Journal Pre-proof

Early behavioral markers for neurodevelopmental disorders in the first 3 years of life: An overview of systematic reviews

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PII: S0149-7634(20)30454-1

DOI: https://doi.org/10.1016/j.neubiorev.2020.06.027

Reference: NBR 3824

To appear in: *Neuroscience and Biobehavioral Reviews*

Received Date: 30 December 2019

Revised Date: 22 June 2020

Accepted Date: 23 June 2020

Please cite this article as: Micai M, Fulceri F, Caruso A, Guzzetta A, Gila L, Scattoni ML, Early behavioral markers for neurodevelopmental disorders in the first 3 years of life: An overview of systematic reviews, *Neuroscience and Biobehavioral Reviews* (2020), doi: https://doi.org/10.1016/j.neubiorev.2020.06.027

RUNNING HEAD: Early behavioral signs for neurodevelopmental disorders

Title: Early behavioral markers for neurodevelopmental disorders in the first 3 years of life: An overview of systematic reviews

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Highlights

- Motor, language development, and temperament in the first three years of life should be carefully investigated to detect neurodevelopmental disorders
- Repetitive/stereotyped behaviors, atypicalities or delays in play, object use, attention, visual and sensory processing, and social engagement are early signs of neurodevelopmental disorders in the first two years of life
- Systematic reviews exploring early markers of neurodevelopmental disorders are needed to build evidence-based surveillance tools.

Abstract

Being able to recognize red flags for neurodevelopmental disorders (NDD) is crucial to provide timely intervention programs. This work aims to support - within a scientific framework - the construction of an instrument capable to early detect all spectrum of NDD and explore all areas of development, detect failures in typical developmental pathways and point out atypical signs at all ages. This overview of reviews provides evidence for differences in children later diagnosed with NDD compared to typically developing peers such as delays in motor, language development and temperament in the first three years of age, repetitive/stereotyped behaviors, atypicalities/delays in play, object use, attention, visual, sensory processing and social engagement in the first and second year, and difficulties in feeding and sleeping in the first year. These behaviors must be carefully observed as potential red flags for NDD. However, data of the systematic reviews are not yet useful to develop an evidence-based clinical screening. It urges to increase efforts in producing systematic reviews on early behavioral markers for each NDD.

Trial registration: CRD42019137731
(https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42019137731).

Keywords: Infant, Neurodevelopmental Disorders, Primary Health Care, Infant Behavior, Neonatal Screening, Signs and Symptoms, Early Detection

Introduction

Neurodevelopmental disorders (NDD) encompass several conditions resulting from atypical brain development, including intellectual developmental disorders, communication disorders, Autism Spectrum Disorder (ASD), Attention Deficit Hyperactivity Disorder (ADHD), specific learning disorder, and motor disorders (DSM-5; American Psychiatric Association, 2013). Precise epidemiological data on NDD are lacking. However, a recent report shows a significant increase from 16.2% to 17.8% of developmental disabilities' prevalence (i.e., ADHD; ASD; blindness; cerebral palsy; moderate to profound hearing loss; learning disability; intellectual disability; seizures; stuttering or stammering; and other developmental delays) among children aged 3 to 7 years in the US between 2009–2017, making NDD one of the most frequent diagnosis in the pediatric population (Trauner, 2019). Much of the overall increase was attributed to ADHD, ASD, and intellectual disabilities (Zablotsky et al., 2019). Other studies showed that among NDD, learning disabilities are the most frequently diagnosed with an estimated prevalence of 8% (Boat & Wu, 2015), followed by developmental language disorders (7%; Laasonen et al., 2018), ASD (approximately 2%; e.g., Baio et al., 2018; Xu et al., 2018; Schendel & Thorsteinsson, 2018), and ADHD (approximately 2%; Willcutt, 2012; Boat & Wu, 2015).

The disorders included under the umbrella category of NDD are usually not considered as independent entities since impairments of different areas often co-occur and multiple diagnoses are the rule rather than the exception (Yeargin-Allsopp et al., 2008). This complexity is reflected upon the intervention program designs, which are typically individualized and focused on the functional impairments rather than merely derived from the diagnostic categorization. The Autism and Developmental Disabilities Monitoring Network study showed that in eleven sites in the US the median age of earliest known ASD diagnosis was 53 months (in the years range: 2000-2012) and about 43% of children received a comprehensive developmental evaluation by age 3 years (in the years range: 2006-2012; Baio et al., 2018). However, parents began to show concerns generally starting by the child age of 12 to 18 months (De Giacomo & Fombonne, 1998; Rogers & DiLalla, 1990; Wimpory et al., 2000; Coonrod, & Stone, 2004), suggesting that earlier detection of clinical signs is potentially achievable. The early identification of signs and symptoms of NDD is the real trigger to start intervention, even before a formal diagnosis is made, with the potential benefit of attenuating the severity of the symptoms and improving children and parents' outcomes (e.g., modifying their anxiety; depressive symptoms; self-efficacy) (Benzies et al., 2013; Cioni et al., 2016; Dawson et al., 2010; Landa et al., 2012; Oberklaid & Drever, 2011; Sullivan et al., 2014; Wetherby & Woods, 2006).

Several tools and methods are available to identify early behavioral markers of NDD. For instance, retrospective studies analyzed parental recall of developmental differences and concerns during the child's first years of life, such as language, speech, and motor delays or atypical sleep, feeding, or play behavior. Home video analyses are useful to recognize signs of peculiar development such as social and communicative competencies, verbal and nonverbal infant-parent interactions, affect regulation, temperament, or play actions. Finally, prospective studies of infants at risk of developing NDD (i.e., siblings of older children with

NDD, infants born preterm, or small for gestational age) begin observing and assessing them as early as 24-36 months. Children later diagnosed with NDD are compared with high-risk (HR) children that do not receive a diagnosis or those with typical development (Zwaigenbaum et al., 2007; 2009).

The present overview of reviews aims to methodically collect systematic reviews and meta-analyses on early markers of NDD before the three years of life. This approach has been proved to be useful in synthesizing, summarizing, and combining relevant data from the literature and in examining the highest level of evidence. The present work attempts to support the future definition of a scientific framework to build an instrument capable to early detect all spectrum of NDD and explore all areas of development, detect failures in typical developmental pathways and point out atypical signs at all ages.

Methods

Search strategy

The protocol for this systematic overview of reviews was registered with PROSPERO: CRD42019137731. This overview of reviews followed the guidelines of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Moher et al., 2009). The search strategy focused on Population, Intervention, Comparison, and Outcomes (PICO) domains. Population: 0-3-year-old children; Intervention: early behavioral signs of NDD; Outcome: neurodevelopmental disorders according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; American Psychiatric Association, 2013). The comparison was not applicable. We developed the search strategy using a combination of MeSH (Medical Subject Headings) and terms to capture the available literature on the topic. Details of the search strategy are presented in Table 1. This search strategy was peer-reviewed by clinicians and methodologist experts in the field.

The search strategy was adapted using appropriate syntax for the following databases: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed, MEDLINE, SCOPUS and Web of Sciences. When available, search filters were applied to limit the search to “Humans”, “Systematic Reviews” and “Meta-Analysis”. We performed the systematic search strategy of articles indexed since the inception to 27 March 2019. We updated searches for all relevant databases within 12 months before publication to 18 March 2020 (Chandler et al., 2013). No language and temporal restrictions have been applied. Conference abstracts, ongoing studies via ClinicalTrials.gov (www.clinicaltrials.gov) and ISRCTN registry were also searched for additional studies. Moreover, the reference lists from identified studies were scanned to identify any other relevant studies. We interrogated PROSPERO (www.crd.york.ac.uk/prospero/) to search for ongoing systematic reviews and OpenGrey (www.opengrey.eu/) to look for the gray literature (e.g., technical or research reports, doctoral dissertations, conference papers, official publications).

Table 1

Search strategy focused on Population, Intervention, Comparison, and Outcomes (PICO) for MEDLINE (Via OVID).

Domain	Search strategy
Population	"Infant"[Mesh:NoExp] OR "Infant, Newborn"[Mesh:NoExp] OR "Siblings"[Mesh] OR "Child"[Mesh] OR "Child, Preschool"[Mesh] OR "Minors"[Mesh] OR "Pediatrics"[Mesh] OR "Fetus"[Mesh:NoExp] OR toddler OR toddlers OR risk infant OR risk infants OR high risk infants OR high risk infant OR low risk infant OR low risk infants OR general population OR general populations OR risk marker OR risk markers OR genetic risk OR genetic risks OR familial risk OR familiar risks OR environmental risk OR environmental risks OR kid OR kids OR under age OR under ages OR kindergarten OR paediatric OR paediatrics OR foetus OR "Infant, Premature"[Mesh] OR "Premature Birth"[Mesh] OR "Infant, Extremely Premature"[Mesh] OR preterm OR "Infant, Small for Gestational Age"[Mesh] OR SGA OR small for gestational age OR infants, small for gestational age

	OR “Infant, Low Birth Weight"[Mesh] OR "Infant, Very Low Birth Weight"[Mesh] OR low for birth weight OR very low for birth weight
Intervention	"Primary Health Care"[Mesh:NoExp] OR "Primary Care Nursing"[Mesh] OR "Neonatal Screening"[Mesh] OR "Outcome and Process Assessment (Health Care)"[Mesh] OR "Symptom Assessment"[Mesh] OR "Signs and Symptoms"[Mesh:NoExp] OR red flag OR red flags OR early marker OR earlier marker OR early sign OR earlier sign OR early signs OR earlier signs OR surveillance protocol OR surveillance protocols OR surveillance OR developmental monitoring OR early identification OR earlier identification OR screening tool OR screening tools OR screening OR developmental screening OR screening instruments OR screening instruments OR symptom OR symptoms OR symptom assessment OR sign OR signs
Comparison	Not applicable
Outcome	"Neurodevelopmental Disorders"[Mesh:NoExp] OR "Developmental Disabilities"[Mesh] OR developmental delay OR developmental delays OR developmental difficulty OR developmental difficulties OR "Autistic Disorder"[Mesh] OR "Autism Spectrum Disorder"[Mesh] OR "Child Development Disorders, Pervasive"[Mesh] OR PDD OR "Asperger Syndrome"[Mesh] OR Autis* OR ASD OR Asperger OR Autistic OR Kanner OR "Attention Deficit Disorder with Hyperactivity"[Mesh] OR Pervasive development OR Pervasive developments OR pervasive disorder OR pervasive disorders OR "Communication Disorders"[Mesh] OR "Language Development Disorders"[Mesh] OR "Social Communication Disorder"[Mesh] OR "Speech Sound Disorder"[Mesh] OR "Stuttering"[Mesh] OR receptive language disorders OR receptive language disorder OR "Language disorders"[MeSH] OR "speech disorders" [MeSH] OR "developmental language disorders"[MeSH] OR "Intellectual Disability"[Mesh] OR "Motor Disorders"[Mesh] OR "Motor skills disorders" [MeSH] OR motor disorder OR "Learning Disorders"[Mesh] OR "Specific Learning Disorder"[Mesh]
Limits	"Neoplasms"[Mesh] OR "Mass Screening"[Mesh]

Selection process

We collected the papers arising from the search strategy in the Systematic Review Rayyan QCRI application (Ouzzani et al., 2016) which also supported the authors in the exclusion of duplicates. Two blinded reviewers, with the support of a third reviewer, screened titles and abstracts, and excluded the papers that did not clearly meet the inclusion criteria. The same authors evaluated the selected papers in their full text for inclusion criteria. Systematic reviews and meta-analyses were included in the present overview of reviews if: (1) reported early behavioral markers for NDD; (2) assessed children younger than 36 months of age in at least 20% of the number of studies. We excluded nonsystematic reviews where studies’ search strategy, selection process, and data extraction process were not specified

(e.g., narrative reviews), and reviews exploring early markers using health technologies (e.g., electroencephalography; eye-tracking). The present overview aims to provide evidence on early behavioral markers that can be easily detected in the clinical practice context.

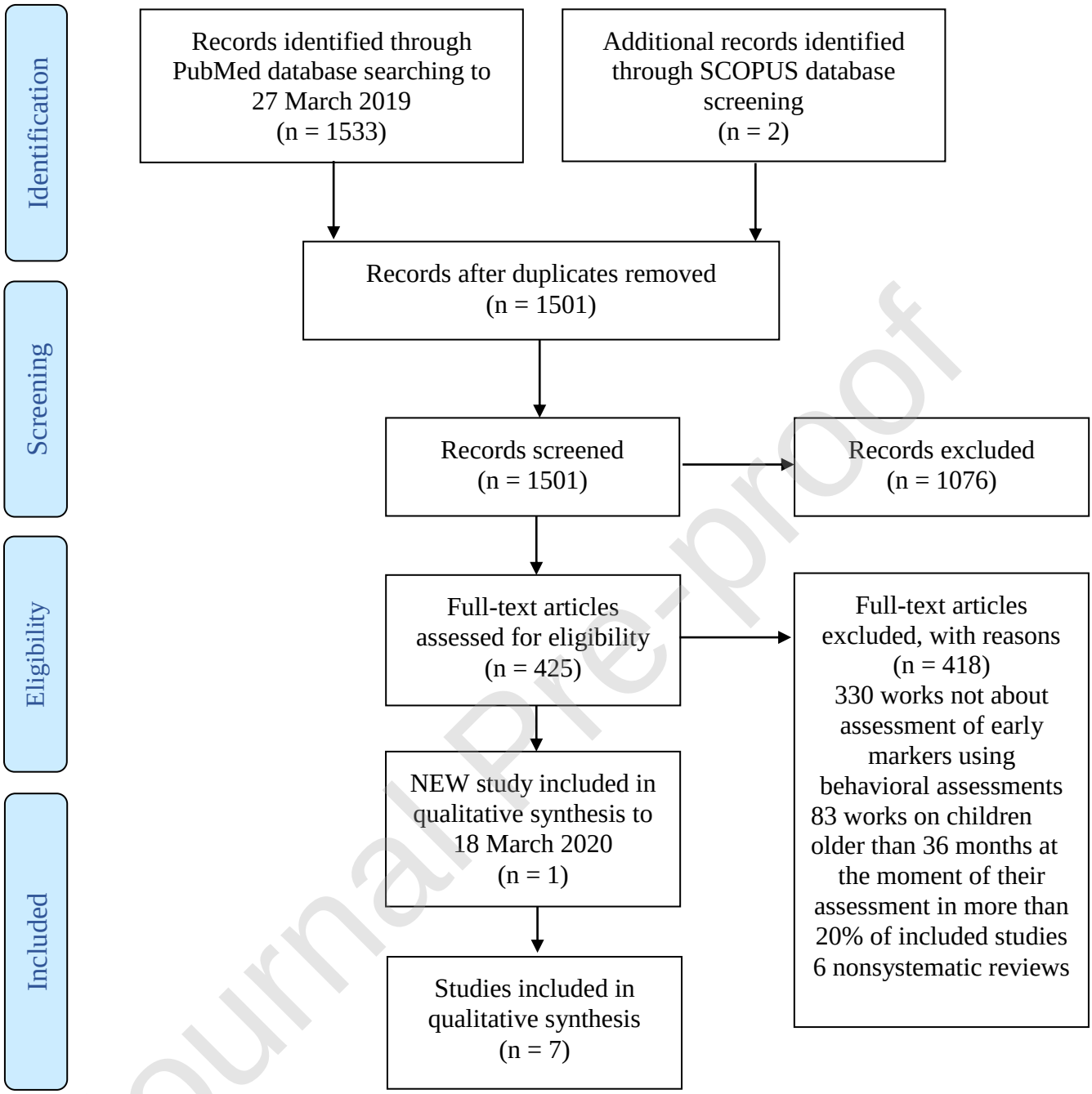

Fig. 1. Flow chart of the literature selection process.

Data extraction and synthesis

To ensure consistency across reviewers, we conducted calibration exercises before starting to extract the data. Three independent reviewers fulfilled a developed data extraction

form (available on request). The data from the included full-texts were extracted and independently cross-checked. We collected data on the target population, early marker assessment tools, age at assessment of the early marker (Table 2), general information about the review (i.e., type of study; funding), methods (i.e., temporal and language restrictions; datasets explored; PICO domains; type of studies included; search strategy; inclusion and exclusion criteria; number of records identified via database searching; number of included studies; gray literature check; references check; risk of bias; publication bias assessment), sample characteristics (i.e., target population - at risk or general population or with NDD symptoms; age at the assessment of the early marker; diagnosis type; assessment instrument) (see Supplementary Material 2). For the meta-analyses, we additionally collected the timepoints of the early markers' assessment, assessment tools, number of studies included in the analysis, sample size, effect size, Confidence Intervals, heterogeneity analysis results, publication bias analysis results, and other sub-analyses (e.g., socioeconomic status and gender as predictors of language outcomes in Fisher et al., 2017). We performed a formal narrative synthesis of the findings from the selected works by grouping the early behavioral markers in developmental domains (e.g., motor, language, social development) and age group (i.e., first, second and third year of life).

Quality assessment of the evidence

The quality of all eligible systematic reviews using the 16-item AMSTAR 2 checklist (Shea et al., 2017) was evaluated for each work by two independent authors. Any disagreements were solved in conjunction with a third author. The AMSTAR 2 checklist has been designed for the quality assessment of systematic reviews, including randomized or non-randomized studies of healthcare interventions, or both. Authors assigned to each domain-specific questions a 'Yes' answer if the rationale described in Shea and colleagues

were satisfied. If no information was provided to rate an item, the item was rated as a 'No'. We provided a 'Partial Yes' response when the rationale of Shea and colleagues was partially satisfied. AMSTAR questions were the following: (1) inclusion of PICO components, (2) protocol registered before the commencement of the review, (3) selection of the study designs for inclusion, (4) adequacy of the literature search, (5) study selection in duplicate, (6) data extraction in duplicate, (7) justification for excluding individual studies and list of excluded studies, (8) detailed description of the included studies, (9) risk of bias from individual studies being included in the review, (10) report on the source of funding for the studies included, (11) appropriateness of meta-analytical methods, (12) assessment of the risk of bias in individual studies on the results, (13) consideration of the risk of bias when interpreting the results of the review, (14) explanation for, and discussion of, heterogeneity observed in the results, (15) assessment of the presence and likely impact of publication bias, (16) report any potential source of conflict of interest (Shea et al., 2017). Inter-rater reliability was calculated using intra-class correlations (McGraw & Wong, 1996). Figure 2 summarizes the AMSTAR 2 results. Scores on each domain-specific questions are reported in Supplementary Material 1.

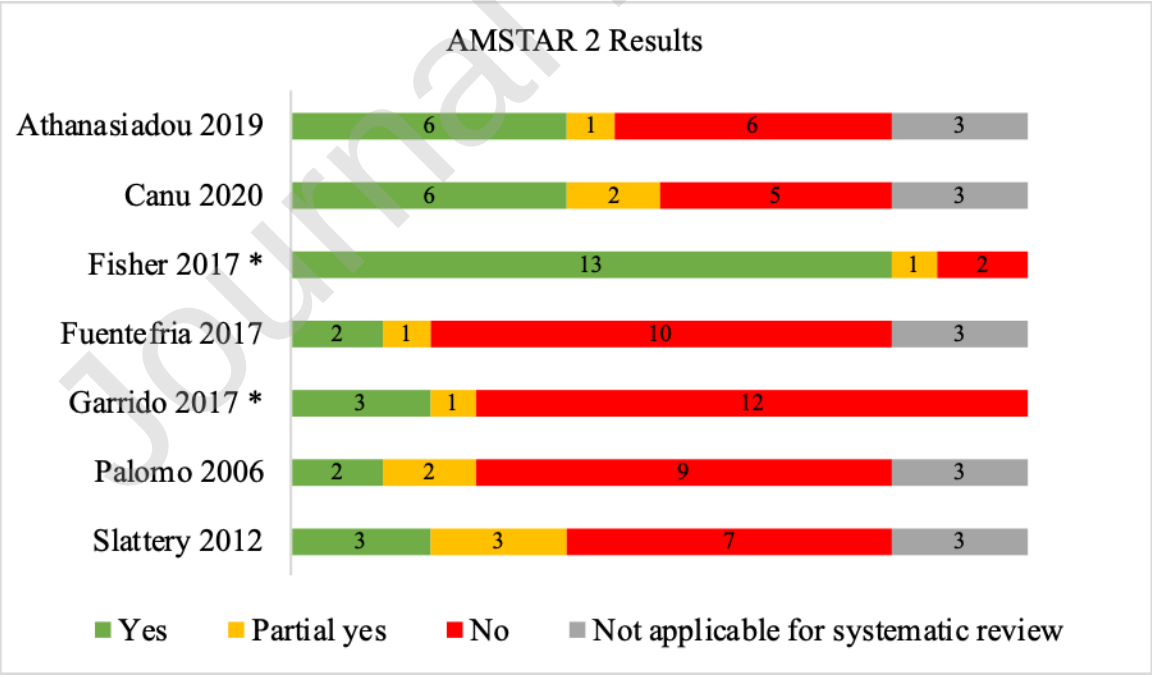

Fig. 2. Summary of the quality assessment score of the included systematic reviews and meta-analyses assessed with AMSTAR 2 checklist. *: meta-analysis. Scores on each domain specific questions were coded as 'Yes', 'No', 'Partial yes', or not applicable for meta-analysis.

Results

Description of studies

The search strategy to 27 March 2019 provided 1,535 works (PubMed, n = 1,533; SCOPUS, n = 2, and none in the other databases). One author removed 34 duplicates. 1,501 works were screened for inclusion and exclusion criteria. Based on the titles and abstracts screening, 1,076 not pertinent works were excluded by at least two independent authors. The remaining 425 works were checked in their full text. Two independent authors excluded 330 works failing to assess early markers using behavioral assessments. Studies exploring early markers thought clinical observation or parental questionnaires were kept. Studies exploring biological markers, assessment of test accuracy, or studies that used health technologies such as functional brain imaging or eye-tracking were excluded. In addition, were excluded 83 works that assessed children older than 36 months of age in more than 20% of the number of included studies. Conflicts were solved between the two authors, but for 19 works the consultation of a third independent author was required. Finally, we evaluated eligible for the data extraction process two meta-analyses (Garrido et al., 2017; Fisher, 2017) and four systematic reviews (Athanasiadou et al., 2019; Fuentefria et al., 2017; Palomo et al., 2006; Slattery et al., 2012). Six works were excluded because of nonsystematic reviews. We performed updated searches for all relevant databases within 12 months before publication to 18 March 2020 which provided 92 works (PubMed, n = 92; SCOPUS, n = 1, and none in the other databases). No duplicates were encountered. Based on the titles and abstracts screening, 92 not pertinent works were excluded by at least two independent authors. One systematic review (Canu et al., 2020) was checked in its full text and was evaluated eligible for the data

extraction process. Figure 1 provides the process of records' identification and screening, and the eligibility and inclusion actions (Moher et al., 2009).

A meta-analysis of the extracted data was not possible since data of the systematic reviews were mostly qualitative and heterogeneous in the description of different neurodevelopmental components. The seven eligible works were informative on behavioral signs alarming for NDD at different ages. We excluded 13 Canu and colleagues' studies as they explored early markers using health technologies (i.e., eye tracking; gap-overlap task). The red flags for the identification of the risk for NDD in high-risk (HR) and low-risk (LR) population pertained mainly to the motor, language, social developmental, play, and temperament domains. Findings, target population, time, and tool of assessment of the early behavioral markers for NDD are displayed for each developmental domain in Table 2. None of the studies provided evidence that the protocol was registered prior to conducting the review or included conflict of interest statements for individual studies within the systematic review. All studies were written in English. All studies declared to have no conflict of interests except for two that did not provide this information.

Table 2

Summary of the results of the systematic reviews and meta-analyses on early behavioral markers for neurodevelopmental disorders.

Reference	Population	Assessment	Finding
Motor development			
			First year of life
Athanasiadou (2019)	HR for NDD, healthy term infants	GMs	Milder GMs abnormalities during the first months of life associated with ADHD, aggressive behavior and minor neurological dysfunction at 4-9-year follow-up (Hadders-Algra & Groothuis, 1999). GMs abnormalities are associated with ADHD together with co-occurrence of psychiatric diagnosis. Fidgety abnormalities associated with problematic and hyperactive behavior at 12 years of age (Hadders-Algra et al., 2009). Spontaneous movement quality at 11-16 weeks showed a positive association with IQ and a trend to an association with attention problems at 7-11 years in preterm born infants (Butcher et al., 2009).
	ADHD, controls	DDST	Gross motor developmental delay in ADHD children at 3 and 9 months of age (Gurevitz et al., 2014).
		NBAS	Less motor maturity at 7/10 days correlated with hyperactivity in children in kindergarten (Jacobvitz & Sroufe, 1987).
		Mother interview	Inability to sit up straight when put on lap (at 6 months) associated with very early or delay in independent walking in ADHD children (Lemcke et al., 2016).
	ADHD	VWS	Good gross motor skills predicted ADHD signs (Jasper et al., 2013).
		SSMTS	Motion variables at 12 months not associated with ADHD at 7 years (Johnson et al., 2014).
Canu (2020)	HR-ASD, HR-TD, HR-DD, LR	ADOS-G, AOSI, Skilled Reaching Rating Scale	No motor impairment in motor control and general motor behavior at 6-12 months of age (Brian et al., 2008). Poorer reach-to-grasp and pronate scores in HR-ASD than HR-TD, and LR. Poorer orient and lift in HR-ASD than LR (Sacrey et al., 2018).

		MSEL	Poorer gross motor skills in HR-ASD than LR at 6 months (Estes et al., 2015). HR-ASD and HR-TD did not differ in gross motor skills at 6 months; poorer fine motor skills in HR-ASD, HR-DD, and HR-TD than LR, not confirmed by post doc comparisons (Libertus et al., 2014). Fine (but not gross) motor skills predicted ASD at 36 months (Iverson et al., 2019). Lower increased motor milestones over time in HR-ASD than HR-TD (Landa & Garrett-Mayer, 2006). HR-ASD, LR, and HR-TD did not differ in fine motor skills (Choi et al., 2018). HR-ASD more likely assigned to the developmental slowing class (TD at 6 months followed by attenuation in developmental rate and severe fine and gross motor delay) than to HR-TD. Broader Autism Phenotype assigned to normative class or language/motor delay class (fine motor delay at 6 months followed by normative development in all areas except in motor development) (Landa et al., 2012).
		PDMS2	Worse visual motor integration in HR-ASD than LR, but no differences in stationary and grasping at 6 months. Visual-motor integration at 6 months predicted ASD at 24-36 months (LeBarton & Landa, 2019).
	HR, TD	Infants seated in a booster seat. Object presented	Less grasping of the rigid ball in HR than TD at 6 months. Between 6 and 9 months: increased grasping of the rigid ball and rattle in HR; reduced grasping of the rigid ball in LR. Between 9 and 12 months: increased grasping of the koosh ball in HR; increased grasping of the rattle in LR. Less dropping of the rigid ball in HR than LR at 6 months, more dropping of objects in HR than LR from 6 to 9 months. Delayed increase in dropping in HR from 12 to 15 months; increased dropping of objects in LR from 6 to 9 months. Less mouthing of the rattle in HR than LR at 6 months (Kaur et al., 2015).
Fuentefria (2017)	Moderate preterm	AIMS	Abnormal motor development at 3 and 9 months were not predictive of motor delay at 4 years of age (in 80%) (Prins et al., 2010).
	Very preterm	AIMS, NSMDA	Early motor skills at 4 months of life predicted motor impairment at 4 years in very preterm children (Spittle et al., 2015).
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer fine motor skills in ASD siblings than LR (small effect size, SMD = -.21, 95% CI [-.39, -.04], n = 1542, k = 12) (Chawarska et al., 2013; Curtin & Vouloumanos, 2013; Ekberg et al., 2016; John et al., 2016; Leonard et al., 2015; Libertus et al., 2014; Macari et al., 2012; Mulligan et al., 2012; Ozonoff et al., 2014; Paul et al., 2011; Young et al., 2011). Poorer gross motor skills in ASD siblings than LR children (small effect size, SMD = -.22, 95% CI [-.40, -.04], n = 738, k = 7) (Curtin et al., 2013; John et al., 2016; Elison et al., 2014; Paul et al., 2011; Leonard et al., 2015; Libertus et al., 2014).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD, and ID and TD differed in unusual posture (Baranek, 1999).
Slattery (2012)	Preterm	NOMAS	Infants with a persistent disorganized sucking pattern after 37 weeks had lower psychomotor developmental scores than infants who regained a normal sucking pattern by 37 weeks old, at 6 and 12 months (Tsai et al., 2010).
			Second year of life
Athanasiadou (2019)	ELBW	NSMDA	Motor development at 24 months (not 12 months) was associated with clinical measures of attention at 7-9 years (Jeyaseelan et al., 2006).

	ADHD, controls	DDST	Gross motor developmental delay in ADHD at 18 months of age (Gurevitz et al., 2014).
Canu (2020)	HR-ASD, HR-TD, LR	ADOS-G, AOSI Skilled Reaching Rating Scale	Atypical motor behavior in HR-ASD than HR-TD and LR. Abnormal motor control in HR-ASD than LR at 18 months (Brian et al., 2008).
		MSEL	Lower scores in Gross and Fine motor scales in HR-ASD than HR-TD and LR at 24 months (Estes et al., 2015). Lower increase over time of motor milestones in HR-ASD than HR-TD (Landa & Garrett-Mayer, 2006). Lower fine motor skills in HR-ASD than HR-TD at 12 months and LR at 18 months. Slower growth rate of fine motor milestones in HR-ASD than LR, but not compared to HR-TD from 6 to 24 months (Choi et al., 2018).
		Home videos	HR-ASD, HR-TD and LR did not differ in postures at 14 months (Nickel et al., 2013).
	HR, TD	Infants seated in a booster seat. Object presented	Lower level of dropping in HR than LR from 12 to 15 months. Delayed increase in dropping in HR than LR from 12 to 15 months; more mouthing of the rattle and rigid ball in HR than LR at 15 months (Kaur et al., 2015).
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer fine motor skills in ASD siblings than LR (small-to-moderate effect size, SMD = -.35, 95% CI [-.46, -.24], *n* = 3177, *k* = 11) (John et al., 2016; Leonard et al., 2015; Macari et al., 2012; Messinger et al., 2015; Ozonoff et al., 2014; Presmanes et al., 2007; Paul et al., 2011; Stone et al., 2007; Toth et al., 2007; Young et al., 2009; 2011). Poorer gross motor skills in ASD siblings than LR (not statistically significant effect, SMD = -.36, 95% CI [-1.20, .05], *n* = 377, *k* = 4) (John et al., 2016; Leonard et al., 2015; Paul et al., 2011; Toth, 2007).
			Third year of life
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer fine motor skills in ASD siblings than LR (small-to-moderate effect size, SMD = -.36, 95% CI [-.54, -.17], n = 2906, k = 6) (Klerk et al., 2014; Leonard et al., 2015; Messinger et al., 2015; Miller et al., 2015; Ozonoff et al., 2014; Schwichtenberg et al., 2013). ASD siblings and LR differed in gross motor skills (SMD = -.44, 95% CI [-.83, -.04], n = 101, k = 1) (Leonard et al., 2015).
Language development			
			First year of life
Athanasiadou (2019)	ADHD, controls	DDST	Significant delay in speech and language development at 9 and 18 months of age in ADHD (Gurevitz et al., 2014).
		Parent observation	Delay in language development in ADHD (Lemcke et al., 2016).
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer expressive language skills in ASD siblings than LR children (moderate effect size, SMD = -.40, 95% CI [-.57, -.23], n = 2044, k = 18) (Chawarska et al., 2013; Curtin & Vouloumanos, 2013; Droucker et al., 2013; Ekberg et al., 2016; Ference & Curtin,

			2013; Hudry et al., 2014; Key & Stone, 2012; Lazenby et al., 2016; Leonard et al., 2015; Libertus et al., 2014; Macari et al., 2012; Mitchell et al., 2006; Mulligan et al., 2012; Ozonoff et al., 2014; Paul et al., 2011; Young et al., 2011; Zwaigenbaum et al., 2005). Poorer receptive language skills in ASD siblings than LR (moderate effect size, SMD = -.44, 95% CI [-.53, -.34], n = 1694, k = 15) (Chawarska et al., 2013; Curtin & Vouloumanos, 2013; Ekberg et al., 2016; Ference & Curtin, 2013; Hudry et al., 2014; Key & Stone, 2012; Lazenby et al., 2016; Leonard et al., 2015; Libertus et al., 2014; Mitchell et al., 2006; Mulligan et al., 2012; Paul et al., 2011; Ozonoff et al., 2014; Zwaigenbaum et al., 2005).
Palomo (2006)	ASD, ID, TD	Home video	ASD and TD differed in simple vocalizations, bubbling complex vocalizations, and words (Maestro et al., 2002; Werner & Dowson, 2005). ASD and TD did not differ in follows verbal instructions, simple vocalizations, bubbling complex vocalizations, and words (Osterling & Dowson, 1994; Osterling et al., 2002; Maestro et al., 2001; Werner et al., 2000).
			Second year of life
Fisher (2017)*	Late-talkers	Language assessment[1]	Preschool-age expressive-vocabulary size accounted for the 6% of the variability in expressive-language outcome (r = .249, p < .01, 95% CI [.133, .358], n = 1113, k = 12) (Dale et al., 2003; Moyle et al., 2007; Hadley et al., 2006; Lee, 2011; Fernald & Marchman, 2012; Peyre et al., 2014; Whitehurst et al., 1991; Bishop et al., 2012; Thal et al., 1991; Rescorla & Schwartz, 1990; Carson et al., 2003).
		Language assessment[2]	Preschool-age receptive language accounted for the 12% of the variability in expressive-language outcome (r = .340, p < .01, 95% CI [.215, .454], n = 527, k = 10) (Rescorla & Schwartz, 1990; Petinou & Spanoudis, 2014; Paul et al., 1991; Henrichs et al., 2011; Hadley et al., 2006; Vuksanovic, 2015; Fischel et al., 1989; Bishop et al., 2012; Lyytinen et al., 2005; Thal et al., 1991).
		Language assessment[3]	Nonsignificant main effect of the correlation between preschool-age phrase speech and expressive-language outcome. Preschool-age phrase speech accounted for the 2% of the variability in expressive-language outcome (r = .122, p = .098, 95% CI [-.022, .261], n = 851, k = 7) (Williams & Elbert, 2003; Hadley et al., 2006; Moyle et al., 2007; Dale et al., 2003; Thal et al., 1991; Rescorla & Schwartz, 1900; Fischel et al., 1989).
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer expressive language skills in ASD siblings than LR (moderate effect size, SMD = -.34, 95% CI [-.45, -.23], n = 3590, k = 18) (Mitchell et al., 2006; Gamliel et al., 2007; Presmanes et al., 2007; Stone et al., 2007; Toth et al., 2007; Yirmiya et al., 2007; Young et al., 2009, 2011; Paul et al., 2011; Macari et al., 2012; Curtin & Vouloumanos, 2013; Droucker et al., 2013; Hudry et al., 2014; Ozonoff et al., 2014; Gangi et al., 2015; Leonard et al., 2015; Messinger et al., 2015; Talbott et al., 2015). Poorer receptive language skills in ASD siblings than LR (moderate effect size, SMD = -.52, 95% CI [-.68, -.37], n = 3243, k = 15) (Mitchell et al., 2006; Gamliel et al., 2007; Presmanes et al., 2007; Stone et al., 2007; Toth et al., 2007; Yirmiya et al., 2007; Young et al., 2009; Paul et al., 2011; Macari et al., 2012; Curtin & Vouloumanos, 2013; Hudry et al., 2014; Ozonoff et al., 2014; Gangi et al., 2015; Leonard et al., 2015; Messinger et al., 2015).

Palomo (2006)	ASD, PDD, TD	Home video	ASD and TD differed in following verbal instructions, making bubbling complex vocalizations, imitating vocalizations, pronouncing words, and two words/phrases (Mars et al., 1998; Maestro et al., 2001; Werner & Dowson, 2005). ASD and TD did not differ in making simple vocalizations (Maestro et al., 2001).
			Third year of life
Garrido (2017)*	ASD Siblings, LR infants	MSEL	Poorer expressive language skills in ASD siblings than LR (moderate effect size, SMD = -.44, 95% CI [-.58, -.30], n = 3422, k = 12) (Gamliel et al., 2007; Yirmiya et al., 2007; Young et al., 2011; Herlihy et al., 2013; Ibañez et al., 2013; Schwichtenberg et al., 2013; Klerk et al., 2014; Miller et al., 2015; Ozonoff et al., 2014; Gangi et al., 2015; Leonard et al., 2015; Messinger et al., 2015). Poorer receptive language skills in ASD siblings than LR (moderate effect size, SMD = -.48, 95% CI [-.60, -.36], n = 3422, k = 12) (Gamliel et al., 2007; Yirmiya et al., 2007; Young et al., 2011; Herlihy et al., 2013; Ibañez et al., 2013; Schwichtenberg et al., 2013; Klerk et al., 2014; Miller et al., 2015; Ozonoff et al., 2014; Gangi et al., 2015; Leonard et al., 2015; Messinger et al., 2015).
Temperament			
			First year of life
Athanasiadou (2019)	ADHD, controls	Parent description	Difficult temperament more frequent in children with ADHD at 9 months (Gurevitz et al., 2014).
Canu (2020)	HR-ASD, HR-TD, LR	CTS (RITQ, TTQ, BSQ)	Lower scores in adaptability scale in HR-ASD than HR-TD at 6 and 12 months. Lower score on the approach scale in HR-ASD than HR-TD at 6 months. Less active behavior in HR-ASD than HR-TD at 6 and 12 months, but not later (del Rosario et al., 2014).
		IBQ, TBAQ or TBAQ-R	Higher scores in distress to limitations and fear in HR than LR at 12 months. Positive affect at 12 months predicted ASD symptoms at 36 months in HR infants (relationship mediated by effortful control at 24 months). Lower activity level at 6 months and more frequent and intense distress reactions, less inhibitory control, less positive anticipation and affective responses at 12 months in HR-ASD than HR-TD and LR (Zwaigenbaum et al., 2005)
		IBQ-R, ECBQ	Lower surgency scores in HR-ASD than HR-TD and LR from 8 to 14 months. Higher negative affect in HR-ASD than HR-TD, HR-DD and LR from 8 months (Pijl et al., 2019).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in positive affect (including social smiles) and conventional communicative gestures (Maestro et al., 2001, 2002; Werner et al., 2002), but no differences for Maestro et al., (2001) and Werner & Dawson (2005). ASD and TD did not differ in negative affect, conventional communicative gestures, moving hands toward desired objects, and vague pointing reaching (Mars et al., 1998; Werner & Dawson, 2005).
			Second year of life
Canu (2020)	HR-ASD, HR-TD, HR-DD, LR	ADOS-G, AOSI	Higher scores on transition and levels of reactivity in HR-ASD than HR-TD and LR at 18 months. Transition and reactivity predicted ASD at 36 months (Brian et al., 2008).
		CTS (RITQ,	Higher score in HR-ASD than HR-TD at 24 and 36 months (del Rosario et al., 2014).

		TTQ, BSQ)	
		IBQ, TBAQ or TBAQ-R	Higher scores on fear, sadness, anger, and lower on inhibitory control, soothability, attention focus, high pleasure, and low pleasure in HR than LR at 24 months. Lower effortful control score at 24 months predicted more ASD symptoms at 36 months (Garon et al., 2016). Lower scores on behavioral approach in HR-ASD than HR-TD and LR at 24 months; HR-TD scored higher than LR. Lower score on emotion regulation in HR-ASD and HR-TD than LR. Below average on behavioral approach and effortful emotion regulation in the 65% of HR-ASD. Higher than average behavioral approach and lower effortful emotion regulation in the 74% of HR-TD. Higher than average effortful emotion regulation in the 70% of LR. Behavioral approach better discriminated between HR-ASD and HR-TD than effortful emotion regulation. Effortful emotion regulation better discriminated between HR-ASD and LR than behavioral approach (Garon et al., 2009).
		IBQ-R, ECBQ	Lower effortful control in HR-ASD than HR-DD, HR-TD and LR at 14 months and at 24 months. A combination of surgency, negative affect and effortful control at 24 months as well as effortful control at 14 months and effortful control and negative affect at 24 months predicted ASD (Pijl et al., 2019).
			Third year of life
Canu (2020)	HR-ASD, HR-TD, LR	CTS (RITQ, TTQ, BSQ)	Higher score in HR-ASD than HR-TD at 24 months and 36 months (del Rosario et al., 2014).
Repetitive/stereotyped behavior			
			First year of life
Canu (2020)	HR-ASD, HR-TD, LR	RSMs, MSEL, VABS	Higher scores on the object and body cluster subscale in HR-ASD and HR-TD than LR at 12 months (Elison et al., 2014). More parental concerns about repetitive and restricted behaviors in HR-ASD than LR starting from 9 months (Sacrey et al., 2015).
		ADOS-G, AOSI	More repetitive interests in HR-ASD than HR-TD and LR at 6-12 months (Brian et al., 2008).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in repetitive motor behaviors and stereotypies (Osterling et al., 2002). ASD and TD did not differ for repetitive motor behaviors and stereotypies (Baranek, 1999; Osterling & Dowson, 1994; Werner & Dowson, 2005). ASD, ID, and TD did not differ in repetitive motor behaviors and stereotypies (Baranek, 1999; Mars et al., 1998; Osterling & Dowson, 1994; Werner & Dowson, 2005).
			Second year of life
Canu (2020)	HR-ASD, HR-TD, LR	ADOS, MSEL	Repetitive behaviors predicted ASD outcome at 18 months in HR-ASD (Chawarska et al., 2014).

		MSEL, VABS	More concerns about repetitive and restricted behaviors in HR-ASD parents than HR-TD parents from 18 months (Sacrey et al., 2015).
		RSMs	Higher rates of RSMs in HR than LR at 12-24 months (Damiano et al., 2013).
			Third year of life
Canu (2020)	HR-ASD, HR-TD, LR	RSMs	Higher rates of RSMs in HR than LR at 24–36 months. Higher object RSM inventory score than the body RSM inventory score in HR-TD but not in HR-ASD (Damiano et al., 2013).
Play and object use			
			First year of life
Canu (2020)	HR-ASD, HR-TD, LR	Parent concerns' interview	Poorer play skills in HR-ASD than HR-TD and LR at 9 months (Sacrey et al., 2015).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD differed than TD and ID in mouthing objects (Baranek, 1999). No differences between ASD and TD in nonsocial gaze/looking at the object not being held by another person/orienting to nonsocial novel stimulus, appropriate use of the object, exploratory activities with the object, and symbolic play (Maestro et al., 2001, 2002; Osterling et al., 2002; Werner & Dowson, 2005; Werner et al., 2000). ID and TD differed in object play rating (i.e., flexibility, variety, appropriateness) (Baranek, 1999).
			Second year of life
Canu (2020)	HR-ASD, HR-TD, HR-DD, LR	Free play assessment	Fewer novel other-directed functional play in HR-ASD than LR at 18 months. Greater levels of non-functional repeated play in HR-ASD than LR (no effect when controlling for verbal age). More nonfunctional repeated play in HR-TD than LR. No between-group difference in symbolic and functional repeated play. HR-DD, HR-TD and LR did not differ on novel functional play (Christensen et al., 2010).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in nonsocial gaze/looking at the object being held by another person/orienting to nonsocial novel stimulus, appropriate use of the object, exploratory activity with the object, and symbolic play (Mars et al., 1998; Maestro et al., 2001; Werner & Dowson, 2005).
Social domain			
			First year of life
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in social orienting and interactions (i.e., to seek out physical contact; anticipate intentions of other; look at the people; face and camera; respond when called by name; avoid physical-social contacts) (Baranek, 1999; Maestro et al., 2001, 2002; Osterling & Dawson, 1994; Osterling et al., 2002; Werner et al., 2000). ASD and TD did not differ in postural attunement, participating in reciprocal social games, imitating actions (Maestro et al., 2001, 2002; Osterling & Dawson, 1994; Osterling et al., 2002; Werner et al., 2000). ASD and TD differed in understanding pointing, looking at the object held by others, and initiating

			pointing to request, and sharing interests (Maestro et al., 2001; Osterling & Dawson, 1994; Osterling et al., 2002; Werner & Daswon, 2005). ASD and TD did not differ in shared attention, gaze alternation and conventional communicative gestures, vague pointing/ reaching (Maestro et al., 2001; Osterling & Dowson, 1994). ID and TD differed in looking at the faces and people, responding when called by name, avoiding physical social contacts, initiating pointing to request, and looking at the object held by others (Baranek, 1999; Osterling et al., 2002). ID and TD did not differ in participating in reciprocal social games (Osterling et al., 2002).
			Second year of life
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in social engagement, looking at people and faces, and responding when called by names (Mars et al., 1998, Werner & Dowson 2005). ASD and TD did not differ in seeking out physical contact, anticipating intentions of other, avoiding physical contact, postural attunement, participating in reciprocal social games, and imitating actions (Maestro et al., 2001; Mars et al., 1998). ASD and TD differed in shared attention, gaze alternation, and initiating pointing to share interest (Maestro et al., 2001; Mars et al., 1998; Werner & Dowson, 2005). ASD and TD did not differ in understanding pointing, looking at the object holds by others, gaze alternation, and initiating pointing to request (Maestro et al., 2001; Mars et al., 1998; Werner & Dawson, 2005).
Sensory processing			
			First year of life
Canu (2020)	HR-ASD, HR-TD, LR	ADOS-G, AOSI	Atypical sensory oriented behavior at 12 months (but not at 6 months) in AOSI predicted ASD at 24 months (Zwaigenbaum et al., 2005).
		MSEL, VABS, parents' interview	More sensory concerns in HR-ASD parents than HR-TD and LR parents at 6 and 9 months (Sacrey et al., 2015).
		SEQ	Higher scores in sensory hyperresponsivity in HR-ASD than HR-TD and LR. Higher scores in tactile modality in HR-ASD than HR-TD at 12 months (Wolff et al., 2019).
Palomo (2006)	ASD, ID, DD, TD	Home video	ID and TD differed in the unusual visual inspection (fixation staring). No group differences in unusual visual inspection, orienting to tactile nonsocial novel stimulus between, orienting to auditory nonsocial novel stimulus, and aversive response to auditory stimulation (Baranek, 1999; Osterling & Dowson, 1994).
			Second year of life
Canu (2020)	HR-ASD, HR-TD, LR	ADOS-G, AOSI	Higher score on the subscale for atypical sensory behavior in HR-ASD and HR-TD than LR at 18 months (Brian et al., 2008).
		ITSP	Higher scores in auditory processing in HR-ASD than HT-TD and LR at 24 months; HR-TD and LR did not differ. Groups did not differ in visual, tactile, vestibular and oral domains (Germani et al., 2014).

		SEQ	Increased total score, hyperresponsivity and visual modality in HR-ASD and HR-TD from 12 to 24 months. Higher scores in all subtests in HR-ASD than HR-TD at 24 months (Wolff et al., 2019).
Palomo (2006)	ASD, ID, DD, TD	Home video	ASD and TD differed in the unusual visual inspection, and aversive response to auditory stimulation (Mars et al., 1998).
Visual processing			
			First year of life
Canu (2020)	HR-ASD, HR-TD, HR-DD, LR	MSEL	Lower scores on the Visual Reception scale in HR-ASD than LR at 6 months. HR-ASD, HR-TD and LR did not differ on the Visual Reception scale at 12 months (Estes et al., 2015). HR-ASD more likely assigned to the developmental slowing class (TD at 6 months followed by attenuation in developmental rate and severe delay in visual processing) than HR-TD. HR-DD assigned to normative class (normative visual processing development; Landa et al., 2012). HR-ASD and HR-TD did not differ on the Visual Reception scale at 6 months (Libertus et al., 2014).
	HR, LR	Infants seated in a booster seat. Object presented	Excessive visual exploration of objects, irrespective of the novelty of the objects (i.e., excessive looking at the rattle at 6 months and at the koosh ball at 12 months) in HR than LR. Increased looking at the koosh ball in LR but not in HR at 12 to 15 months (Kaur et al., 2015).
			Second year of life
Canu (2020)	HR-ASD, HR-TD, LR	MSEL	Lower scores on the Visual Reception scale in HR-ASD than HR-TD and LR at 24 months (Estes et al., 2015). HR-ASD and HT-TD did not differ in visual processing at 14 months. Lower increase over time in HR-ASD than HT-TD. Lowest increase over time in HR-ASD (Landa & Garrett-Mayer, 2006).
		ITSP	HR-ASD, HR-TD, and LR did not differ in visual processing at 24 months (Germani et al., 2014).
	HR, LR	Infants seated in a booster seat. Object presented	Increased looking at the koosh ball in LR, but not in HR from 12 to 15 months (Kaur et al., 2015).
Attention			
			First year of life
Canu (2020)	HR-ASD, HR-TD, LR	AOSI	Poorer visual tracking in HR-ASD than LR at 7 months (Gammer et al., 2015). Disengagement score at 12 months predicted ASD at 24 months (Zwaigenbaum et al., 2005).
			Second year of life

Canu (2020)		AOSI, ADOS-G (videorecorded and coded)	HR-TD and LR did not differ in engagement of attention in AOSI at 14 months (Gammer et al., 2015). Less look away from the target before the grasp was complete and during the grasp in HR-ASD compared to HR-TD and LR from 12 months; no differences at 36 months. Less moves of infant's hand towards a target before visually engaging it in HR-ASD than HR-TD and LR. More disengagement and re-engagement on the target prior grasp it in HR-ASD than LR (group by age interaction no longer significant after post-hoc analyses) (Sacrey et al., 2013).
Feeding and Sleeping			
			First year of life
Athanasiadou (2019)	ADHD, controls	Parent interview	Feeding and sleeping difficulties in ADHD at 3 months. Feeding difficulties in ADHD at 6 months (Gurevitz et al., 2014).
Palomo (2006)	ASD, TD	Home video	ASD and TD did not differ in negative, positive, and flat affect (Maestro et al., 2001; Mars et al., 1999; Werner & Dawson, 2005).
Slattery (2012)	Neonatal AI stroke	Feeding assessment	Neonatal feeding problems not a predictor of speech delay (Barkat-Masih et al., 2010).
		NOMAS	Association of early feeding problems with neurodevelopmental delay (Meyer Palmer & Heyman, 1999; Mizuno & Ueda, 2005).

*: meta-analysis; NDD: Neurodevelopmental Disorders; HR: High-Risk; LR: Low-Risk; ADHD: Attention Deficit Hyperactivity Disorder; ASD: Autism Spectrum Disorder; PDD: Pervasive Developmental Disorders; ID: Intellectual Disabilities; DD: developmental disabilities; ELBW: Extremely Low Birth Weight; TD: Typically Developing children; HR-ASD: HR for ASD diagnosed with ASD; HR-TD: HR for ASD typically developing infants; HR-DD: HR for ASD diagnosed with developmental delay; GMs: General Movements; IQ: Intelligent Quotient; DDST: Denver Developmental Screening Test; NBAS: Neonatal Behavioral Assessment Scale; VWS: Van Wiechen Scheme, AI: arterial ischemic; Van Wiechen scheme is the Dutch equivalent of the Bayley scales; SSMTS: Skill Spector Motion Tracking Software; ADOS-G: Autism Diagnostic Observational Schedule-Generic; AOSI: Autism Observation Scale for Infants; MSEL: Mullen Scales of Early Learning; AIMS: Alberta Infant Motor Scale; NSMDA: Neuro-Sensory Motor Developmental Assessment; NOMAS: Neonatal Oral Motor Assessment Scale; CTS: Carey Temperament Scale; RITQ: Revised Infant Temperament Questionnaire; TTQ: Toddler Temperament Questionnaire; BSQ: Behaviour Style Questionnaire; IBQ: Infant Behavior Questionnaire; TBAQ: Toddler Behaviour Assessment Questionnaire; ECBQ: Early Childhood Behavior Questionnaire; RSMs: Repetitive and Stereotyped Movement Scales; VABS: Vineland Adaptive Behavior Scale; SEQ: Sensory Experiences Questionnaire; ITSP: Infant Toddler Sensory Profile; PDMS-2: Peabody Developmental Motor Scales – 2.

Language/communication assessment[1] includes British Ability Scales (BAS) Verbal subtests, Bus Story Test, Children's Communication Checklist – Second Edition (CCC-2), Test of Early Grammar Impairment (TEGI) (Bishop et al., 2012); Mean length of utterance in a language sample (MLU), MSEL Language subtests (Carson et al., 2003); MacArthur Communicative Development Inventories (CDI) Vocabulary, Grammar, and Abstract Language (Dale et al., 2003); MLU, McCarthy Scales of Children's Abilities (MSCA) Verbal subtests, number of different words in a language sample (NDW) (Feldman et al., 2005); CDI Vocabulary, index of productive syntax (IPSyn), MLU, NDW (Hadley & Holt, 2006); CDI Words and sentences form, Reynell Developmental Language Scales – Revised (RDLS-R), Preschool Language Scale – Third Edition (PLS-3) (Lee, 2011); (CDI Vocabulary, NDW, and PLS Semantic items) and (CDI Grammar, MLU, PLS-3 Syntax items) (Moyle et al., 2007); Évaluation du langage oral de l'enfant aphasique (ELOLA), Developmental Neuropsychological Assessment; (NEPSY) subtests (Peyre et al., 2014); Expressive One-Word Picture Vocabulary Test (EOWPVT), Illinois Test of Psycholinguistic Abilities (ITPA) (Whitehurst et al., 1991); IPSyn, MLU, RDLS-R Expressive (Rescorla & Schwartz, 1990); Early Language Inventory (ELI), MLU (Thal et al., 1991).

Language/communication assessment[2] includes BAS Verbal subtests, Bus Story Test, CCC-2, TEGI (Bishop et al., 2012); EOWPVT, Illinois Test of; Psycholinguistic Abilities (ITPA) Verbal subtests (Fischel et al., 1989); CDI Vocabulary, IPSyn, MLU, NDW (Hadley & Holt, 2006); Early Social Communication Scales (ESCS) (Vuksanovic, 2015); Language Development Survey (LSD) Vocabulary (Henrichs et al., 2011); Boston Naming Test (BNT), Inflectional Morphology Test (Lyytinen et al., 2005); VABS Expressive subdomain,; Developmental Sentence Scoring (DSS) (Paul et al., 1991); PLS-3 Expressive subtests (Petinou & Spanoudis, 2014); IPSyn, MLU, RDLS-R (Rescorla & Schwartz, 1990); ELI, MLU (Thal et al., 1991).

Language/communication assessment[3] includes CDI Vocabulary, Grammar, and Abstract Language (Dale et al., 2003); EOWPVT, ITPA Verbal subtests (Fischel et al., 1989); CDI Vocabulary, IPSyn, MLU, NDW (Hadley & Holt, 2006); CDI Words and sentences, PLS-3, Test of Language Development–3: Primary (TOLD-3), SALT = Systematic Analysis of Language Transcripts (Moyle et al., 2007); IPSyn, MLU, RDLS-R Expressive (Rescorla & Schwartz, 1990); ELI, MLU (Thal et al., 1991); MLU, NDW (Williams & Elbert, 2003).

Feeding assessment: Feeding minor dysfunctions/major dysfunctions assessment; Neonatal Oral-Motor Assessment Scale (NOMAS); Infants were evaluated during the bottle-feeding of room-temperature breast milk from their mother at the regular feeding time (Mizuno & Ueda, 2005).

Risk of biases assessment

The case 2A intra-class correlation between reviewers was high (0.95; 95% CI = 0.93-0.97). Risk of bias overall rating ranged from 2.5 to 13.5 (Mean = 5.58; Standard Deviation = 3.76). One study was rated as having moderate risk bias and the other six having a critically low risk of bias, indicating not satisfactory methodological quality in the included literature. Moderate rating was assigned when the systematic review had more than one weakness in non-critical domains. Critically low rating was assigned to a systematic review when presented weaknesses in more than one critical domain and not provided an accurate and comprehensive summary of the available studies (Shea et al., 2017). Critical domains were the following: item 1, protocol not registered before the commencement of the review; item 4, lack of adequacy of the literature search; item 7, no justification for excluding individual studies and no list of excluded studies; item 9, risk of bias from individual studies not being included in the review; item 11, meta-analytical methods not appropriate; item 13, lack of consideration of risk of bias when interpreting the results of the review; item 15, lack of assessment of publication bias. In the included studies, the most common weaknesses were observed for the critical domains number 2, 7, 9, and 13. Risk of bias ratings of the included systematic reviews are reported in the Supplementary Material 1.

Developmental domains

The early markers detected in each behavioral domain are presented by age group: first, second and third year of the child life. The present narrative synthesis provides an overall picture of the relevant findings and aims to suggest early markers of NDD useful for timely clinical detection.

Motor development

Both fine and gross motor impairments have been associated with NDD occurrence in the general population (Athanasiadou et al., 2019) and high-risk infants (i.e., siblings of children with a diagnosis of ASD, preterm and low birth weight infants; Canu et al., 2020; Fuentefria et al., 2017; Garrido et al., 2017; Palomo et al., 2006). The first early motor signs of NDD were mainly the abnormality in fluency, complexity, and variability of general movements. It should be noted that early motor signs have been mainly assessed directly by clinicians or trained researchers.

First year. ADHD diagnosis in infants at both low and high-risk for NDD was found to be predicted in the first year of life by delays in gross motor milestones (Gurevitz et al., 2014; Jaspers et al., 2013), abnormal general movements (Hadders-Algra & Groothius, 1999), and less motor maturity on the composited Brazelton factor compared to sex- and age-matched comparison groups (Jacobvitz & Soufe, 1987; in Athanasiadou et al., 2019). In the Athanasiadou's review, only the paper by Johnson and colleagues (2014) did not find any correlations between motion variables at 12 months and ADHD diagnosis at 7 years. The motor skills assessed through the Abnormal Involuntary Movement Scale (AIMS) at 4 months in children born very preterm (< 32 months) were associated with motor coordination abilities evaluated by the Movement ABC-2 at age 4 (Spittle et al., 2015). The strength of the association was improved when results from longitudinal assessment (4, 8, and 12 months) at each time points were combined (Fuentefria et al., 2017). Poorer fine and gross motor skills and unusual postures have been reported in siblings of children with ASD compared to the general population (Estes et al., 2015; Kaur et al., 2015; Landa & Garrett-Mayer, 2006; Sacrey et al., 2018; in Canu et al., 2020; Garrido et al., 2017; Osterling et al., 2002; in Palomo et al., 2006). In addition, fine motor skills – but not gross motor skills – and visual-motor integration at 6 months predicted 24-36 months ASD diagnosis (Iverson et al., 2019; LeBarton & Landa, 2019; in Canu et al., 2020). It should be noted that some studies did not

confirm these findings (Brian et al., 2008; Choi et al., 2018; LeBarton & Landa, 2019; Libertus et al., 2014; in Canu et al., 2020; Baranek, 1999; Osterling & Dowson, 1994; Werner & Dowson, 2005; in Palomo et al., 2006). Early unusual postures have been observed in siblings of children with ASD and infants later diagnosed with intellectual disabilities (Baranek, 1999; in Palomo et al., 2006) compared to the general population.

Second year. The motor skills in extremely low birth weight infants were strongly associated with clinical measures of attention at 7-9 years old (Jeyasseelan et al., 2006; in Athanasiadou et al., 2019). Children later diagnosed with ADHD showed heterogenous fine and gross motor skills developmental deviations: 13.6% of children started to walk independently before 11 months of age, while the 11.3 % later than 15 months, and the 8.4% sat alone after 8 months (Lemcke et al., 2016; in Athanasiadou et al., 2019). As at 9 months, Gurevitz and colleagues (2014) showed that delays in gross motor milestones at 18 months predicted a later ADHD diagnosis. Poorer fine (Choi et al., 2018; Estes et al., 2015; Kaur et al., 2015; Landa & Garrett-Mayer, 2006; in Canu et al., 2020; Garrido et al., 2017) and gross motor skills were observed in siblings of children with ASD compared to the general population (Landa & Garrett-Mayer, 2006, but not in Garrido et al., 2017). In addition, siblings of children with ASD, who later received the same diagnosis showed atypical motor control compared to typically developing (TD) siblings of children with ASD and LR infants (Brian et al., 2008; in Canu et al., 2020). Motor control skills at 18 months contributed to predict later ASD diagnosis (Brian et al., 2008; in Canu et al., 2020). No differences between HR and LR infants were observed on postures (Nickel et al., 2013; in Canu et al., 2020).

Third year. Garrido and colleagues (2017) identified only one study that assessed gross motor skills in children at 36 months, so a meta-analysis was not conducted for that age. The only study (Leonard et al., 2015) identified showed larger differences in gross motor

skills between high-risk and low-risk children compared to comparison children group at 7 months of age.

Language development

Delays in language acquisition were observed in children that later were diagnosed with ADHD in the first two years of life and poorer language skills in children with ASD compared to TD children in the first three years of life. Language skills were again mainly assessed using tests performed by experts.

First year. Delay in language and speech development (combined words) at 9 months assessed with the Denver Developmental Screening Test (DDST) was observed in children later diagnosed with ADHD (Gurevitz et al., 2014; in Athanasiadou et al., 2019). Children later diagnosed with ASD or pervasive developmental disorder not otherwise specified (PDD-NOS) or Autism (for brevity, ASD) showed differences compared to TD in making simple vocalizations in the first 6 months of life, complex vocalizations and pronouncing words at 12 months of life (Maestro et al., 2002; Werner & Dowson, 2005; in Palomo et al., 2006). Children at high risk of developing ASD showed poorer expressive and receptive language skills compared to TD at 12 months (Garrido et al., 2017).

Second year. As well as in the first year of life, also at 18 months were observed significant delays in speech and language development such as fewer words or not putting together words in children later diagnosed with ADHD compared to comparison groups (Gurevitz e al., 2014; Lemcke et al., 2016; in Athanasiadou et al., 2019). Palomo and colleagues (2006) highlighted the presence of differences between children with ASD and TD children in pronouncing complex vocalizations, following verbal instructions, initiate vocalizations between 12 and 30 months, and in the pronunciation of words and two words/phrases at 24 months (Mars et al., 1998; Maestro et al., 2001; Werner & Dowson,

2005). Children at risk of developing ASD showed poorer expressive and receptive language skills compared to low-risk children (Garrido et al., 2017).

Third year. The Garrido and colleagues (2017) meta-analysis showed that children at risk for developing ASD had poorer expressive and receptive language skills compared to low-risk children at 36 months assessed with the Clinical Evaluation of Language Fundamentals-Preschool (CELF-P), Reynell Developmental Language Scales (RDLS), Mullen Scales of Early Learning (MSEL), MacArthur-Bates Communicative Development Inventories (MCDI) and Vineland Adaptive Behaviour Scales-2nd Edition (VABS).

Temperament

Temperament differences have been observed between children with NDD and TD infants, and predicted later diagnosis of ASD and ADHD (Athanasiadou et al., 2019; Canu et al., 2020; Palomo et al., 2006). Temperament has been assessed using the AOSI, parent questionnaires (i.e., Carey Temperament Scale; Toddler Behaviour Assessment Questionnaire; Early Childhood Behavior Questionnaire; Infant Behavior Questionnaire) (Canu et al., 2020), and home videos (Palomo et al., 2006).

First year. Children later diagnosed with ASD significantly differed to TD in positive affect (including social smiles), conventional communicative gestures from birth to 6 months and from 8 to 10 months (Maestro et al., 2001, 2002; Werner et al., 2002; in Palomo et al., 2006), reported lower level of approach (del Rosario et al., 2014), adaptability and less active behavior at 6 and 12 months (del Rosario et al., 2014; Zwaigenbaum et al., 2015), higher scores in distress to limitations and fear (Garon et al., 2016) and more frequent and intense distress reactions, less inhibitory control, less positive anticipation and affective responses at 12 months (Zwaigenbaum et al., 2015), and lower surgency scores from 8 to 14 months (Pijl et al., 2019; in Canu et al., 2020). Lower positive affect scores at 12 months predicted ASD

symptoms at 36 months (Garon et al., 2016; in Canu et al., 2020). Difficult temperament was found more frequently in the group that later developed ADHD compared to TD (Guerevitz et al., 2014; in Athanasiadou et al., 2019).

Second year. Siblings of children with ASD, who later received the same diagnosis showed less effortful control than TD starting from 14 months (Pijl et al., 2019), and higher scores on effortful emotion regulation at 24 months (del Rosario et al., 2014). In addition, effortful control at 24 months (Garon et al., 2009), transition and reactivity scores (Brian et al., 2008) predicted ASD symptoms at 36 months (Canu et al., 2020).

Third year. Higher scores in temperament scores in siblings of children with ASD, who later received the same diagnosis than TD has been reported at 36 months (del Rosario et al., 2014; in Canu et al., 2020).

Repetitive/stereotyped behavior

Differences in repetitive and stereotyped behaviors between siblings of children with ASD and general population have been observed through the first two years of the infants' life using standardized tests (i.e., Autism Diagnostic Observational Schedule, ADOS; Repetitive and Stereotyped Movement Scales), report of parents' concerns (Canu et al., 2020), and home videos (Palomo et al., 2006).

First year. Repetitive/stereotyped behaviors have been reported in siblings of children with ASD compared to the general population at 6-12 months (Brian et al., 2008; Elison et al., 2014; Sacrey et al., 2015; in Canu et al., 2020; Osterling et al., 2002; in Palomo et al., 2006). On the contrary, other studies did not find any differences between children with ASD, intellectual disabilities and TD (Baranek, 1999; Mars et al., 1998; Osterling & Dowson, 1994; Werner & Dowson, 2005; in Palomo et al., 2006).

Second year. Also, in the second year of infants' life, repetitive/stereotyped behaviors have been observed in siblings of children with ASD compared to the general population (Sacrey et al., 2015; Damiano et al., 2013; in Canu et al., 2020), and - at 18 months - predicted later ASD diagnosis (Chawarska et al., 2014; in Canu et al., 2020).

Third year. Damiano and colleagues (2013) found no clear differences in repetitive body movements between siblings of children with ASD and typically developing siblings of children with ASD.

Play and object use

Starting from 9 months of infants' age, differences in play and object use have been observed between infants at risk for NDD and TD. Play was assessed by parent questionnaire, free play to explore functional, symbolic and repeated play (Canu et al., 2020), and home videos (Palomo et al., 2006).

First year. Significant differences were observed at 9 to 12 months between children that later were diagnosed with ASD, TD, and children with intellectual disabilities in mouthing objects (Baranek, 1999; in Palomo et al., 2006) and play skills (Sacrey et al., 2015; in Canu et al., 2020). Children with intellectual disabilities between 9 to 12 months differed in the play with objects' flexibility, variability and appropriateness compared to TD (Baranek, 1999; in Palomo et al., 2006).

Second year. At 18 months, siblings of children with ASD, who later received the same diagnosis compared to TD had significantly fewer novel self-directed and other-directed functional play behavior, greater levels of non-functional repeated play (Christensen et al., 2010; in Canu, 2020), differed in nonsocial gaze/looking at the object being held by another person/orienting to nonsocial novel stimulus, differed in the appropriate use of the object and exploratory activity with the object, and symbolic play (Mars et al., 1998; Maestro

et al., 2001; Werner & Dowson, 2005; in Palomo et al., 2006). On the contrary, Christensen and collaborators (2010) found that siblings of children with ASD, who later received the same diagnosis and TD did not differ in functional repeated and symbolic play (Canu, 2020).

Social development

Social development as early marker of NDD was explored only by Palomo and colleagues (2006) in their systematic review. Home videos reported differences between children with ASD and TD in social behaviors from birth to 24 months. In addition, similar differences between children with intellectual disabilities and TD were observed from 9 to 12 months.

First year. Palomo and colleagues (2006) described studies exploring home movies showing that children later diagnosed with ASD were significantly different from TD in social orienting and interactions from birth to 12 months, in pointing's understanding, and in looking at the objects held by others at 12 months. They were also different in the initiating pointing to request from 12 to 30 months. Children with intellectual disabilities compared to TD differed in avoiding physical and social contacts from 9 to 12 months, in looking at faces/ people, responding when called by name, initiating pointing to request and looking at the object held by others at 12 months (Baranek, 1999; Mars et al., 1998; Maestro et al., 2001, 2002; Osterling & Dowson, 1994; Osterling et al., 2002; Werner et al., 2000; in Palomo et al., 2006).

Second year. Children later diagnosed with ASD showed in their second year of life differences compared to TD in social engagement, gaze alternation, and in looking at faces from 12 to 30 months. They differed in sharing attention from 18 to 24 months, in looking at people, responding when called by names at 24 months, and initiating pointing to share

interest from 12 to 24 months (Mars et al., 1998; Maestro et al., 2001; Werner & Dowson, 2005; in Palomo et al., 2006).

Sensory processing

Early differences in sensory processing between children with ASD, intellectual disabilities and TD started to be observed at 6 months (Canu et al., 2020; Palomo et al., 2006), using the Infant Toddler Sensory Profile (ITSP), the clinical observation during the administration of standardized test (i.e., Autism Observation Scale for Infants, AOSI), parent-report measures such as Sensory Experience Questionnaire (Canu et al., 2020), and home videos (Palomo et al., 2006).

First year. Parents' first concerns for sounds, texture and visual inspection in siblings of children with ASD, who later received the same diagnosis compared to TD and LR has been observed starting from at 6 months (Sacrey et al., 2015); at 12 months parents were concerned for higher tactile and hyper-sensory responsivity (Wolff et al., 2019). In addition, the use of parts of the body or play materials in stereotyped, self-stimulatory ways at 12 months, but not at 6 months, predicted ASD at 24 months (Zwaigenbaum et al., 2005). Significant differences between children with intellectual disabilities and TD in unusual visual inspection (fixation/staring) were observed in home videos between 9 to 12 months (Baranek, 1999; Osterling & Dowson, 19994; in Palomo et al., 2006).

Second year. Parents' concerns for higher tactile and hyper-sensory responsivity in siblings of children with ASD, who later received the same diagnosis compared to TD and LR, increased from 12 to 24 months (Wolff et al., 2019). Siblings of children with ASD diagnosed with the same diagnosis showed more atypical sensory behaviors compared to LR at 18 months (Brian et al., 2008), abnormalities in the auditory processing at 24 months

(Germani et al., 2014; in Canu et al., 2020), unusual visual inspection, and aversive response to auditory stimulation (Mars et al., 1998; in Palomo et al., 2006).

Visual processing

Canu and colleagues (2020) showed abnormal visual processing in infants at risk for developing ASD compared to TD and LR infants starting from 6 months of age, using clinical observation during the administration of the MSEL, the overall looking behavior during free play situations, and one of the sensory domains of the ITSP questionnaire (Canu et al., 2020).

First year. At 6 months of infants' age, abnormal visual processing discriminated children with high ADOS scores, eligible for later diagnosis of ASD, from HR and LR infants (Landa et al., 2012). In addition, siblings of children with ASD, who later received the same diagnosis had excessive visual exploration irrespective of the novelty of the objects compared to LR infants at 6 and 12 months (Kaur et al., 2015), and lower scores in visual reception at 6 months (Estes et al., 2015). In contrast, Libertus and collaborators (2014) did not find any differences at 6 months between infants at risk for ASD and TD.

Second year. Siblings of children with ASD, who later received the same diagnosis compared to TD and LR showed lower scores in visual processing at 24 months (Estes et al., 2015), and atypical looking at the object at 12 to 15 months (Kaur et al., 2015). On the contrary, in other studies, the differences in abnormal visual processing were not observed at 14 months (Landa & Garrett-Mayer, 2006) and at 24 months (Germani et al., 2014; in Canu et al., 2020).

Attention

In the Canu and colleagues (2020) study, poorer attentional skills (e.g., disengagement of attention, and poorer visual tracking) were observed in infants at risk for ASD. Attention was explored through various play situations, the administration of standardized test (i.e., ADOS; AOSI), a visual orienting task, and parent report (i.e., Infant Behavior Questionnaire) (Canu et al., 2020).

First year. Poorer visual tracking was observed at 7 months in sibling of children with ASD later diagnosed with ASD compared to LR infants (Gammer et al., 2015). In addition, disengagement of attention scores at 12 months predicted the diagnosis of ASD at 24 months (Zwaigenbaum et al., 2015).

Second year. siblings of children with ASD, who later received the same diagnosis showed from 12 until 24 months no disengagement of attention from the target after it was grasped compared to TD and LR infants (Sacrey et al., 2013). No group differences were observed in looking time towards the target before the hand movement (Gammer et al., 2015; Sacrey et al., 2013) and visual tracking at 14 months (Gammer et al., 2015).

Feeding and sleeping

First year. Feeding or sleeping difficulties were observed being significantly correlated with ADHD and neurodevelopmental delay, but not with speech delay (Slattery et al., 2012). Neurodevelopmental delay risk was observed being higher for children with a disorganized early sucking (Tsai et al., 2010; in Slattery et al., 2012). Infants at high risk for NDD (i.e., very low birth weight) presenting difficulties in early sucking were more likely to show delays at 6 and 12 months on motor skills assessed with the Psychomotor Developmental Index of the Bayley Scales of Infant Development (Medoff-Cooper & Gennaro, 1996; Tsai et al., 2010; in Slattery et al., 2012). Barkat-Masih and colleagues

(2010) did not find that feeding difficulties in infants with neonatal ischemic stroke were predictive of later speech delay or cerebral palsy (Slattery et al., 2012).

Discussion

More than 1500 publications were screened. The eligible studies were two meta-analyses and five systematic reviews from critically low to moderate risk of bias. This overview of reviews provided evidence for delays in motor and language development, and temperament through the first three years of life in children later diagnosed with NDD. In addition, repetitive/stereotyped behaviors, reduced social engagement, atypicalities or delays in play, object use, attention, visual and sensory processing, and social engagement in the first and second year has been reported in children later diagnosed with or presenting NDD symptoms compared to TD peers. Feeding and sleeping difficulties have been observed in infants at high risk for NDD only in their first year of life. These results suggest that language and motor skills are crucial during the first three years of the child's life and confirm the well-established strong interaction between language, motor, and social domains either in clinical/at-risk or in the general population (e.g., Bedford et al., 2016; Benassi et al., 2016; Leonard & Hill, 2014). In the first year of infants' life, poorer fine and gross motor skills, repetitive motor behaviors, stereotypes, and unusual postures have been observed in infants at high risk for NDD in some (Canu et al., 2020; Garrido et al., 2017; Osterling et al., 2002; in Palomo et al., 2006), but not all studies (Brian et al., 2008; Choi et al., 2018; LeBarton & Landa, 2019; Libertus et al., 2014; Nickel et al., 2013; in Canu et al., 2020; Baranek, 1999; Osterling & Dowson, 1994; Werner & Dowson, 2005; in Palomo et al., 2006). These discrepancies in the results may be partially due to a lack of power due to the small samples size of some studies and to the heterogeneity of the motor development assessments.

It is worth noticing that the present study found just a few systematic reviews exploring early markers of NDD. Despite the high prevalence of developmental language disorders (7%; Laasonen et al., 2018) and Specific Learning Disorder (8%; Boat & Wu, 2015), we have not found any systematic reviews which satisfy our inclusion criteria. Intellectual Disabilities (Palomo et al., 2006) and Motor Disorders (Fuentefria et al., 2017) were marginally explored; more studies have been performed on ASD (Canu et al., 2020; Garrido et al., 2017; Palomo et al., 2006) and ADHD (Athanasiadou et al., 2019). In addition, among the systematic reviews explored, some developmental domains such as cognitive skills, play, sensory processing, visual processing, attention, feeding, and sleeping were rarely described. Future systematic reviews should collect data on the specific tool or technology used to identify early markers of NDD. Moreover, it urges to systematize the assessment and the developmental domains that should be investigated in order to orient professionals toward an accurate and prompt neurodevelopmental surveillance of NDD. The majority of the studies included in the systematic reviews were conducted in the USA. More research efforts should be dedicated to describing how NDD screening has been developed in other countries besides the USA.

The seven systematic reviews included in our work (Athanasiadou et al., 2019; Canu et al., 2020; Fuentefria et al., 2017; Fisher et al., 2017; Garrido et al., 2017; Palomo et al., 2006; Slattery et al., 2012) focused on the population at risk such as sibling of children with ASD, late talkers, and children born preterm, but none took into consideration the behavioral patterns that may alert parents and professionals in the general population. The need for detecting early signs of NDD come up from evidence showing that infants/toddlers with developmental delays and/or behavioral deficits improved their language and cognitive skills when underwent through early individualized and appropriated interventions (Cioni et al.,

2016; Dawson et al., 2010; Landa et al., 2011; Oberklaid & Drever, 2011; Wetherby & Woods, 2006).

Pediatricians play a key role in the early recognition of NDD signs. In the clinical settings, the early behavioral markers for NDD identification need to be routinely assessed in the pediatric surveillance protocol. Recently, the American Academy of Pediatrics (AAP) described a model of active developmental surveillance at any well-baby check-ups for the early identification of neurodevelopmental and medical conditions (https://www.aap.org/ accessed in July 2019). Developmental surveillance is a longitudinal process that relies on repeated clinical observation of the child (Smith, 2016). The surveillance aims not only at detecting delays or disorders very early in life but also at intervening promptly to promote child development (Glascoe & Robertshaw, 2007). The administration of disorder-specific or developmental delays screening tests may be part of the surveillance practice (Lipkin et al., 2019; Schonwald et al., 2009). However, there is lack of consensus on screening tools for NDD other than ASD (Vitrikas et al., 2017), and the effectiveness of universal screenings for ASD has been widely debated (Vitrikas et al., 2017; Robins et al., 2016; Silverstein & Radesky 2016; Yuen et al., 2018; Siu et al., 2016). Moreover, the minority of pediatricians tend to administer general developmental screenings (Radecki et al., 2011) mainly for time constraints due to clinical demands and staffing requirements (Vitrikas et al., 2017).

Several screening programs are already in place in the clinical practice, but, to our knowledge, no standardized protocols have been developed for the assessment of all developmental domains and targeted to the identification of all NDD. Thus, future research should be devoted to design and implement an easy, feasible, affordable, and multi-observational protocol including a set of standardized observational items that will improve the early detection of NDD in the general and at-risk population. This tool should be as flexible as possible to be included in the already established well-child care visits and

adaptable to the different socio-cultural contexts. The tool should be able to explore all areas of development, detect the failure in typical developmental pathways, and point out the atypical signs. Moreover, it should be evidenced-based and accurate as possible to minimize under detection and over-referrals, and it should be able to be applied to all ages. It should be affordable, brief, and appropriate for the general and at-risk population. Finally, it should catch the specific domains where the child shows flaws or differences/delays to the typical developing trajectories to promote specific support. The behavioral observation of red flags for NDD (unlike for instance the biological assessment) is not invasive, relatively easy to perform for pediatricians during well-baby check-ups and affordable for the health care system. In addition, caregivers can be actively involved in the monitoring program of their child development by observing, for example, feeding, sleeping, social behaviors, and communicative vocalizations emitted already in the first year of their child's life. Finally, clinicians should empower parents by providing them with examples of typical, atypical and delayed developmental trajectories.

This overview of reviews may lead to defining the scientific framework through which professionals will be able to develop a new tool for the early detection of NDD. Here, we provided an overall picture of the relevant findings on early markers of NDD potentially useful to refer the child at the child psychiatric units and make a timely clinical diagnosis. However, given the paucity of data collected among systematic reviews, the present protocol should be updated when the scientific literature will provide further systematic reviews that explore early behavioral markers for any NDD. Future systematic reviews, as it was for the included studies here, should consider collecting data on the tools available to identify early markers of NDD and/or the specific behavioral item-red flag that supported clinicians in detecting the behavioral delay. It urges to systematize the assessment of early markers of NDD in order to orient professionals toward the most specific and sensible tool.

Conclusions

To our knowledge, the present overview of systematic reviews is the first work collecting systematic reviews on early NDD signs. We aimed to identify behavioral markers useful for blending evidence-based surveillance protocols for the early NDD' detection to be implemented in every well-baby check-up. Delays or unusual patterns in several developmental domains such as motor, language, temperament, social, sensory, play, attention, visual processing, feeding, and sleeping should be identified and considered as early warnings in the first three years of life. Evidence highlights the importance of assessing the child's developmental domains using a holistic approach instead of considering them in isolation.

Despite the large presence of studies on early NDD markers in the scientific literature, the systematic reviews and meta-analyses are still scarce and, at present, they do not provide solid and consistent data. Thus, they do not provide sufficient background to define identifiable signs at specific timepoints for early NDD' recognition on the general population. For these reasons, high-quality systematic reviews and meta-analyses exploring early markers of NND in the first three years of life should be encouraged. In order to keep clinicians informed on the research state of the art on this specific field, the present overview of reviews should be updated when more systematic reviews on the topic will be available.

The present work may represent a fruitful starting point to outline an evidence-based monitoring program that may serve general and at risk for NDD population during programmed well-baby check-ups. Future studies should forthfill this monitoring program in order to empower the early identification of NDD which is a priority for the promotion of infants/toddlers specific competences programs and the improvement of children' developmental trajectories and parental outcomes.

Declarations of interest

None.

Acknowledgements

This project has received funding from the Italian Ministry of Health Project – Capitolo 2S57 [Articolo 1, comma 401, Legge 28 dicembre 2015, n. 208, recante "Disposizioni per la formazione del bilancio annuale e pluriennale dello Stato (legge di stabilità 2016)"], the "Italian Autism Spectrum Disorders Network: filling the gaps in the National Health System care" NET-2013-02355263, the "Fetal ultrasound screening for Neurodevelopmental Disorders in normal and high-risk pregnancies" In H2020-ITN.2014-BRAINVIEW 'Integrated view on discreptions of early brain development' G.A. 642996.

This work has been promoted by the ISS Neurodevelopmental Disorders group, composed by representative members of: Federazione Italiana Medici Pediatri – FIMP (Paolo Biasci, Mattia Doria, Donella Prosperi, Antonio Gulino); Società Italiana di Pediatria – SIP (Alberto Villani, Giovanni Cerimoniale), Società Italiana di Neuropsichiatria dell'infanzia e dell'adolescenza – SINPIA (Antonella Costantino, Massimo Molteni, Annalisa Monti, Renato Scifo, Carlo Calzone, Roberto Tombolato, Francesco Nardocci), Associazione culturale Pediatri – ACP (Federica Zanetto, Michele Gangemi, Gherardo Rapisardi), Società Italiana di Neonatologia – SIN (Fabio Mosca, Odoardo Picciolini, Francesca Gallini), Sindacato Medici Pediatri di Famiglia – SiMPeF (Rinaldo Missaglia, Mariaconcetta Torrieri), Istituto Superiore di Sanità (Maria Luisa Scattoni, Francesca Fulceri, Martina Micai, Andrea Guzzetta, Elena Finotti).

We thank Giulia Galati for the logistic and technical organization of the ISS Neurodevelopmental Disorders group meetings and manuscript writing.

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