. This instrument provides standard scores, percentiles and age equivalents.

3.5.3. Measures of temperament

Instruments considered as measures of temperament evaluated different primitive qualities and abilities that determine infant's self-regulation and reactions towards daily situations in the first year of life.

The **Fussy Baby Scale**, is a subscale of the "**Infant Characteristics Questionnaire" (ICQ)**. The ICQ (Bates et al., 1979) is a short parent-reported screening instrument designed to evaluate infant's difficult temperament. It can be applied to infants from 3 to 36 months old and contains 24 items rated on a seven-point scale (1: optimal traits; 7: difficult temperament). Specifically, the Fussy Baby subscale, composed by 9 items, has been identified as the most valid factor of the ICQ and best predictor for future temperament because of its reliability over time. The fussy-difficult scale includes items related to infant's general mood and difficulties, crying, soothability and behaviors related to protesting or being upset.

Furthermore, the "**Infant Behavior Questionnaire- Revised- Short Form" (IBQ-R-SF)** (Gartstein and Rothbart, 2003), which is the short form of the IBQ (Rothbart and Derryberry, 1981), can be administered to infants from 3 to 12 months of age. IBQ-R-SF is a parent-reported questionnaire used to identify caregiver's perceptions about infant's behaviors that are indicative of their temperamental reactivity and their abilities for self-regulation. IBQ-R-SF includes 91 items in which parents are asked to rate the frequency of different infant's behaviors on a seven-point scale (1: never; 7: always). This questionnaire includes three dimensions: Orienting/Regulation (behaviors as cuddliness, engagement with parents, quiet play, duration of attention and soothability), Negative affectivity (behaviors related with fear, sadness and recovery after stress) and Surgency/Extraversion (activity, enjoyment of high intensity tasks, perceptual sensitivity and behaviors as vocal reactivity, smiling and laughter).

3.5.4. Measures of behavioral and emotional development

Instruments were classified as measures of behavioral and emotional domains when they evaluated aspects related to children's behaviors and social-emotional development.

The **"Strengths and Difficulties Questionnaire" (SDQ)** is employed to assess infant's social-emotional development (Goodman, 1997). SDQ is a parent-reported behavioral screening test which can be administered to children from 3 to 16 years old. The questionnaire is divided in five scales: emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems and prosocial behavior. The complete questionnaire includes 25 items responded according to the following answers: "0- not true", "1- some-what true", "2- certainly true", "can't say" or "not applicable". Total scores for each domain can be calculated and a global score can also be obtained adding up the scores of each domain, excepting the prosocial behavior scale.

The **"Ages and Stages Questionnaire: Socio-emotional, second edition" (ASQ: SE)** (Squires et al., 2015), is a parent-reported measure which can be administered to children between 2 and 60 months. This tool allows to identify children with a high risk of developing social and emotional issues, children who need further evaluations and typically-developing children. The number of items depends on children's age (from 19 to 39 items) and they are answered both by open answers or according to the following options: "often or always", "sometimes", "rarely or never", and "check if this is a concern".

The **"Achenbach System of Empirically Based Assessment" (ASEBA)** (Achenbach and Rescorla, 2001) consist of a set of questionnaires used to assess behavioral and emotional problems in children and adolescents aged from 6 to 18 years. Specifically, the **"Child Behavior Checklist" (CBCL)** can be completed by parents, while the **"Teacher's report Form" (TRF)** is completed by teachers**.** This instrument contains 113 items, scored on a three-point Likert scale (0 =absent; 1 =occurs sometimes; 2 =occurs often), and must be answered according to situations reported in the previous 6 months. This instrument is composed of 8 subscales: anxious/depressed; withdrawn/depressed; somatic complaints; social problems; thought problems; attention problems; rule-breaking behavior; and aggressive behavior. These scales can be grouped in two factors: internalizing and externalizing symptoms. Internalizing problematic behaviors are the ones which are self-directed and focused on oneself, meanwhile externalizing problematic behaviors are directed towards other people. Using this tool, raw scores, T scores and percentiles can be obtained.

Particularly, 9 studies evaluated children's global neurodevelopment and its subdomains using the following scales: BSID-III (Azziz-Baumgartner et al., 2022), ASQ (Ayed et al., 2022; Borren et al., 2018; Cheng et al., 2021; Mulkey et al., 2022; Shuffrey et al., 2022; and Wu et al., 2021), DDST (Liu et al., 2022) and Prechtl's Method (Aldrete-Cortez

et al., 2022). However, from the mentioned studies, only Borren and colleagues (2018) and Wu et al. (2021) employed a measure of global neurodevelopment, while the other studies focused on the analysis of the different subdomains. Two studies evaluated specific functions: vocabulary and visual-motor integration by PPVT-III and VMI-5, respectively (Parker et al., 2016); and intelligence by WISC (Ellman et al., 2009). Two studies evaluated temperamental outcomes using: ICQ (Borren et al., 2018) and IBQ-R-SF (Freedman et al., 2020). Finally, 3 studies explored behavioral and socio-emotional development employing: SDQ (Hall et al., 2021); CBCL and TRF (Parker et al., 2016); and ASQ:SE-2 (Wu et al., 2021).

From the instruments mentioned above, 6 are based on professional evaluations (BSID-III, Prechtl's Method, WISC, DDST, PPVT-III and VMI-5), 6 are based on parental reports (ICQ, ASQ, ASQ:SE-2, IBQ-R-SF, SDQ, CBCL) and one is completed by children's teachers (TRF).

3.6. Risk of bias assessment

Only studies with scores above 70% were considered as having a good quality, while studies with lower scores were considered as having important quality limitations (See Table 2). The quality of selected studies was variable: 3 low-quality studies presented scores below 40% (Cheng et al., 2021; Mulkey et al., 2022; and Parker et al., 2016), 6 studies were mid-quality, between 41% and 70% (Aldrete-Cortez et al., 2022; Ayed et al., 2022; Borren et al., 2018; Freedman et al., 2020; Hall et al., 2021; and Liu et al., 2022), and 4 studies presented scores above 70% (Azziz-Baumgartner et al., 2022; Ellman et al., 2009; Shuffrey et al., 2022; and Wu et al., 2021), which indicated good quality.

Specifically, the majority of the studies presented greater difficulties to fit on "Lost to follow-up sample bias" and "Adjustment to infant's age range" criteria, thus indicating that most of the studies had a lost of more than 5% of the sample and had a wide range of ages among the evaluated participants. Noticeably, as it can be seen, some studies had an inadequate cases and controls definition, which importantly limit the conclusions of the studies.

3.7. Main findings

The main results of the revised studies are represented in Fig. 3.

3.7.1. Effects of maternal respiratory infections during pregnancy on infant's global development and its subdomains

Revised studies have obtained diverse results regarding global development and its specific subdomains.

Only one study reported a significant association between maternal gestational respiratory Influenza and overall developmental functioning (Borren et al., 2018). Authors observed that confirmed Influenza infection, when it occurred in early pregnancy (before 8 weeks), had a small negative effect on global development at 7 months of age, although this relationship was not found when infection occurred in later stages.

When considering global developmental subdomains and Influenza infection, Borren and colleagues (2018) concluded that exposure to maternal Influenza during early pregnancy is related to fine motor alterations in 7-months-old children, while exposure on late pregnancy (9–40 weeks) is associated with greater difficulties on communication subdomain. However, Azziz-Baumgartner et al. (2022) did not find statistically significant differences among children prenatally exposed and non-exposed to Influenza virus regarding BSID-III subdomains, neither at 1 nor 2 years.

Regarding the association between SARS-CoV-2 prenatal maternal infections and specific subdomains, low and mid-quality studies consistently concluded that exposure to maternal infection is significantly related to lower scores on the fine motor subdomain, suggesting possible motor delays on exposed infants (Aldrete-Cortez et al., 2022; Ayed et al., 2022; Cheng et al., 2021; Liu et al., 2022; and Mulkey et al., 2022). On the other hand, high-quality studies reported that the alterations found among children born during the COVID-19 pandemic could be a consequence of the pandemic situation (Shuffrey et al., 2022, Wu et al., 2021).

With regard to low and mid-quality studies, Aldrete-Cortez and colleagues (2022) concluded that infants born to mothers with SARS-CoV-2 during gestation presented a poorer motor performance at 3–5 months postpartum, defined as lower MOS total scores. Specifically, exposed children presented higher rates of absent or abnormal fidgety movements and more alterations on movement and postural patterns. Additionally, Liu and colleagues (2022) reported fine motor abnormalities in infants prenatally exposed to SARS-CoV-2, already detectable at 1–2 months of age. However, these alterations disappeared at 13 months, suggesting that developmental alterations may be transient and reversible after postnatal training. Moreover, Cheng and colleagues (2021) found that fine motor abnormalities were significantly higher on children around 9 months of age exposed to prenatal maternal infection when compared to non-exposed children. In accordance with these results, Ayed and colleagues (2022) concluded that 10–12 months infants born to infected mothers presented a higher risk of developmental delays in the ASQ-3 subdomains, especially when infection occurred in the first and second trimesters of pregnancy. Noticeably, fine motor alterations were the most prevalent deficits. In this line, Mulkey et al. (2022) reported that the risk of developmental delays may depend on maternal SARS-CoV-2 symptomatology. Specifically, infants up to 15 months born to symptomatic mothers seem to have a greater tendency to present scores below the cut-off values in the ASQ-3 when compared to infants born to asymptomatic women and children with neonatal infection. Interestingly, this tendency seems to be particularly significant in fine motor and personal-social subdomains.

Finally, 2 high-quality studies reported associations between infant's neurodevelopmental patterns and COVID-19 pandemic-related situations, but failed to confirm the association with infection itself. On the one hand, Shuffrey and colleagues (2022) did not observe significant differences between children born to infected and non-infected mothers on any of the ASQ-3 subdomains. Nevertheless, authors found that 6-months-old children in the pandemic cohort presented significantly lower scores on gross motor, fine motor and personal-social domains when compared to infants born previous to the pandemic. Additionally, a greater proportion of infants born during COVID-19 pandemic met the gross motor cutoff, indicating a higher prevalence of motor delays. Interestingly, concerning timing of pregnancy, post-hoc analyses indicated that first trimester of pregnancy in the peak of the pandemic was associated with worse gross motor, fine motor and personal-social scores. On the other hand, Wu and colleagues (2021) reported that 3-moths-old infants in the infection cohort presented significantly lower scores on fine motor, problem solving and personal-social subdomains. Noteworthy, while SARS-CoV-2 maternal infection did not explain the risk of developmental delays nor the ASQ-3 scores, the length of mother-infant separation after birth was negatively correlated with worst gross motor performance. Furthermore, using a mediation model, authors suggested that SARS-CoV-2 infection had an indirect effect on the gross motor development mediated by the length of mother-infant separation, which is not explained by infection itself.

3.7.2. Effects of maternal respiratory infections during pregnancy on specific child neurodevelopmental functions

None of the studies who explored the relationship between prenatal exposure to infection and specific functions could confirm any significant associations in children from the general population (Parker et al., 2016; Ellman et al., 2009).

Firstly, regarding unspecified respiratory infections, Parker et al. (2016) did not find significant associations between maternal report of respiratory infections and receptive vocabulary neither visual-motor integration abilities in children from 5 to 10 years of age.

Secondly, regarding Influenza B maternal infection, Ellman and colleagues (2009) did not observe significant differences on IQs between

exposed and non-exposed controls around 7 years of age. However, when studying children later diagnosed with psychotic disorders, they found a significant interaction between maternal influenza B infection and case status for verbal IQ scores. Post hoc analyses revealed that exposed cases presented reduced IQ scores on all WISC subdomains when compared to unexposed cases, although only differences on verbal IQ were statistically significant. Finally, regarding WISC subscales, authors found a significant interaction between case status and maternal Influenza B for the VIQ subtests of "Information" and "Digit Span". Post-hoc analyses indicated that cases prenatally exposed to maternal Influenza had a poorer performance on "Information" subtest when compared to unexposed cases.

3.7.3. Effects of maternal respiratory infections during pregnancy on child temperament

From the 2 studies which explored this possible association, one concluded that the effects of infection on temperament may depend on the timing of exposure (Borren et al., 2018), while the other study concluded that these effects could be mediated by maternal choline levels (Freedman et al., 2020).

Firstly, concerning unspecified maternal respiratory infections, Freedman and colleagues (2020) reported worse scores in the "Regulation" dimension, especially in the Attention subdomain, in children born to mothers who reported upper respiratory infections during pregnancy, but only when maternal choline levels were lower than 7.5 μM. However, infants from infected mothers who had choline levels higher than 7.5 μM showed no effects of infection on the mentioned domains when compared with children from non-infected mothers ($p = .48$). On the other hand, regarding Influenza virus, Borren and colleagues (2018) could not confirm an overall relationship between maternal Influenza infection and temperamental scores. When considering the timing of exposure, infants who were born to mothers with serologically confirmed Influenza in early gestation (GW 0–8 and weeks before conception) showed a tendency towards a more difficult temperament. Additionally, authors describe a smaller association between maternal reported Influenza infection during late pregnancy (GW 9–40) and worse scores in the mentioned scale. Noteworthy, these results must be interpreted with caution since the overall model is not statistically significant.

3.7.4. Effects of maternal respiratory infections during pregnancy on child psychosocial and emotional development

From the 3 studies which evaluated social-emotional outcomes, 2 reported significant associations with prenatal maternal reported respiratory infections (Hall et al., 2021; Parker et al., 2016). Although the subdomains affected are different on each study, both articles remark the existence of an association between prenatal infections and total behavioral and emotional problems.

In regard to unspecified maternal infections, Hall and colleagues (2021) observed a significant association between maternal reported infection and worse scores on all SDQ subdomains, except prosocial behavior. However, on the fully adjusted model (See Table 1 for further

Table 2
Results of the risk of bias assessment.

	SELECTION			COMPARABILITY	DEVELOPMENTAL EVALUATION			TOTAL
	Adequate case definition	Definition of control group	Sample size	Control for covariates	Quality of neurodevelopmental assessments	Adjustment to infant's age range	Lost to follow-up sample bias	
Aldrete-Cortez et al., 2022 SARS-CoV-2	2	0	1	1	2	2	0	**8 57%**
Ayed et al., 2022 SARS-CoV-2	2	0	2	2	1	1	0	**8 57%**
Azziz-Baumgartner et al., 2022 Influenza	2	0	2	2	2	2	0	**10 71%**
Borren et al., 2018 Influenza	1	2	2	2	1	1	0	**9 64%**
Cheng et al., 2021 SARS-CoV-2	2	1	0	0	1	0	0	**4 29%**
Ellman et al., 2009 Influenza	1	2	2	1	2	1	1	**10 71%**
Freedman et al., 2020 Unspecified infection	0	0	2	1	2	0	1	**6 43%**
Hall et al., 2021 Unspecified infection	0	0	2	2	2	1	1	**8 57%**
Liu et al., 2022 SARS-CoV-2	2	2	1	1	1	0	0	**7 50%**
Mulkey et al., 2022 SARS-CoV-2	2	0	1	0	1	1	0	**5 36%**
Parker et al., 2016 Unspecified infection	0	0	2	1	2	0	0	**5 36%**
Shuffrey, 2022 SARS-CoV-2	2	2	2	2	1	2	0	**11 79%**
Wu et al., 2021 SARS-CoV-2	2	1	2	2	1	2	1	**11 79%**

Summarized results of the risk of bias assessment, performed using an adaptation of the "NOS" (Wells et al., 2009). Items are scored as 2 (best possible score), 1 (medium score), or 0 (worst score) and the sum of the 7 items represent the final punctuation for each article. Final scores are represented as a percentage, being 100% the best possible score. Articles with a final score above 70% were considered as high-quality (represented in green), articles with scores between 40% and 69% were considered as mid-quality (represented in yellow), and articles with final scores above 39% were considered as low-quality (represented in red).

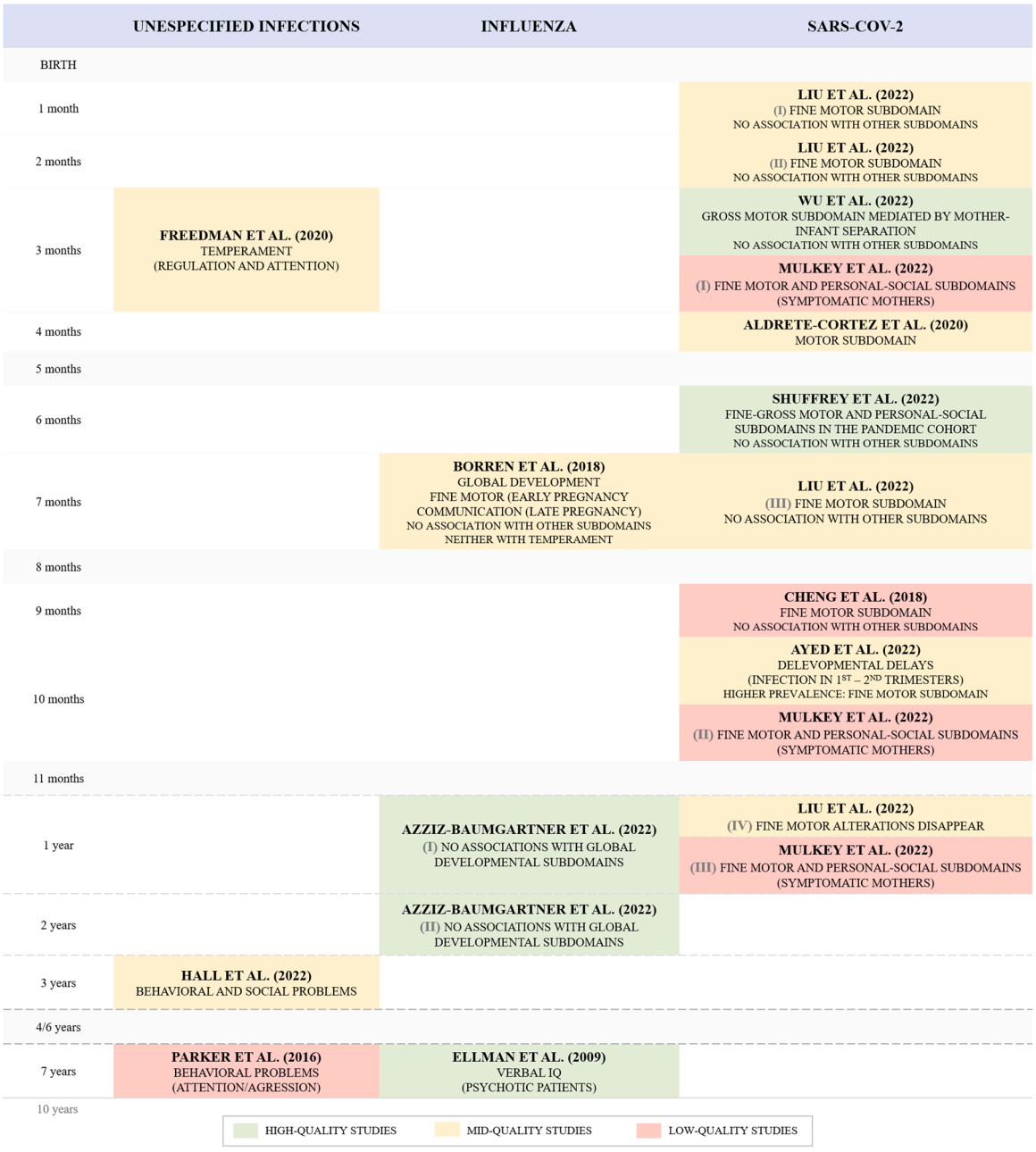

Fig. 3. Summary of the main findings of the revised studies. Studies are classified according to infant's age at evaluation, which ranged from birth to 7 years, and according to the type of viral infection (unspecific respiratory infections, Influenza and SARS-CoV-2). High quality studies are represented in green, mid-quality studies in yellow and low-quality studies in red. Non-significant results for the different evaluated subdomains are not represented in this figure.

information about the covariates), only associations with total difficulties and emotional symptoms remained significant. Moreover, when studying hospital recorded infections by using an unadjusted model, relationships between infection and higher scores on total difficulties, emotional symptoms and peer relationship problems were found. When combining both maternal and hospital reported infections, in the fully adjusted model, only associations with total difficulties and emotional symptoms subscales were significant.

Secondly, Parker and colleagues (2016) observed that children between 5 and 10 years born to mothers who reported unspecified upper respiratory infections during pregnancy presented increased punctuations in "Total problems" subscale of the CBCL and TRF scales when compared to children with no maternal report of infection. These differences were especially noticeable for "Attentional problems" and "Aggressive behavior" subdomains. Additionally, this relationship was stronger for infections that occurred during mid pregnancy when compared to early infections and absence of infections.

Contrary, Wu and colleagues (2021) concluded that children prenatally exposed to SARS-CoV-2 did not present a higher risk of social-emotional delays at 3 months (surpassing the clinical threshold) neither worse ASQ:SE-2 scores.

4. Discussion

Children neurodevelopment is a highly-orchestrated process which can be affected not only by postnatal environment, but also by prenatal adverse events. Given the COVID-19 pandemic and the high prevalence of other viral respiratory infections during pregnancy (Collier et al., 2009), the identification of early unspecific developmental risk markers in children prenatally exposed to maternal infection is of great social and

clinical interest.

To fulfill this need of information, the present systematic review is the first to summarize the evidence of 13 articles that address the relationship between maternal respiratory viral infections and children neurodevelopmental outcomes. In this study, we considered neurodevelopment as a continuous and multidimensional process which can be mainly divided in 4 subdomains: i) general development; ii) specific functions; iii) temperament; and iv) behavioral-emotional development.

4.1. General development

Although some of the studies included in this review found alterations on specific developmental subdomains in children exposed to maternal respiratory viral infections, the results are not clear enough to conclude that the mentioned infections modify the overall children developmental patterns.

In fact, from the 2 studies evaluating general development, only Borren and colleagues (2018) confirmed an association between maternal infection and impaired global development. Specifically, the study of Borren and colleagues (2018), that employed both maternal self-report of infection and antibodies testing for Influenza, showed that confirmed maternal infection predicted worse overall developmental scores in infants around 7 months of age.

Secondly, regarding particular neurodevelopmental subdomains, the 5 studies considered as mid and low methodological quality reported a significant effect of maternal infection, particularly on the fine motor subdomain, for both SARS-CoV-2 (Aldrete-Cortez et al., 2022; Ayed et al., 2022; Cheng et al., 2021; Liu et al., 2022; and Mulkey et al., 2022) and Influenza infections (Borren et al., 2018). Specifically, these alterations were observed in children below 1 year of age, indicating that infection effects could be especially noticeable in the earliest stages of development. In line with these results, a recent study by Edlow and colleagues (2022) reported that infants prenatally exposed to maternal SARS-CoV-2 presented a significantly higher risk of being diagnosed with a neurodevelopmental disorder in the first year of life. Interestingly, according to the authors, the most prevalent diagnoses are related to motor function, followed by language and speech dysfunctions. Nevertheless, as reported by Liu and colleagues (2022), the identified fine motor delays seem to be a transient condition that can be corrected at the end of the first year of life by means of specific parental guided postnatal stimulation.

Besides offspring's age, timing of exposure to prenatal maternal infection seems to play a key role on children developmental outcomes, regardless of the virus. Interestingly, Borren and colleagues (2018) report that early pregnancy may be a period of vulnerability for motor alterations and late pregnancy a period of vulnerability for language deficits. Although the importance of these results, it should be highlighted that author's definition of late pregnancy period substantially differs from the usual obstetrical classification, which usually defines late gestation from 28 weeks on, with the beginning of the third trimester (World Health Organization, 2022d). In accordance with these results, the study by Ayed et al. (2022) also concluded that the risk of developmental delays in infants around 10–12 months of age, especially prevalent on the motor subdomain, is higher when SARS-CoV-2 infection occurs in the first and second trimesters of pregnancy.

The results from both studies suggest that maternal infection could interfere with primary processes of brain development which occur during early pregnancy as neurulation, neurogenesis or cell migration, while later exposure may affect cortical structure and functioning, affecting complex functions as language (Thompson and Nelson, 2001). According to Schepanski et al. (2018), maternal immune activation in front of infections, particularly the imbalance between pro and anti-inflammatory cytokines, may play an etiopathogenic role on developmental alterations, since the abovementioned brain developmental processes are sensitive to this cytokine's imbalance. Although these results must be interpreted with caution due to the methodological limitations of these articles, previous studies have demonstrated that both the timing and severity of exposure to different stressors influence on the consequences they may have (Kapoor et al., 2008). Fetal brain developmental patterns across pregnancy seem to determine the vulnerability of the different structures and connections to the prenatal insults, being the first stages of pregnancy a period of special vulnerability for severe alterations as schizophrenia and late pregnancy a period of vulnerability for the dysregulation of stress-response systems and emotional outcomes (Khandaker et al., 2013; Davis et al., 2011). In that sense, regarding COVID-19 pandemic, a recent study reported differential methylation patterns of genes related to stress regulation among infants born to women who were in the first trimester of pregnancy during the lockdown period (Nazzari et al., 2022).

Finally, none of the 3 studies considered as high-quality observed significant associations between maternal respiratory infections and infant's developmental outcomes neither for Influenza (Azziz-Baumgartner et al., 2022) nor SARS-CoV-2 viruses (Shuffrey et al., 2022; and Wu et al., 2021). Specifically, regarding the COVID-19 recent pandemic, both Shuffrey et al. (2022) and Wu et al. (2021) concluded that the motor and personal social alterations reported in infants born during this period could be mainly a consequence of the pandemic situation (e.g.: maternal stress-related behaviors and perceptions or mother-infant separation after birth), rather than maternal infection itself. In fact, Shuffrey and colleagues (2022) reported worse motor and persona-social scores in infants born to mothers whose first trimester of pregnancy coincided with the peak of the COVID-19 pandemic. These results, besides suggesting that pandemic-related stress plays an important role on infant's development, reinforce the idea that prenatal adverse environments have a greater impact when they occur in early pregnancy. Interestingly, although authors did not directly explore this association, it should be noticed that Aldrete-Cortez and colleagues (2022) also identified a non-optimal median motor performance in children exposed and non-exposed to infection, but born during the COVID-19 pandemic, suggesting a possible environmental effect. Lastly, Azziz-Baumgartner and colleagues (2022) did not find significant differences on any of the developmental subdomains among children exposed to maternal gestational Influenza. Noteworthy, these children were not exposed to pandemic-related situations during the Influenza outbreak. Moreover, it should be considered that authors evaluated children at 1 and 2 years of age, highlighting once again the beneficial effects that postnatal stimulation may have on mitigating the adverse consequences of maternal infection.

Since COVID-19 outbreak supposed an exceptional situation, further studies will help to understand whether infant's developmental alterations are related to the maternal infection itself or to the pandemic-related stress which affect mother-infant behaviors.

4.2. Specific neurodevelopmental functions

The studies which separately evaluated specific neurodevelopmental functions did not report significant associations between maternal viral respiratory infections and vocabulary, visual motor integration nor intelligence (Ellman et al., 2009; Parker et al., 2016).

Firstly, Parker and colleagues (2016) found no associations between maternal reported infections and child performance on vocabulary or visual-motor integration tasks. The conclusions of this study are severely limited by the design, since maternal retrospective reports of symptoms may bias the classification of cases and controls. To the best of our knowledge, no previous studies have reported associations between prenatal viral respiratory infections and alterations on visuospatial abilities.

Secondly, the study by Ellman and colleagues (2009), employing a good methodological design, demonstrated the association between maternal infection and verbal IQ scores at 7 years old children who were later diagnosed with an adult psychotic disorder. However, this association was not reported among the group of non-psychotic subjects. In

fact, this study indicates a special affectation of the verbal subdomain, suggesting that infants exposed to prenatal infection may be a clinically different subgroup of psychotic patients, as demonstrated with other infections (Calkova et al., 2022). Since adult psychotic disorders, especially schizophrenia, have been extensively related to maternal gestational infections, the identification of altered neurodevelopmental milestones in exposed children could be considered a putative risk factor to establish preventive strategies prior to the onset of the disorder.

4.3. Early temperament

Traditional theories on the origins of temperament indicate that it is strongly influenced by genetics (Rothbart, 1989), but also by biological stressful events occurring during the prenatal period, including infections (Kagan and Snidman, 2004). Two studies included in this review that focused its attention on early temperament showed controversial results.

On the one hand, the study by Freedman and colleagues (2020) reported an association between unspecified maternal respiratory infections and children's difficulties for regulation and attention, but only in those children born to mothers with low choline levels. These results are consistent with previous reports which claim that choline is a nutrient that has crucial effects on offspring's brain development and is believed to mitigate the adverse effects that maternal inflammation has on the fetus (Caudill et al., 2018). Noteworthy, the longitudinal follow-up of Freedman's cohort has allowed to confirm the positive effects of choline on social-emotional development and cognitive performance at 4 years of age (Hunter et al., 2021).

Interestingly, Freedman's findings are in line with studies on older children, as the one by Parker and colleagues (2016) included in this review, which concluded that unspecific maternal respiratory infections lead to greater attentional problems in late infancy, suggesting that both prenatal environment and early temperament might play a key role on personal and social future adaptation. In this regard, prenatal exposure to infection has been also linked to ADHD, which comprises symptoms of inattention, hyperactivity and impulsivity (Posner, Polanczyk and Sonuga-Barke, 2020), although results are inconsistent and possibly affected by the recalling bias present in retrospective designs.

On the other hand, regarding Influenza infection, the study by Borren et al. (2018) failed to confirm an overall association between maternal Influenza and offspring's temperament at 7 months of age, although those exposed at early stages seem to show a tendency towards a more difficult temperament.

Noticeably, studies which employed biological markers have not been able not confirm the association between temperamental attentional problems and maternal immune activation (Chudal et al., 2020) nor infections (Borren et al., 2018) during pregnancy. Further studies including biological confirmation of respiratory infections are needed, since recent studies have demonstrated that changes on offspring's temperament may be mediated by maternal stressful conditions. In that sense, a recent study by Provenzi et al. (2021) has demonstrated that COVID-19 pandemic-related maternal stress is associated to infants' difficult temperament at 3 months in absence of SARS-CoV-2 maternal infection, being the main mediator the epigenetic changes on the offspring genome.

4.4. Behavioral and emotional development

Contradictory results were found regarding the impact of infection on behavioral and socioemotional development.

Firstly, the study by Hall and colleagues (2021), revealed that maternal reported respiratory infections are related to worse social-emotional outcomes at 3 years, with special emphasis on emotional and global problems. These results are in good agreement with the findings of Parker et al. (2016), which also confirmed a positive association between maternal reported unspecific infections and child's overall behavioral and emotional problems. Furthermore, this study showed that children born to infected mothers present higher attentional and behavioral problems, especially when the fetus is exposed in mid-pregnancy. However, it should be noticed that both studies present several limitations on their methodological design, specially related to the definition of cases and control groups.

Contrary, the study by Wu and colleagues (2021) could not confirm significant associations between exposure to infection and social-emotional outcomes at 3 months-old babies. Noteworthy, this study presents one of the greatest punctuations in the risk of bias scale and a good characterization of exposed and non-exposed groups. However, since most of the participants were infected in the third trimester, it cannot be discerned whether the effects of infection may be only noticeable when it occurs in early pregnancy. Moreover, it should be highlighted that children were evaluated at 3 months of age, a time when complex social-emotional abilities are in early phases of development.

To the best of our knowledge, only a few studies have addressed the implications of maternal infections on offspring's social-emotional development. A previous study by Green et al. (2018) confirmed that children born to mothers with any kind of hospital-recorded infections presented higher emotional vulnerabilities at 5 years of age. Additionally, Dombrowski et al. (2003) discovered that maternal fever was associated with worse psychological and behavioral outcomes in the offspring, especially when this immune activation occurred in the second trimester of pregnancy, as reported by Parker and colleagues (2016).

Besides maternal immune activation, social-emotional difficulties could be also mediated by the dysregulation of temperament in early childhood, as identified by Freedman et al. (2020) for the attentional domain. Furthermore, the contribution of other postnatal factors cannot be denied. For instance, better parental strategies and household characteristics have been related to better emotion regulation skills at the age of 3 years (Kao et al., 2020), a time of crucial importance for the cognitive and emotional development. Moreover, it should be noticed that maternal psychological status (e.g.: stress, depressive symptomatology, or adverse life events) have been also reported to influence social-emotional development beyond the prenatal period through parenting practices (Vásquez-Echeverría et al., 2022).

4.5. Strengths and limitations

In the present systematic review, several concerns should be considered, many of them related with the design of the studies included and the difficulty of properly identifying maternal infectious status.

The variety of methodological designs employed and the diversity of child developmental domains makes it difficult to obtain generalizable conclusions. Moreover, this heterogeneity hinders the possibility of conducting a meta-analysis. In that sense, although the optimal design would include a clinical and molecular control of maternal infections and a comprehensive follow-up of the offspring, at least until puberty or adolescence, the existing literature shows the great complexity of performing epidemiological and longitudinal studies. In this regard, it should be specially highlighted the importance of categorizing maternal infections based on clinical diagnosis and serology or microbiological testing and not only on retrospective self-reported symptoms. Interestingly, according to our results, the studies which exhaustively controlled maternal infectious status and associated conditions during pregnancy could not detect substantial changes on the different domains of children's neurodevelopment.

Furthermore, a limitation of the studies addressing the direct relationship between gestational maternal infections and subtle changes on development is derived by the very nature and the plasticity of the child brain, which is especially vulnerable to the context of breeding and to the stressful conditions that surround their caregivers (Bronfenbrenner and Ceci, 1994). Particularly, psychosocial stress is commonly

associated to epidemic phenomena and to pregnancy itself, and is known to disturb infant's brain development through different pathways, especially by the increase of glucocorticoids and by maternal immune activation (Krontira et al., 2020). In addition, other factors as socio-economic status (SES) should be also considered, since mothers with lower SES have greater probabilities of suffering from infections, as demonstrated in the recent COVID-19 pandemic (Patel et al., 2020), but also a greater tendency of having children with worse performance on neurodevelopmental assessments and a higher risk for developing mental and neurodevelopmental disorders (Hackman et al., 2010).

Additionally, it would be of great interest to analyze the implication of timing of exposure to infection. According to the results of this review, consequences of infection may vary depending on the brain structures that are being formed when infection occurs, being early and mid-pregnancy a period of special vulnerability for offspring's neurodevelopmental alterations.

Nevertheless, this review presents great strengths. Firstly, to the best of our knowledge, it is the first systematic review to summarize the evidence of articles linking maternal respiratory viral infections and subtle developmental deviations on the offspring, which can be used as risk markers for the appearance of future more severe disorders. The search and selection process were conducted in accordance with PRISMA guidelines to avoid possible bias and, in addition, a risk of bias assessment was performed for each of the included articles. Additionally, only studies employing standardized instruments were included, being especially remarkable the use of batteries which evaluate different developmental subdomains. Moreover, since different respiratory infections and neurodevelopmental domains were included, we were able to evaluate the specific effects each infectious agent may have on offspring's neurodevelopmental domains, evaluating also the impact of children's age. The conclusions of this review could be greatly considered for future pandemics.

5. Conclusions

The present review highlights the difficulty of exploring the impact of maternal respiratory infections during pregnancy on infant's development. With regard to general development and its specific subdomains, mid and low-quality studies consistently reported early motor alterations on the offspring, especially among children born to SARS-CoV-2 infected mothers (Aldrete-Cortez et al., 2022; Ayed et al., 2022; Cheng et al., 2021; Liu et al., 2022; and Mulkey et al., 2022), but also from mothers infected with Influenza (Borren et al., 2018). These identified deviations seem to be especially detectable in the first year of life and reversible in later stages. However, none of the high-quality studies could replicate these results (Azziz-Baumgartner et al., 2022; Shuffrey et al., 2022; and Wu et al., 2021), suggesting a possible impact of the SARS-Cov-2 pandemic situation on infant's development. Noteworthy, COVID-19 pandemic has increased maternal risk factors (e.g.: reduction of social activities, higher risk of poverty, fear of infection, etc.), consequently increasing depressive and anxious symptoms (COVID-19 Mental Disorders Collaborators, 2021). Besides prenatal factors, restrictive pandemic measures and mother-infant separation at birth seems to have influenced familiar interactions, offspring's social stimulation and mother-infant attachment, probably determining the development of some of the abovementioned domains.

Additionally, revised studies could not identify alterations on vocabulary, visual-motor integration (Parker et al., 2016) nor intelligence in children from the general population, although worse verbal IQ scores were reported among exposed individuals who later developed adult psychiatric disorders (Ellman et al., 2009).

Moreover, the revised studies seem to indicate that unspecified maternal infections may also lead to temperamental, behavioral and emotional alterations, specially related to the attentional domains (Hall et al., 2021; Parker et al., 2016) Even though these alterations seem to be mild and specific of some subdomains, the possible comorbidity with later impairment in other domains should not be underestimated. In fact, previous reports indicate that temperament is tightly associated with behavioral, attentional and motor outcomes (Rothbart et al., 2000), while behavioral problems are also usually associated with cognitive, language and learning difficulties (Hinshaw, 2002).

To sum up, the results of this review suggest that maternal status and environmental conditions may be more explicative of the offspring's neurodevelopment than the history of respiratory viral infections during pregnancy. However, revealing results point out to possible deviations on early motor, temperamental and later behavioral and social-emotional domains. Other aspects as the impact of the severity and timing of infection must be explored on further studies.

According to the estimations of the World Health Organization (2022c), new pandemic and epidemic waves produced by unknown infectious agents will appear in the incoming years. Further studies are needed to deeply understand the physiology of the immune system of pregnant women and how their bodies react to viruses and vaccines, but also to social-stress associated conditions. In that way, better care strategies could be implemented for both pregnant women and their children, avoiding restrictive measures as mother-infant separation or lockdown. Considering both obstetrical and mental health implications, taking care of pregnant women's health will not only improve their wellbeing but will also avoid the consequences that pandemics may have on the cohorts of children exposed to those situations.

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Conflict of interest

All authors declare that they have no conflict of interest regarding the publication of this manuscript.

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Appendix A. - Systematic review protocol

Team members

The systematic search will be conducted independently by two reviewers: N.SM-G and A.C-Q. The process of articles screening and selection will be conducted independently by N.SM-G and A.C-Q. When necessary, a third author (L.M-F) will help to reach an agreement.

Reasons and aims of this systematic review

Viral respiratory infections are the most prevalent infections during pregnancy. Nevertheless, the impact that these infections may have on offspring's neurodevelopment have been less studied when compared to severe neurotropic viruses (e.g: zika or cytomegalovirus).

Therefore, the main aims of this systematic review are:

- To identify of the existing literature linking maternal gestational viral respiratory infections and offspring's neurodevelopment.
- To explore the possible consequences that maternal viral respiratory infections may have on offspring's developmental outcomes during early and middle childhood.

Inclusion/exclusion criteria

Inclusion criteria:

1. Human studies
2. Studies which explore the relationship between maternal viral respiratory infections during pregnancy and offspring's neurodevelopmental milestones in mother-infant dyads.
3. Articles containing information about maternal viral respiratory infections during pregnancy:
   1. The following infections will be included: influenza, parainfluenza, rhinovirus, adenovirus, coronavirus, metapneumovirus, bocavirus and respiratory syncytial virus.
   2. No limitations regarding the type of measures will be applied. Biological confirmation of infections in any tissue, by the presence of antigens or antibodies (e.g: PCR, antigens test and antibodies test), will be accepted.
   3. In absence of biological confirmation of infection, self-reported symptoms of respiratory infections and medical diagnosis will be accepted.
4. Articles containing an evaluation of offspring's neurodevelopment before 10 years old:
   41. Neuropsychological evaluations of global child development or any related subdomains will be accepted: global development (including cognition, language, motor, personal-social development); other neuropsychological functions (e.g.: executive functions, processing speed, memory, intelligence, arithmetic, visuospatial abilities, non-verbal reasoning, attention, sensorial abilities, and learning); temperament; social outcomes; behavioral outcomes; and emotional development.
   42. Neuropsychological evaluations must be addressed to assess normative milestones achieved though neurodevelopment.
   43. Only articles including standardized and validated measures will be selected.

Exclusion criteria:

1. Abstracts, congresses publications, book chapters and letters to editors will be excluded.
2. Studies evaluating the impact of bacterial or non-respiratory viral infections will be rejected.
3. Articles evaluating children older than 10 years will be excluded.
4. Articles including exclusively clinical evaluations addressed to the diagnosis of psychiatric and neurodevelopmental disorders will not be accepted.
5. Articles including current categorical DSM or ICD diagnosis of psychiatric or neurodevelopmental disorders, but not evaluations of normative developmental milestones, will be rejected.
6. Articles including non-standardized neurodevelopmental measures will be excluded.
7. Articles written in languages different from English and Spanish will be excluded.

Databases and keywords

Prior to the systematic search, possible keywords will be identified by both authors employing the UNESCO Thesaurus. The following terms were identified and will be employed in the search:

Respiratory virus; influenza; flu; respiratory syncytial virus; parainfluenza; metapneumovirus; rhinovirus; coronavirus; adenovirus; bocavirus; cold; prenatal; antenatal; pregnan* ; matern* ; newborn; child* ; infant; offspring; prescholar; baby; neurodevelopment* ; development* ; cogniti* ; emoti* ; behavior* ; motor; social; psychologic* ; temperament* .

The systematic search will be conducted in three databases: PubMed, Web of Science and PsychInfo. The process will be performed independently by two authors (N.SM-G and A.C-Q). Data extracted from the three databases will be managed using EndNote X9 software.

Data extracted from the articles

The following data will be extracted from the selected articles: 1) Authors, year and country; 2) Type of study, procedure and date of data collection; 3) Sample size; 4) Maternal information: age, type of virus/symptoms and detection; 5) Offspring's information: age, sex, neuropsychological evaluations, parental/professional report; 6) Statistical analysis; and 7) Main findings. Additionally, information about the methodological design of each study was extracted to design a risk of bias assessment.

Appendix B. - Literature search strategy

Search strategy in PubMed

SOURCE	National Library Of Medicine
DATABASE	PubMed
DATE	November 24th, 2022
RESEARCHERS	N.SM-G & A.C-Q
LANGUAGE LIMITATIONS	Not applied
DATE LIMITATIONS	Not applied
OTHER FILTERS	Not applied

The systematic search was conducted independently by two authors (N.SM-G and A.C-Q) on the 24th of November 2022. The search was conducted as follows:

#1	("Respiratory virus"[All Fields] OR ("influenza s"[All Fields] OR "influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "influenza"[All Fields] OR "influenzas"[All Fields] OR "influenzae"[All Fields] OR ("influenza, human"[MeSH Terms] OR ("influenza"[All Fields] AND "human"[All Fields]) OR "human influenza"[All Fields] OR "flu"[All Fields])) OR "respiratory syncytial virus"[All Fields] OR ("parainfluenzae"[All Fields] OR "paramyxoviridae infections"[MeSH Terms] OR ("paramyxoviridae"[All Fields] AND "infections"[All Fields]) OR "paramyxoviridae infections"[All Fields] OR "parainfluenza"[All Fields]) OR ("metapneumovirus"[MeSH Terms] OR "metapneumovirus"[All Fields] OR "metapneumoviruses"[All Fields]) OR ("rhinovirus"[MeSH Terms] OR "rhinovirus"[All Fields] OR "rhinoviruses"[All Fields]) OR ("coronavirus"[MeSH Terms] OR "coronavirus"[All Fields] OR "coronaviruses"[All Fields]) OR ("adenoviridae"[MeSH Terms] OR "adenoviridae"[All Fields] OR "adenovirus"[All Fields] OR "adenoviridae infections"[MeSH Terms] OR ("adenoviridae"[All Fields] AND "infections"[All Fields]) OR "adenoviridae infections"[All Fields]) OR ("bocavirus"[MeSH Terms] OR "bocavirus"[All Fields] OR "bocaviruses"[All Fields]) OR ("common cold"[MeSH Terms] OR ("common"[All Fields] AND "cold"[All Fields]) OR "common cold"[All Fields] OR "cold"[All Fields] OR "cold temperature"[MeSH Terms] OR ("cold"[All Fields] AND "temperature"[All Fields]) OR "cold temperature"[All Fields]))
#2	("prenatal"[All Fields] OR "prenatally"[All Fields] OR "prenatals"[All Fields] OR ("antenatal"[All Fields] OR "antenatally"[All Fields]) OR "pregnan* "[All Fields] OR "matern* "[All Fields])
#3	#1 AND #2
#4	(("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "newborn"[All Fields] OR "newborns"[All Fields] OR "newborn s"[All Fields] OR "child* "[All Fields] OR ("infant"[MeSH Terms] OR "infant"[All Fields] OR "infants"[All Fields] OR "infant s"[All Fields]) OR ("offspring"[All Fields] OR "offspring s"[All Fields] OR "offsprings"[All Fields]) OR "prescholar"[All Fields] OR ("infant, newborn"[MeSH Terms] OR ("infant"[All Fields] AND "newborn"[All Fields]) OR "newborn infant"[All Fields] OR "baby"[All Fields] OR "infant"[MeSH Terms] OR "infant"[All Fields]))
#5	#2 AND #4
#6	("neurodevelopment*"[All Fields] OR "development*"[All Fields] OR "cogniti*"[All Fields] OR "emoti*"[All Fields] OR "behavior*"[All Fields] OR ("motor"[All Fields] OR "motor s"[All Fields] OR "motoric"[All Fields] OR "motorically"[All Fields] OR "motorics"[All Fields] OR "motoring"[All Fields] OR "motorisation"[All Fields] OR "motorised"[All Fields] OR "motorization"[All Fields] OR "motorized"[All Fields] OR "motors"[All Fields]) OR ("social behavior"[MeSH Terms] OR ("social"[All Fields] AND "behavior"[All Fields]) OR "social behavior"[All Fields] OR "sociality"[All Fields] OR "social"[All Fields] OR "socialisation"[All Fields] OR "socialization"[MeSH Terms] OR "socialization"[All Fields] OR "socialise"[All Fields] OR "socialised"[All Fields] OR "socialising"[All Fields] OR "socialities"[All Fields] OR "socializations"[All Fields] OR "socialize"[All Fields] OR "socialized"[All Fields] OR "socializers"[All Fields] OR "socializes"[All Fields] OR "socializing"[All Fields] OR "socially"[All Fields] OR "socials"[All Fields]) OR "psychologic* "[All Fields] OR "temperament* "[All Fields]))
#7	#4 AND #6

No additional filters regarding the time of publication, type of study nor language were used.

Search strategy in web of science

SOURCE	Clarivate
DATABASE	Web of Science Core Collection
DATE	November 24th, 2022
RESEARCHERS	N.SM-G & A.C-Q
LANGUAGE LIMITATIONS	Not applied
DATE LIMITATIONS	Not applied
OTHER FILTERS	Not applied

The systematic search was conducted independently by two authors (N.SM-G and A.C-Q) on the 24th of November 2022. The search was conducted as follows:

#1	ALL=
#2	(“Respiratory virus” OR (influenza OR flu) OR “respiratory syncytial virus” OR parainfluenza OR metapneumovirus OR rhinovirus OR coronavirus OR adenovirus OR bocavirus OR cold))
#3	#1 AND #2
#4	(prenatal OR antenatal OR pregnan* OR matern*))
#5	#2 AND #4
#6	(newborn OR child* OR infant OR offspring OR prescholar OR baby)
#7	#4 AND #6
#8	(neurodevelopment* OR development* OR cogniti* OR emoti* OR behavior* OR motor OR social OR psychologic* OR temperament*))
#9	#6 AND #8

No additional filters regarding the time of publication, type of study nor language were used.

Search strategy in APA PsycInfo®

SOURCE	EBSCO HOST
DATABASE	APA PsycInfo®
DATE	November 24th, 2022
RESEARCHERS	N.SM-G & A.C-Q
LANGUAGE LIMITATIONS	Not applied
DATE LIMITATIONS	Not applied
OTHER FILTERS	Not applied

The systematic search was conducted independently by two authors (N.SM-G and A.C-Q) on the 24th of November 2022. The search was conducted as follows:

#1	Any field:
#2	("Respiratory virus" OR (influenza OR flu) OR "respiratory syncytial virus" OR parainfluenza OR metapneumovirus OR rhinovirus OR coronavirus OR adenovirus OR bocavirus OR cold))
#3	#1 AND #2
#4	(prenatal OR antenatal OR pregnan* OR matern*))
#5	#2 AND #4
#6	(newborn OR child* OR infant OR offspring OR prescholar OR baby)
#7	#4 AND #6
#8	(neurodevelopment* OR development* OR cogniti* OR emoti* OR behavior* OR motor OR social OR psychologic* OR temperament*))
#9	#6 AND #8

No additional filters regarding the time of publication, type of study nor language were used.

Search in other sources

In addition to the systematic search, we identified possible articles in the following sources: 1) references of the articles identified; 2) hand-search in different journals; 3) doctoral theses repositories; 4) systematic and non-systematic reviews analyzing similar topics. None of the 4 articles identified by other sources were included since they had been previously identified in the systematic search or they did not fit the inclusion criteria to be included in this review. One article was included after journal's peer review process.

Selection process

The systematic search yielded a total of 6458 articles. After removing duplicates, articles were screened for title and then for abstracts and full text. Articles were screened independently by two researchers (N.SM-G and A.C-Q). Only in case of disagreement, a third author (L. M-F) helped to reach consensus.

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