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Predictive validity of the Standardized Infant NeuroDevelopmental Assessment (SINDA) to identify 4–5 year-old children at risk of developmental delay in a low-risk sample

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ABSTRACT

Background: Early detection of developmental problems is important as it allows for early intervention. Previous studies, in high-risk infants, found high predictive values of atypical scores on the Standardized Infant NeuroDevelopmental Assessment (SINDA) for later neurodevelopmental disorders (i.e., cerebral palsy, intellectual disability).
Aims: The present study explored SINDA's predictive values to identify risk of developmental delay at 4–5 years.
Study design: Cohort study.
Subjects: 786 low-risk Dutch children (367 boys; median gestational age: 40 (27–42) weeks; mean birth weight: 3455 (SD 577) grams).
Outcome measures: The SINDA was assessed at 2–12 months and risk of developmental delay was assessed using the Ages and Stages Questionnaire (ASQ) at 4–5 years. SINDA's predictive values were determined for five ASQ domains and the total ASQ score for children at risk of marked (all ASQ domains deviant) and any (one or more ASQ domains deviant) developmental delay.
Results: Presence of one atypical SINDA scale score showed low to moderate sensitivities (12–88 %, depending on the SINDA scale and ASQ domain involved), moderate to high specificities (66–94 %), low positive predictive values (PPVs; 3–16 %), and high negative predictive values (NPVs; 95–100 %) for children at risk of marked and any developmental. Presence of multiple atypical SINDA scale scores predicted deviant ASQ domains slightly better (sensitivities = 11–62 %, specificities = 90–98 %, PPVs = 6–30 %, and NPVs = 95–100 %).
Conclusions: In low-risk infants, SINDA's predictive value is low for detecting children at risk of marked and any developmental delay at 4–5 years, as reflected by the low sensitivities. One of the explanations is the relatively low prevalence of developmental delay in low-risk populations. This might have consequences for the application of the SINDA in general healthcare settings (e.g. child health clinics), but further studies are needed to draw this conclusion.

1. Introduction

From gestation onwards, a child's life is characterised by a rapidly moving development in different areas such as cognitive, motor, socio-emotional, and language development [1]. Some children experience developmental problems as part of the presence of a neuro-developmental disorder (i.e., autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD), developmental coordination disorder (DCD), intellectual disability (ID), and cerebral palsy (CP)) [2,3]. These disorders, with a total prevalence between 1 and 8 %

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[4–10], have an early onset and are characterised by developmental deficits that lead to impairments of functioning [2]. Children with developmental problems may need healthcare support to participate in daily life activities [11], which should ideally be provided early [11–14] based on timely detection of developmental problems. Early intervention may be beneficial due to the high plasticity of the young brain, being more susceptible to interventions [15–17]. To early identify developmental problems, instruments to facilitate detection are essential. Many studies on instruments for the early detection of developmental problems focused on children with or at risk of neurodevelopmental disorders. Yet, a substantial proportion of children with neurodevelopmental disorders do not have easily identifiable risk factors. Hence, it is important to evaluate whether available tools when administered in the general population can detect children at risk for (neuro)developmental problems.

A relatively new instrument for the early recognition of neurodevelopmental disorders such as CP and ID in infants is the Standardized Infant NeuroDevelopmental Assessment (SINDA) [18]. This instrument assesses, in only 15–25 min, the development of infants between 6 weeks and 12 months old in three scales: a neurological, developmental, and socio-emotional scale. A SINDA assessment can be performed by trained healthcare professionals and is relatively easy to learn and administer [18,19]. It requires inexpensive materials that can be purchased in a regular toy store.

Previous studies evaluated the psychometric properties of the SINDA [19–21] in 109 to 223 infants at risk of neurodevelopmental disorders. They showed that in these high-risk populations, the SINDA neurological scale accurately predicted CP (sensitivity = 91–100 % and specificity = 81–96 %) and developmental delay (based on the Bayley Scales for Infant Development (BSID) [22]; sensitivity = 50–78 % and specificity = 91–94 %) [19,20]. Furthermore, the SINDA developmental scale accurately predicted ID (sensitivity = 79 %, specificity = 92 %) [21]. Lastly, the SINDA emotionality and self-regulation behaviours showed high specificity (85 % and 98 %, respectively), but low sensitivity (32 % and 40 %, respectively) for later emotional and behavioural problems [21].

Although these results in high-risk populations are promising, the SINDA's ability to identify children at risk for later developmental problems in a low-risk population is not known. It is important to examine exactly this as the SINDA may contribute to early detection of developmental problems as part of standard care in, for example, general healthcare centres such as child health clinics. Therefore, the current study aimed to investigate the predictive validity of the SINDA to identify children at risk of developmental delay, assessed with the Ages and Stages Questionnaire (ASQ) [23], at 4 to 5 years of age in a low-risk sample. The ASQ is a developmental screening questionnaire that examines skill attainment in several developmental domains (communication, fine motor, gross motor, problem-solving, and personal-social skills).

To investigate the SINDA's predictive validity for children at risk of developmental delay, we first examined the predictive values for risk of marked developmental delay, which we defined as having deviant scores on all ASQ domains. We hypothesised that deviant scores on the SINDA neurological and developmental scales would predict the risk of marked developmental delay, but less well than in high-risk populations. Particularly, predictive values for developmental problems are lower in low-risk populations than in high-risk populations [18,24] because these problems are less prevalent in low-risk populations. Additionally, in infancy, it is difficult to identify a high risk for later developmental problems, as the neural networks in the young brain are still developing and temporary structures, such as the cortical subplate, mediate behaviour to a significant extent [25,26].

Second, we investigated if deviant scores on the SINDA scales predicted the risk of any developmental delay, defined by one or more deviant ASQ domain scores. Again, we expected relatively low predictive values of the SINDA scales for the ASQ domains for the same reasons as stated before. Third, we explored if SINDA's predictive values for risk of both marked and any developmental delay increased when the prediction was based on deviant scores on multiple SINDA scales compared to a deviant score on only one scale.

2. Methods

2.1. Participants

The current paper is based on a follow-up study of the IMP-SINDA project in which norm data was collected for the Infant Motor Profile (IMP) and the SINDA between 2017 and 2019. In the IMP-SINDA project, 1100 infants between 2 and 12 months old and representative of the general Dutch infant population were assessed with the SINDA. The infants lived in the three Northern provinces of the Netherlands. More details on the sample and procedure of the IMP-SINDA project have been described previously [27]. When the children were 4 or 5 years of age, their parents were invited to participate in a follow-up study, the BIRD (Biomarkers in Infants at Risk of Developmental disorders) study, which consisted of two parts: an online questionnaire in the total sample (BIRD I) and a live assessment in a selected sample (BIRD II). The current study is based on data of the BIRD I study that started in 2020.

2.2. Procedure

Parents completed a one-hour online questionnaire concerning the development of their child (including the ASQ) and their family situation. The parents who completed the questionnaire received a gift voucher. For the IMP-SINDA project, permission had been obtained from the Medical Ethical Committee of the UMCG (METc 2016/294); the committee deemed additional permission for the BIRD I online questionnaire study not needed (METc 2020/528). The study was conducted according to the declaration of Helsinki, the General Data Protection Regulation (GDPR), and Dutch regulations and legislations regarding research.

2.3. Measures

Standardized Infant NeuroDevelopmental Disorder (SINDA). The SINDA is a developmental infant assessment that consists of three scales [18]. The neurological scale examines spontaneous movements, cranial nerves, motor reactions to postural stimulation, muscle tone, and reflexes. It consists of 28 dichotomous items which are assessed in less than ten minutes. Each item is scored as 0 (atypical) or 1 (typical). A sum score of 21 or lower is considered atypical which indicates a high risk of CP or developmental delay. The developmental scale measures cognitive, fine motor, gross motor, and communicative capacities of the child. This scale consists in total of 113 dichotomous items covering the entire age range of 6 weeks to 12 months. For each month of age, 15 age-specific items from the total set are assessed in 5 to 15 min (age-dependent) to form a score on the developmental scale. Again, each item is scored as 0 (atypical) or 1 (typical), and a sum score of seven or lower is considered atypical. In high-risk infants, an atypical developmental SINDA scale outcome indicates a high risk of ID. The socio-emotional scale evaluates four types of behaviour: interaction, emotionality, self-regulation, and reactivity, which are all scored as 0 (atypical) or 1 (typical). The scores are based on the observation of the assessor during the assessment of the neurological and developmental scales; examples of typical and atypical behaviour are described in the SINDA manual. The developers of the SINDA did not define a total score for the socio-emotional scale. However, for the current study, we made a composite score for the socio-emotional scale; if at least one out of four behaviours was atypical, the composite SINDA socio-emotional scale outcome was classified as atypical. The reliability of the SINDA neurological scale score was examined in a high-risk sample of 24 infants [20]. The interrater reliability and the intrarater agreement were excellent (ICC =

0.93–0.97 and ICC = 0.92–0.95, respectively). Furthermore, the inter-rater reliabilities of the SINDA developmental scale and socio-emotional scale were assessed in a sample of 60 children and were high for both scales (ρ = 0.91–0.97, k = 0.78–0.90, respectively) [21].

The Ages and Stages Questionnaire (ASQ). The ASQ [23] is a widely used developmental screening questionnaire [28]. In the current study, the Dutch versions of the ASQ for children of 48 and 60 months old were used. The ASQ consists of 30 items equally distributed over five developmental domains: communication, gross motor, fine motor, problem-solving, and personal-social skills. A parent or caregiver completes the questionnaire, and for some items the child needs to be actively involved and has to perform certain tasks. Items assess whether or not a developmental skill is achieved and can be answered with 'yes' (ten points), 'sometimes' (five points), or 'not yet' (zero points). Subsequently, the score of each developmental domain is calculated by the sum of scores on all corresponding items. The total score represents the mean of the five developmental domain scores. Cut-off scores have been established for different ages and domains. In the current study, we used the Dutch norms [29,30] to generate a dichotomous variable for each domain of the ASQ; on or below the cut-off of two standard deviations below the mean (atypical score) or above the cut-off (typical score). Additionally, we made a dichotomous score to identify the risk of marked developmental delay (0 = atypical scores on all domains, 1 = no atypical scores on all domains). The psychometric properties of the ASQ have been thoroughly investigated [28–32]. The internal consistency was moderate to high (α = 0.61–0.83) [29,32]. Furthermore, ASQ scores were related to the concurrent need for special education (sensitivity = 88–89 %, specificity =0.68–93 %) [30] and (severe) developmental delay (sensitivity = 77–84 %, specificity = 77–81 %) [31] in children from both low-risk and at-risk (e.g. due to prematurity) populations. Developmental delay in the latter systematic review and meta-analysis was based on the association between ASQ and reference tests such as the BSID. Based on the moderate association, the ASQ can identify children at risk of developmental delay but cannot serve as a final judgement on the presence of developmental delay. Therefore, we investigate the predictive value of the SINDA to identify children at risk of developmental delay.

2.4. Statistical analyses

All statistical analyses were performed in IBM SPSS Statistics (version 28) [33] or in R-studio (version 2023.6.0.421) [34]. First, we inspected the data by examining the missing values and the background characteristics of the study population with descriptive statistics. Additionally, we performed independent sample t-tests and chi-square tests (significance level $p < .05$) to examine whether selective drop-out had occurred. Second, to assess the predictive validity of the SINDA scale scores to identify children at risk of marked (all ASQ domains atypical) and any (one or more ASQ domains atypical) developmental delay, we performed crosstabulations of each SINDA scale outcome (categorised as typical or atypical) and the ASQ domains (categorised as typical or atypical), simultaneously relative risk ratios were obtained. The relative risk ratio indicates the relative risk for an atypical ASQ domain score based on an atypical SINDA scale score in infancy. In addition, the sensitivities (true positives), specificities (true negatives), positive predictive values (PPV; proportion of children with atypical SINDA scale scores and later an atypical ASQ domain score), and negative predictive values (NPV; proportion of children with typical SINDA scale scores and later a typical ASQ domain score) including their confidence intervals were calculated using the package 'Statistical analysis in epidemiology' (Epi) in R-studio. Third, to investigate whether the SINDA was a better predictor if an infant had atypical scores on multiple SINDA scales, we repeated the abovementioned analyses, but with alternative predictors based on the different combinations of atypical SINDA scale outcomes (i.e., atypical scores on two SINDA scales (three combinations) or atypical scores on all SINDA scales). Predictive values were considered 'low' when being 66 % or lower, 'moderate' when being between 67 % to 89 %, and 'high' when being 90 % or higher [35].

3. Results

3.1. Participants

In supplementary Fig. 1, a flow diagram is shown to provide insight into the inclusion and drop-out of participants. Among 1100 invited children, parents of 867 parents (79 %) were interested in participating in the current study. However, for 78 children (9 %) the ASQ was not completed and three children were too young to participate. Therefore, they were excluded from the analyses. This resulted in a total of 786 participants in the current study (71 % of the original sample). Table 1 presents demographic information, background characteristics, SINDA scale scores, and ASQ domain scores of the study group. At the time of ASQ completion, the children were aged 48 to 70 months (median = 55 months) and there were 419 boys (53 %) and 367 girls (47 %). The included sample was similar compared to the drop-out group in terms of sex, gestational age, birth weight, prematurity, twins, and being small-for-gestational-age. In the included sample, there were relatively more mothers and fathers with a high educational level (51 % vs 30 %, χ^2 = 44.293, $p < .001$ and 43 % vs 34 %. χ^2 = 9.714, p = .008, respectively) and there were relatively more Dutch mothers and fathers (93 % vs 83 %, χ^2 = 29.034, $p < .001$ and 93 % vs 80 %, χ^2 = 38.718, $p < .001$, respectively) than in the drop-out group. Based on the parental educational level and ethnicity, our sample was no longer fully representative of the Dutch infant population. Nonetheless, our sample can still be considered low-risk based on the infants' characteristics such as

Table 1
Demographic information and SINDA and ASQ scores of study sample (n = 786).

Socio-demographic background	
Sex: boys/girls; *n (%)*	367 (47 %)/ 419 (53 %)
Maternal education: low/middle/high[c]; *n (%)*	56 (7 %)/ 322 (41 %)/ 398 (51 %)
Maternal ethnicity: Dutch/non-Dutch; *n (%)*	731 (93 %)/ 54 (7 %)
Paternal education: low/middle/high[c]; *n (%)*	79 (10 %)/ 354 (45 %)/ 334 (43 %)
Paternal ethnicity: Dutch/non-Dutch; *n (%)*	722 (93 %)/ 56 (7 %)
Perinatal background	
Gestational age in weeks; median (range)	40 (27–42)
Birth weight in grams; *M (SD)*	3455 (577)
Prematurity (<37 weeks): yes/no; *n (%)*	54 (7 %)/ 732 (93 %)
Small-for-gestational-age (< 10th percentile): yes/no; *n (%)*	78 (10 %)/ 707 (90 %)
Twins: yes/no; *n (%)*	11 (3 %)/ 764 (97 %)
SINDA	
Age[a]b SINDA assessment in months; median (range)	7 (2–12)
SINDA – Neurological scale; median (range)	25 (11–28)
SINDA – Developmental scale; median (range)	10 (1–15)
ASQ	
Age ASQ in months; median (range)	55 (48–71)
ASQ – Communication; median (range)	60 (0–60)
ASQ – Fine motor; median (range)	55 (0–60)
ASQ – Gross motor; median (range)	55 (5–60)
ASQ – Problem-solving; median (range)	60 (0–60)
ASQ – Personal-social; median (range)	60 (0–60)
ASQ – Total; median (range)	56 (1–60)

Note. n = sample size, M = mean, SD = standard deviation, SINDA = Standardized Infant NeuroDevelopmental Assessment, ASQ = Ages and Stages Questionnaire.

[a] = corrected age (chronological age minus number of weeks being born before due date).

[b] = among others: oxygen deprivation, low Apgar scores.

[c] = low: no or primary school, pre-vocational secondary education, or secondary vocational education level 1, middle: senior general secondary education, pre-university education or vocational secondary education level 2–4, high: higher professional education and university education.

Table 2
Sensitivity, positive predictive value (PPV), specificity, and negative predictive value (NPV) including 95 % confidence intervals of the SINDA (one atypical scale and multiple atypical scales) for ASQ outcomes (n = 786).

	One atypical SINDA scale				
	Sensitivity in % [95%CI]	Specificity in % [95%CI]	PPV in % [95%CI]	NPV in % [95%CI]	Relative Risk Ratio [95% CI]
					Atypical ASQ
SINDA Neuro					
ASQ: all domains atypical	25 [3 – 65]	93 [91 – 95]	4 [0 – 13]	99 [98 –100]	4.52 [.93 – 21.86]
SINDA Neuro					
ASQ: Communication	18 [8 – 33]	94 [92 – 95]	15 [7 – 27]	95 [93 –97]	3.01 [1.47 – 6.16]
ASQ: Fine motor	12 [3 – 32]	93 [91 – 95]	6 [1 – 15]	97 [96 –98]	1.94 [0.60 – 6.29]
ASQ: Gross motor	21 [9 – 39]	94 [92 – 95]	13 [5 – 25]	96 [95 –98]	3.65 [1.66 – 8.02]
ASQ: Problem-solving	32 [13 – 57]	94 [92 – 95]	11 [4 – 23]	98 [97 – 99]	6.26 [2.48 – 15.81]
ASQ: Personal–social	18 [7 – 35]	94 [92 – 95]	11 [4 – 23]	96 [95 – 98]	3.01 [1.30 – 6.98]
ASQ: Total	18 [8 – 34]	94 [92 – 95]	13 [5 – 25]	96 [94 – 97]	3.06 [1.41 – 6.63]
SINDA Dev					
ASQ: all domains atypical	62 [24 – 91]	85 [82 – 87]	4 [1 – 9]	100 [99 – 100]	9.07 [2.20 – 37.46]
SINDA Dev					
ASQ: Communication	43 [28 – 59]	86 [83 – 89]	16 [10 – 23]	96 [94 – 98]	4.14 [2.35 – 7.27]
ASQ: Fine motor	46 [26 – 67]	85 [83 – 88]	9 [5 – 16]	98 [97 – 99]	4.61 [2.11 – 10.04]
ASQ: Gross motor	39 [23 – 58]	86 [83 – 88]	11 [6 – 18]	97 [95 – 98]	3.54 [1.81 – 6.92]
ASQ: Problem-solving	68 [43 – 87]	86 [83 – 88]	11 [6 – 18]	99 [98 – 100]	11.79 [4.57 – 30.43]
ASQ: Personal–social	45 [28 – 64]	86 [83 – 88]	12 [7 – 19]	97 [96 – 98]	4.54 [2.35 – 8.75]
ASQ: Total	50 [33 – 67]	86 [84 – 89]	16 [10 – 23]	97 [96 – 98]	5.44 [2.97 – 9.98]
SINDA SE					
ASQ : all domains atypical	88 [47 – 100]	66 [63 – 70]	3 [1 – 5]	100 [99 – 100]	13.45 [1.66 – 108.78]
SINDA SE					
ASQ: Communication	59 [43 – 74]	67 [64 – 71]	10 [6 – 14]	97 [95 – 98]	2.78 [1.55 – 4.97]
ASQ: Fine motor	58 [37 – 78]	67 [63 – 70]	5 [3 – 9]	98 [96 – 99]	2.69 [1.21 – 5.98]
ASQ: Gross motor	55 [36 – 72]	67 [63 – 70]	7 [4 – 10]	97 [95 – 98]	2.31 [1.18 – 4.50]
ASQ: Problem-solving	84 [60 – 97]	67 [64 – 70]	6 [3 – 9]	99 [98 – 100]	10.25 [3.01 – 34.87]
ASQ: Personal–social	61 [42 – 77]	67 [63 – 70]	7 [5 – 11]	97 [96 – 99]	2.96 [1.49 – 5.85]
ASQ: Total	61 [43 – 76]	67 [64 – 70]	9 [5– 13]	97 [95 – 98]	2.95 [1.56 – 5.55]

	Multiple atypical SINDA scales				
	Sensitivity in % [95%CI]	Specificity in % [95%CI]	PPV in % [95%CI]	NPV in % [95%CI]	Relative Risk Ratio [95% CI]
					Atypical ASQ
SINDA Neuro + Dev					
ASQ: all domains atypical	25 [3 – 65]	98 [96 – 99]	10 [1 – 32]	99 [98 – 100]	12.77 [2.74 – 59.40]
SINDA Neuro + Dev					
ASQ: Communication	14 [5 – 27]	98 [97 – 99]	30 [12 – 54]	95 [93 – 96]	6.05 [2.89 – 12.65]
ASQ: Fine motor	12 [3 – 32]	98 [96 – 99]	15 [3 – 38]	97 [96 – 98]	5.47 [1.78 – 16.86]
ASQ: Gross motor	15 [5 – 32]	98 [97 – 99]	25 [9 – 49]	96 [95 – 98]	6.84 [2.95 – 15.87]
ASQ: Problem-solving	26 [9 – 51]	98 [97 – 99]	25 [9 –49]	98 [97 – 99]	13.68 [5.45 – 34.31]
ASQ: Personal–social	15 [5 – 32]	98 [97 – 99]	25 [9 – 49]	96 [95 – 98]	6.84 [2.95 – 15.87]
ASQ: Total	16 [6 – 31]	98 [97 – 99]	30 [12 – 54]	96 [94 – 97]	7.18 [3.39 – 15.21]
SINDA Neuro + SE					
ASQ: all domains atypical	25 [3 – 65]	96 [95 – 97]	6 [1 – 21]	99 [98 – 100]	8.12 [1.71 – 38.61]
SINDA Neuro + SE					
ASQ: Communication	16 [7 – 30]	97 [95 – 98]	23 [10 – 41]	95 [93 – 97]	4.61 [2.24 – 9.50]
ASQ: Fine motor	12 [3 – 32]	96 [95 – 98]	10 [2 – 26]	97 [96 – 98]	3.48 [1.10 – 11.05]
ASQ: Gross motor	15 [5 – 32]	97 [95 – 98]	16 [5 – 34]	96 [95 – 98]	4.35 [1.80 – 10.50]
ASQ: Problem-solving	32 [13 – 57]	97 [95 – 98]	19 [7 – 37]	98 [97 –99]	11.24 [4.58 – 27.60]
ASQ: Personal–social	15 [5 – 32]	97 [95 – 98]	16 [5 – 34]	96 [95 – 98]	4.35 [1.80 – 10.50]
ASQ: Total	16 [6 – 31]	97 [95 – 98]	19 [7 – 37]	96 [94 – 97]	4.57 [2.06 – 10.11]
SINDA Dev + SE					
ASQ: all domains atypical	62 [24 – 91]	89 [87 – 91]	06 [2 – 13]	100 [99 – 100]	13.05 [3.17 – 53.69]
SINDA Dev + SE					
ASQ: Communication	34 [20 – 50]	90 [88 – 92]	17 [10 – 26]	96 [94 – 97]	4.05 [2.26 – 7.26]
ASQ: Fine motor	38 [19 – 59]	90 [87 – 92]	10 [5 – 18]	98 [96– 99]	4.70 [2.12 – 10.42]
ASQ: Gross motor	33 [18 – 52]	90 [87 – 92]	12 [6 – 21]	97 [95 – 98]	3.92 [1.97 – 7.80]
ASQ: Problem-solving	58 [33 –80]	90 [87 – 92]	12 [6 – 21]	99 [98 – 100]	10.77 [4.45 – 26.06]
ASQ: Personal–social	39 [23 – 58]	90 [88 – 92]	15 [8 – 24]	97 [96 – 98]	5.09 [2.62 – 9.87]
ASQ: Total	37 [22 – 54]	90 [88 – 92]	16 [9 – 25]	97 [95 – 98]	4.57 [2.46 – 8.50]
SINDA Neuro + Dev + SE					
ASQ: all domains atypical	25 [3 – 65]	98 [97 – 99]	12 [1 – 36]	99 [98 – 100]	15.08 [3.28 – 69.39]
SINDA Neuro + Dev + SE					
ASQ: Communication	11 [4 – 25]	98 [97 – 99]	29 [10 – 56]	95 [93 – 96]	5.80 [2.61 – 12.87]
ASQ: Fine motor	12 [3 – 32]	98 [97 – 99]	18 [4 – 43]	97 [96 – 98]	6.46 [2.13 – 19.61]
ASQ: Gross motor	15 [5 – 32]	98 [97 – 99]	29 [10 – 56]	96 [95 – 98]	8.08 [3.55 – 18.36]
ASQ: Problem-solving	26 [9 – 51]	98 [97 – 99]	29 [10 – 56]	98 [97 – 99]	16.16 [6.56 – 39.77]
ASQ: Personal–social	12 [3 – 28]	98 [97 – 99]	24 [7 – 50]	96 [95 – 97]	6.24 [2.47 – 15.79]
ASQ: Total	13 [4 – 28]	98 [97 – 99]	29 [10 – 56]	96 [94 – 97]	6.85 [3.05 – 15.38]

Note. SINDA = Standardized Infant NeuroDevelopmental Assessment, Neuro = neurological scale, Dev = developmental scale, SE = socio–emotional scale, ASQ = Ages and Stages Questionnaire, 95% CI = 95 % confidence interval, PPV = Positive Predictive Value, NPV = Negative Predictive Value.

gestational age, birth weight, and rate of prematurity.

3.2. Predictive validity of the SINDA to identify children at risk of marked developmental delay

At age 4 or 5, 8 out of 786 children (1 %) had atypical ASQ outcomes in all domains. As shown in Table 2, the sensitivities of the SINDA scales for the risk of marked developmental delay ranged between 25 % [95 % CI = 3–65 %] and 88 % [95 % CI = 47–100 %] and the specificities varied from 66 % [95 % CI = 63–70 %] to 93 % [95 % CI = 91–95 %]. The socio-emotional SINDA scale showed the highest sensitivity (88 %). The PPVs of the three SINDA scales were low, ranging from 3 % [95 % CI = 1–5 %] to 4 % [95 % CI = 0–13 %], but the NPVs were high, ranging from 99 % [95 % CI = 98–100 %] to 100 % [95 % CI = 99–100 %]. The relative risk ratios for atypical ASQ domain scores ranged from 4.51 [95 % CI = 0.93–21.83] to 13.43 [95 % CI = 1.66–108.57] (see Table 2).

3.3. Predictive validity of the SINDA to identify children at risk of any developmental delay

At age 4 or 5, relatively few children had an atypical ASQ domain outcome (communication: 5 %, fine motor: 3 %, gross motor: 4 %, problem-solving: 2 %, personal-social: 4 %, total: 5 %). As shown in Table 2, the sensitivities of the SINDA scales for the various ASQ domain outcomes ranged from 12 % [95 % CI = 3–32 %] to 84 % [95 % CI = 60–97 %] and the specificities varied from 66 % [95 % CI = 63–70 %] to 94 % [95 % CI = 92–95 %]. The socio-emotional SINDA scale had the highest sensitivity for the ASQ problem-solving domain outcome (84 %). The PPVs of the SINDA scales for the respective ASQ domain outcomes were relatively low and ranged from 5 % [95 % CI = 3–9 %] to 16 % [95 % CI = 10–23 %]. However, the NPVs of the SINDA scales for the ASQ domain outcomes were high and varied from 95 % [95 % CI = 93–97 %] to 99 % [95 % CI = 98–100 %]. The relative risk ratios ranged from 1.93 [95 % CI = 0.60–6.28] to 11.78 [95 % CI = 4.56–30.38] for atypical ASQ domain scores (Table 2).

3.4. Predictive validity of multiple atypical SINDA scales to identify children at risk of marked developmental delay

Four possible combinations of atypical scores on multiple SINDA scales were present: 1) atypical neurological and developmental scales, 2) atypical neurological and socio-emotional scales, 3) atypical developmental and socio-emotional scales, and 4) atypical neurological, developmental, and socio-emotional scales. As displayed in Table 2, the sensitivities and specificities of atypical scores on multiple SINDA scales for the risk of marked developmental varied from 25 % [95 % CI = 3–65 %] to 62 % [95 % CI = 24–91 %] and from 89 % [95 % CI = 87–91 %] to 98 % [95 % CI = 96–99 %], respectively. The combination of atypical SINDA developmental and socio-emotional scales showed the highest sensitivity (62 %) for atypical ASQ outcomes in all domains. The PPVs of the SINDA combinations were slightly higher than for one atypical SINDA scale, but still relatively low and ranged from 6 % [95 % CI = 1–21 %] to 12 % [95 % CI = 1–36 %]. The NPVs of the SINDA combinations for the risk of marked developmental delay continued to be high, varying from 99 % [95 % CI = 98–100 %] to 100 % [95 % CI = 99–100 %]. The relative risk ratios for atypical ASQ domain scores ranged from 8.11 [95 % CI = 1.71–38.56] to 15.06 [95 % CI = 3.27–69.30] (Table 2).

3.5. Predictive validity of multiple atypical SINDA scales to identify children at risk of any developmental delay

As shown in Table 2, the sensitivities of atypical scores on multiple SINDA scales for the ASQ domain outcomes ranged from 11 % [95 % CI = 4–25 %] to 58 % [95 % CI = 33–80 %] and the specificities varied from 90 % [95 % CI = 87–92 %] to 98 % [95 % CI = 97–99 %]. Furthermore, the PPVs varied between 10 % [95 % CI = 2–26 %] to 30 % [95 % CI = 12–54 %] and the NPVs between 95 % [95 % CI = 93–97 %] to 99 % [95 % CI = 98–100 %]. For atypical ASQ domain scores, the relative risk ratios ranged from 3.48 [95 % CI = 1.10–11.03] to 16.13 [95 % CI = 6.55–39.72] (Table 2).

4. Discussion

In the current study, we examined the predictive validity of the SINDA assessed in infancy to identify children at risk of developmental delay at 4 to 5 years in a low-risk sample. Overall, the SINDA showed low to moderate sensitivities, high specificities, low PPVs, and high NPVs. Furthermore, the relative risk ratios showed that the likelihood of being at risk of developmental delay at 4 to 5 years of age is higher for children with atypical than typical SINDA scores. Additionally, two or more atypical SINDA scales (in particular an atypical developmental and socio-emotional SINDA scale) slightly better predicted the risk of developmental delay at 4 or 5 years of age than only one atypical SINDA scale, especially for children at risk of any developmental delay.

The predictive values of the SINDA in this study differ from those in high-risk infants. This difference can be partially attributed to the low versus high-risk nature of the groups; the predictive values of an instrument in a low-risk population may be lower than in a high-risk population [18]. For example, the predictive values of definitely abnormal general movements were lower in a general population sample than in high-risk infants [24]. This might be the case because in the general population most children develop typically and therefore will fall within population norms [29,30,36]. In our study, only 1 % ($n = 8$) of the children had atypical outcomes on all ASQ domains and 5 % of the children had an atypical total ASQ outcome. The predictive validity of the SINDA was not better for children at risk of marked developmental delay than for children at risk of any developmental delay. A second explanation for the low to moderate sensitivity in our study is the different outcome measure. In studies among high-risk infants, the main outcomes were clinically classified CP or ID. This is very different from the current study, in which we used the ASQ, a screening questionnaire that represents the parental interpretation of behaviour in a developmental domain. Additionally, in the high-risk infants studies, the majority of children with atypical SINDA scale outcomes were diagnosed with CP. We do not know how many children were diagnosed with CP in the current study, but based on the prevalence of CP in Europe (0.1–0.2 %) [9], it can be surmised that few children ($\leq$2) would have been diagnosed with CP. Lastly, a possible explanation is that early detection of other developmental problems, such as ASD and DCD, is difficult because behaviour is still mediated by temporary circuitries in the cortical subplate and cerebellum, before changing into permanent circuitries around 12 months post-term [25,26].

The high specificities that we found suggest that an atypical score at the SINDA often indicates a risk of developmental delay at 4–5 years of age. However, since the majority of children in the current sample had typical ASQ scores at age 4–5 years (95 %), as expected in a low-risk population, SINDA scale scores are less indicative of a risk of developmental delay at 4–5 years old than the specificities suggest. Nonetheless, the relative risk ratio showed that, even in a low-risk population, infants with atypical SINDA scale scores had a higher likelihood of being at risk of developmental delay at 4–5 years of age than infants with typical SINDA scale scores. The relative risk ratio varied widely between the various atypical SINDA scale outcomes and ASQ domain scores (2–16). Especially, infants with an atypical SINDA developmental, socio-emotional, or multiple atypical SINDA scale outcomes were between 8 and 16 more likely to have an atypical score on all ASQ domains or the ASQ problem-solving domain. This indicates that atypical scores on these ASQ domains are best predicted by atypical SINDA scale outcomes. Nonetheless, it is important to interpret this cautiously as there were only few infants with an atypical score on all ASQ domains (8 children; 1 %) or on the ASQ problem-solving domain (19 children; 2 %). Overall, the results showed that atypical SINDA scale outcomes are less helpful in

detecting 4–5-year-olds at risk of developmental delay in a low-risk population than in detecting children with CP and ID in a high-risk group. Our results might imply that in low-risk settings, such as child health clinics, it is not useful to assess all infants with the SINDA, but to restrict SINDA assessments to infants with parental or professional concerns. Additional studies with a better design are needed to evaluate this suggestion.

A strength of the study is the investigation of the predictive validity of the SINDA and later developmental outcome in a low-risk population. It is important to investigate the pertinence of potential screening instruments in a low-risk population, to assess the instruments' potential use for early detection (and intervention) of developmental problems in general infant healthcare such as child health clinics. Another strength is the considerable size of our study group, which has resulted in robust findings. In addition, we used a transdiagnostic approach, by focusing on developmental domains that may be impaired in children with different types of neurodevelopmental disorders. Nevertheless, the study also has some limitations. First, we lacked data on the children and families in the interval between the IMP-SINDA project and the current study. Hence, we cannot account for a potentially positive effect of early intervention in infants with atypical SINDA scale scores. Second, there was selective drop-out in terms of parental educational level and ethnicity; there were more parents with a higher educational level and Dutch ethnical background in the current sample compared to the drop-out group. Therefore, the sample was no longer representative of the general Dutch infant population, which may have affected the outcomes. Third, we used a screening questionnaire to identify if a child was at risk of developmental delay instead of a clinical assessment. Additionally, we did not have any information on potential clinical diagnoses of the children. In future research, it may be helpful to investigate SINDA's predictive validity for particular neurodevelopmental disorders in a low-risk sample. Perhaps the SINDA predicts specific behaviours belonging to specific neurodevelopmental disorders better than identifying children at risk of developmental delay.

In conclusion, we found that infants with atypical scores on the SINDA were relatively more often identified as at risk for developmental delay later in life than infants with typical SINDA scale scores. Nonetheless, the low sensitivities indicate that it might not be useful to apply the SINDA in all infants of the general population to detect children at risk of later developmental delay, as this may be associated with increased concerns and costs. However, additional research is needed to draw this conclusion. For the time being, we recommend using the SINDA in a general healthcare setting only in infants with parental and/or professional developmental concerns, to improve monitoring of the child's development over time.

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CRediT authorship contribution statement

Selena J. Rosinda: Writing – original draft, Visualization, Project administration, Methodology, Investigation, Formal analysis, Conceptualization. **Pieter J. Hoekstra:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Mijna Hadders-Algra:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Annelies de Bildt:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Kirsten R. Heineman:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

Mijna Hadders-Algra is one of the authors of the SINDA manual.

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