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ORIGINAL ARTICLE

Harnessing the power of child development records to detect early neurodevelopmental disorders using Bayesian analysis

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Abstract

Aim: This study aims to analyse the developmental data from public health nurses (PHNs) to identify early indicators of neurodevelopmental disorders (NDDs) in young children using Bayesian network (BN) analysis to determine factor combinations that improve diagnosis accuracy.

Methods: The study cohort was 501 children who underwent health checkups at 18 and 36-month. Data included demographics, pregnancy, delivery, neonatal factors, maternal interviews, and physical and neurological findings. Diagnoses were made by paediatricians and child psychiatrists using standardised tools. Predictive accuracy was assessed by the receiver operating characteristic (ROC) curve analysis.

Results: We identified several infant/toddler factors significantly associated with NDD diagnoses. Predictive factors included meconium-stained amniotic fluid, 1 min Apgar score, and early developmental milestones. ROC curve analysis showed varying predictive accuracies based on evaluation timing. The 10-month checkup was valid for screening but less reliable for excluding low-risk cases. The 18-month evaluation accurately identified children at NDD risk.

Conclusion: The study demonstrates the potential of using developmental records for early NDD detection, emphasising early monitoring and intervention for at-risk children. These findings could guide future infant mental health initiatives in the community.

KEYWORDS
developmental records, infancy, neonatal, neurodevelopmental disorders, predictive accuracy

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; AUC, area under the curve; BIF, borderline intellectual function; BN, Bayesian network; CI, confidence interval; CPT, conditional probability table; DAG, directed acyclic graph; DCD, developmental coordination disorder; DR-PHN, developmental record; ESSENCE, Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations; ESSENCE-Q, ESSENCE-Questionnaire; IDDs, intellectual developmental disorders; KSPD2001, Kyoto Scale of Psychological Development 200; NDDs, Neurodevelopmental disorders; NPV, negative predictive value; PHNs, public health nurses; PPV, positive predictive value; ROC, receiver operating characteristic; SDQ, Strengths and Difficulties Questionnaire; SLDs, speechlanguageand communication disorders; UI, utility index.

1 | INTRODUCTION

Neurodevelopmental disorders (NDDs) encompass conditions associated with differences in brain development and function, including autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder

(ADHD), intellectual developmental disorder (IDD), borderline intellectual function (BIF), developmental coordination disorder (DCD), and speech, language, and communication disorders (SLD), among others, posing challenges in learning, behaviour, and social interactions.[1] Overlap or co-morbidity of these conditions is the rule rather than the exception. And many of the early signs also overlap. This clinical fact is clearly stated as the concept in Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) by Gillberg. The prevalence of ESSENCE is about 10 per cent of children, and even into adulthood about 5 per cent are thought to have serious ESSENCE problems. ESSENCE reflects the notion that many children with NDDs present with a range of non-specific symptoms in early childhood, such as delays in general intellectual, motor, language/communication, and social development, atypical responses to sensory stimuli, hyper- or hypoactivity, impulsivity, and problems with sleeping and feeding.[2,3]

Early identification and intervention for NDDs in infants and young children are essential for optimising long-term outcomes.[4,5] However, early detection remains challenging because of subtle or absent symptoms.[6] Previous studies suggested that pregnancy-related abnormalities,[7–9] delivery-related abnormalities, and neonatal conditions are potential risk factors for NDDs; however, no research has comprehensively examined these factors together.

In Japan, municipal public health nurses (PHNs) are well-positioned to identify and monitor potential signs of NDDs during daily interactions with infants and their parents. They conduct regular infant health checkups and have access to comprehensive records documenting the child's developmental stage and general health status, including records from pregnancy and birth. These records provide valuable insights into prenatal issues and children's growth patterns, motor skills, language development, and social interactions. These data are filed and stored as each child's "developmental record" (DR-PHNs). However, no studies have systematically analysed these data to examine the risk and possible early identifier indicators of NDDs.

A Bayesian network (BN) model is used to determine the probability distribution for an event based on many joint variables/items. We previously assessed on motor development items from DR-PHNs and investigated the potential of early motor development problems to predict future NDD diagnosis using a BN model.[10] There was a correlation between early motor development problems and an increased likelihood of being diagnosed with an NDD later in life. Nevertheless, this predictive measure lacked the necessary sensitivity to serve as a screening tool for NDDs.

This study aimed to examine items from all DR-PHNs for children up to 18-month old to determine the combination of items that would predict NDD diagnosis with a higher probability, using a BN as the analytical method, as in the previous study. These findings will promote the use of DR-PHNs, which are collected in daily work by PHNs but are not yet used for developmental disorder screening, for earlier identification and support of children at risk of developmental disorders.

Key notes

- This study used Bayesian network analysis to identify early indicators of neurodevelopmental disorders (NDDs) from developmental data by public health nurses.
- Key predictive factors included meconium-stained amniotic fluid, 1 min Apgar score, and early developmental milestones, with ROC curve analysis showing varying accuracies.
- The findings emphasise early monitoring and intervention, highlighting the potential of developmental records for early NDD detection and future infant mental health initiatives.

2 | METHODS

2.1 | Participants

The participants included 501 children (256 boys and 245 girls): 243 who were brought to Kami or Aki City between April 2014 and March 2015 for 18-month checkups and 258 who were brought to Kami or Aki City during the same period for 36-month checkups. As the period was 1 year long, no children had both examinations during this period. These participants were the same participants included in our previous study.[10] None of the children were suspected of having visual or hearing impairments. All data were collected with informed consent from the parents.

2.2 | Procedure

At the first stage of the checkups, paediatricians with experience in neurodevelopmental assessment and NDDs examined the children. The diagnostic procedure remained the same for all children, involving a review of all development records since birth, evaluation of the ESSENCE-Questionnaire (ESSENCE-Q)[11,12] records completed by the mothers, PHNs, and psychologists to determine if more detailed neurodevelopmental examinations were indicated. The ESSENCE-Q is a brief, 12-item screening questionnaire designed to identify potential neurodevelopmental problems in children and is intended for use in both clinical and research settings. It is suggested to be beneficial as a parent questionnaire or a short interview conducted by a specialist.[11,13]

Children suspected of possibly having NDDs underwent a secondary health checkup administered by a child psychiatrist with extensive clinical experience with young children. During this secondary checkup, the psychiatrist reviewed all records in detail, interviewed the mothers, and observed the children's behaviours using the ESSENCE-Q structure. Children who displayed potential symptoms of NDDs, based on the assessment results, were directed to neurodevelopmental clinics. Secondary checkups were scheduled on a different day in about a month (although a few cases came after a few months) at the same place, but individually. The first visit to the neurodevelopmental clinics was usually one to 2 months after the secondary checkups.

Data from all developmental areas, including the ESSENCE-Q completed by the mothers and specialists, based on the observation of the children's behaviours and interviews with the mothers, were assessed at the neurodevelopmental clinic to confirm the diagnosis. Moreover, the Kyoto Scale of Psychological Development 2001 (KSPD2001)[14] was utilised to assess cognitive function. Sociability and communication were evaluated through the Diagnostic Interview for Social and Communication Disorders.[15] In addition, the Japanese version of the Strengths and Difficulties Questionnaire (SDQ) for parents,[16] a comprehensive tool used to assess various aspects of mental health and development in children, such as behaviour, emotion, and interpersonal relationships, was used. The assessments above mentioned were conducted for every child who visited the clinics. Assessments using the ESSENCE-Q, KSPD2001, and SDQ were conducted every 6 months.

TABLE 1 Items used in the analysis.

Type of information	Items	Values considered problems
Demographic information	Sex	n.a. (256 boys, 245 girls)
	Birth order	First born
	Age of the father at birth	<20, >40 (M = 32.4, SD = 5.65)
	Age of the mother at birth	<20, >35 (M = 30.4, SD = 4.98)
Pregnancy-related abnormalities	Threatened preterm labor	YES
	Hyperemesis gravidarum	YES
	Urinary sugar during pregnancy	YES
	Toxaemia of pregnancy	YES
	Infections	YES
	Medication use	YES
	Paternal smoking	YES
	Maternal smoking	YES
Delivery-related abnormalities	Caesarean delivery	YES
	Delayed delivery	YES
	Fetal distress	YES
	Meconium-stained amniotic fluid	YES
	Polyhydramnios	YES
	Premature rupture of membranes	YES
Neonatal conditions	Apgar score at 1 min	<8(M = 8.7, SD = 0.76)
	Apgar score at 5 min	<8(M = 9.1, SD = 0.56)
	Gestational age	<37 weeks
	Birth weight	<2500 g(M = 3017, SD = 410.6)
	Head circumference	≤31 cm, ≥36 cm(M = 33.3, SD = 1.33)
	Neonatal asphyxia	YES
	Intracranial haemorrhage	YES
	Neonatal seizures	YES
	Jaundice	YES
Items obtained from interviews with the mothers	At 4-month checkups	See Table 2
	At 10-month checkups	
	At 18-month checkups	
Physical and neurological findings by the paediatricians	At 4-month checkups	See Table 3
	At 10-month checkups	
	At 18-month checkups	

Children with hyperactivity, impulsivity, and inattention problems and those suspected of having ASD were assessed using the ADHD rating scale[17] and the Autism Spectrum Screening Questionnaire,[18] respectively. In addition, occupational therapists (or/and specialised psychologists) and the child psychiatrist (or a paediatric neurologist) assessed children's motor-perceptual performance based on clinical

TABLE 2 Interviews with mothers.

Checkups	Item	Values considered problems
4 Months	*Do you feel your baby's neck is still wobbly when you hold them?*	YES
	When you hold your baby, does your baby's body feel floppy?	YES
	Do your baby's limbs feel tight and stiff when you hold them?	YES
	Does your baby lie on their stomach with arms supporting their body and head up?	NO
	Does your baby bring their hands to their mouth?	NO
	Does your baby play with their hands together in front of them?	NO
	Does your baby follow moving objects with their eyes?	NO
	Does your baby show interest in toys and other objects?	NO
	Does your baby shake or lick toys?	NO
	Does your baby laugh aloud when you feed them?	NO
	Does your baby make sounds such as oohs and aahs?	NO
	Does your baby turn their head when you call to them?	NO
10 Months	*Does your child crawl?*	NO
	Does your child hold on and stand by themselves?	NO
	Does your child walk while holding onto things?	NO
	Does your child stand on their own?	NO
	Does your child walk when held by both hands?	NO
	Can your child pick up small objects with their fingers?	NO
	Does your child look at the parent when you say "no"?	NO
	Have you ever worried about your child's hearing?	YES
	Does your child show what they want without crying?	NO
	Do you receive the thing you ask for from your child when you make the "give me the thing" gesture?	NO
	Does your child imitate the pronunciation of their parents?	NO
	Does your child follow you?	NO
	Does your child imitate gestures such as waving?	NO
	Does your child imitate their parents?	NO
18 Months	*Can your child walk well?*	NO
	Can your child squat and lift objects?	NO
	Can your child climb stairs when you hold their hand lightly?	NO
	Does your child scribble with a pencil?	NO
	Can your child stack two or more blocks?	NO
	Does your child turn around when you whisper their name from behind?	NO
	Does your child make eye contact?	NO
	Do you worry that your child's eye contact or eye movements are unusual?	YES
	Does your child point to things they know when asked?	NO
	Can your child say at least one meaningful word?	NO
	Does your child show interest in other children?	NO
	Does your child play well with other children?	NO
	Does your child imitate what their parents do?	NO
	Can your child drink water from a cup?	NO
	Does your child eat meals by themselves?	NO
	Is your child a picky eater?	YES

observations of behaviours, such as standing, walking, throwing, and retrieving a ball, in diagnosing DCD. Specialists continued consistent, unstructured clinical observations throughout the study, conducting interviews and collecting reports from parents, nursery school teachers, and kindergarten teachers in nearly every examination. Diagnoses were reviewed every 6 months, with all information obtained up to that point checked and re-evaluated. The regular assessments described above were repeated until the child reached 6 years of age. On completion of these procedures, diagnoses were made on the basis of the diagnostic criteria for childhood mental and neurodevelopmental disorders set out in the International Statistical Classification of Diseases and Related Health Problems-10 and the Diagnostic and Statistical Manual of Mental Disorders-IV. The diagnoses included in the analysis were ASD, ADHD, DCD, SLD, BIF/IDD, and others, such as tics, reactive attachment disorder, and social anxiety disorder.

2.3 | Items from DR-PHNs

- Demographic information, pregnancy-related abnormalities, delivery-related abnormalities, neonatal conditions (the items relating to this type of information are set out in Table 1).
- Items obtained from interviews with the mothers at 4-, 10-, and 18-month checkups (Table 2).

TABLE 3 Physical and neurological examinations by paediatricians.

	Examinations	4 Months	10 Months	18 Months
Physical	Macrocephaly	✓	✓	✓
	Microcephaly	✓	✓	✓
	Abnormal findings of anterior fontanel	✓	✓	✓
	Facial appearance	✓	✓	✓
	Nystagmus	✓	✓	✓
	Strabismus	✓	✓	✓
	Vision abnormalities	✓	✓	✓
	Hearing abnormalities	✓	✓	✓
	Auricular abnormalities	✓	✓	
	Torticollis	✓		
Neurological	Head control	✓		
	Pursuit vision	✓	✓	
	Posture	✓	✓	
	Muscle tone	✓	✓	
	Triggering reflex	✓	✓	
	Morrow reflex	✓		
	Tonic neck reflex	✓		
	Vertical suspension	✓	✓	
	Ventral suspension	✓	✓	
	Prone position	✓	✓	
	Grasping	✓	✓	
	Pull-up standing		✓	
	Parachute reflex		✓	
	Hopping reaction		✓	
	Gait			✓
	Gross motor development			✓
	Fine motor development			✓
	Speech and language development			✓
	Social interaction			✓
	Hyperactivity			✓
	Interest in surrounding environment			✓

Note: Check marks (✓) indicate which examinations have been undertaken at each developmental stage.

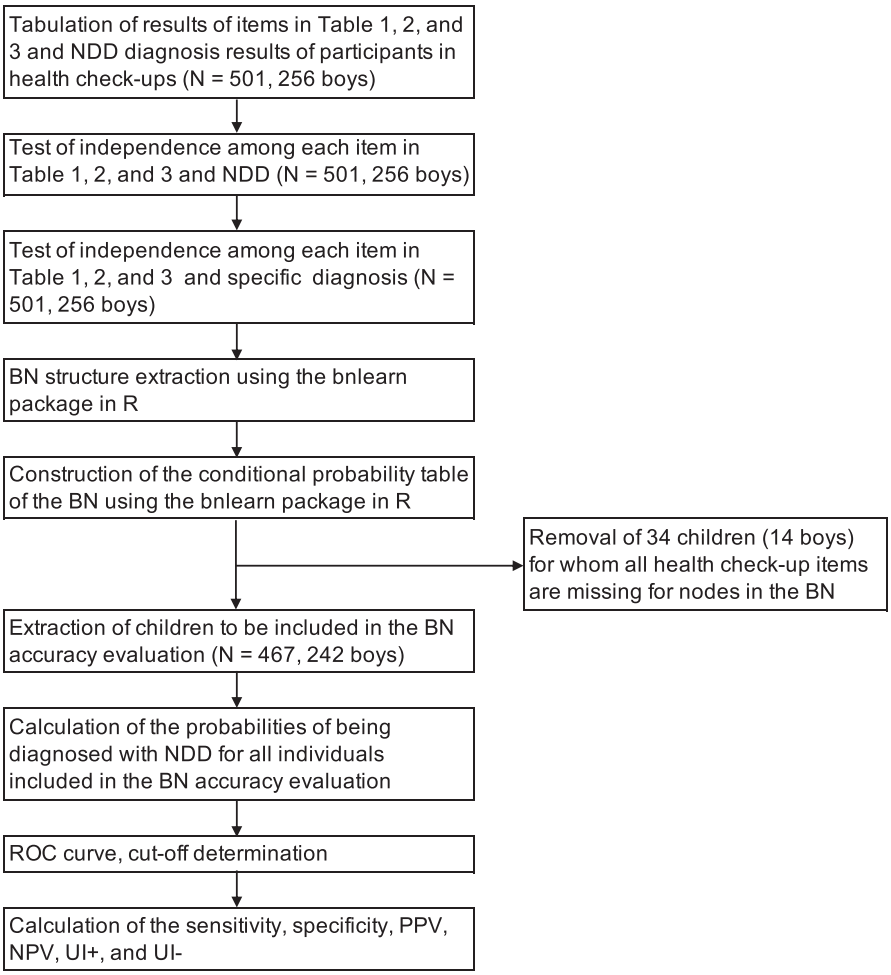

FIGURE 1 Flow chart showing the analytical process. BN, Bayesian network; NDD, neurodevelopmental disorder; NPV, negative predictive value; PPV, positive predictive value; ROC, receiver operating characteristic; UI +, positive utility index; UI −, negative utility index.

- Physical and neurological findings assessed by paediatricians at 4-, 10-, and 18-month checkups (Table 3).

2.4 | Analysis

The analysis process involved several steps (Figure 1). First, independence tests were conducted between each explanatory variable and NDD diagnoses. The purpose was to identify items with a significant relationship to the diagnoses and ensure their inclusion in the later constructed BN. Fisher's exact test was used to investigate the relationships between diagnoses and each item in Tables 1–3, inferring population characteristics and extracting significant health checkup items. The predetermined significance level was set at $p < 0.05$.

Next, the directed acyclic graph (DAG) of the BN was constructed using all items from Tables 1–3, NDD diagnosis, and diagnosis types (BIF/IDD, ASD, ADHD, DCD, SLD, and other NDDs) as candidate nodes. Structure learning was performed using one of the diagnosis types and all the items in Tables 1–3 as node candidates. Arrow lines from each diagnosis type to the node NDD were manually added after repeating the structure learning for all diagnosis types. In the structure learning, the graph structure was determined based on dependencies found using the semi-interleaved HITON-PC algorithm, using a χ^2 test for conditional independence. This algorithm effectively identifies dependencies between nodes through hypothesis testing of conditional independence and connects them with undirected arrow lines (undirected arcs). The direction of the arrow lines was set manually, considering the meanings of nodes connected by the arrow lines. Among the items in Tables 1–3, some items for which the path of arrows leading to diagnosis types were not extracted in the structural learning, despite associations with the diagnosis types found in the independence test. In this case, the arrows were manually added from the items to establish the path to the diagnostic type associated with the independence test.

The conditional probability table (CPT) of the BN was derived from the obtained DAG and the data for the analysed participants. The statistical software R (R Foundation for Statistical Computing), specifically the "bnlearn" package, was used in the DAG structure creation and CPT derivation.

The predictive accuracy of NDD diagnosis using the aforementioned BN (the accuracy with which items that were considered problems in Tables 1–3 predict the diagnosis of some NDDs) was assessed as follows:

TABLE 4 Diagnoses of children with NDD.

NDD diagnoses	Number of cases	Average age in months (SD) at diagnosis	Notes
ADHD	12 (7 boys)	55.8 (19.9)	–
ASD	9 (7 boys)	40.7 (14.0)	Three boys had previously been diagnosed with an ESSENCE disorder before the evaluation.
ADHD+SLD	7 (6 boys)	ADHD: 50.0 (15.2), SLD: 56.1 (10.9)	-
IDD/BIF	6 (5 boys)	52.8 (13.2)	–
ASD + ADHD	4 (4 boys)	ASD: 56.3 (10.0), ADHD: 56.3 (10.0)	One boy had previously been diagnosed with an ESSENCE disorder before the evaluation.
ADHD+BIF	3 (2 boys)	ADHD: 47.0 (7.9), BIF: 54.7 (12.5)	–
SLD	3 (2 boys)	36.0 (8.5)	One boy had previously been diagnosed with an ESSENCE disorder before the evaluation.
ADHD+DCD	3 (3 boys)	ADHD: 44.0 (6.2), DCD: 41.7 (2.5)	–
RAD	1 (1 girl)	53	–
ASD + DCD	1 (1 boy)	ASD: 33, DCD: 28	–
ASD + IDD	1 (1 boy)	ASD: 30, IDD: 37	–
ASD + SLD	1 (1 girl)	unknown	One girl had previously been diagnosed with an ESSENCE disorder before the evaluation.
DCD + ADHD+BIF	1 (1 girl)	DCD: 34, ADHD: 42, BIF: 50	–
ASD + DCD + Tics	1 (1 boy)	ASD: 48, DCD: 48, Tics: 48	–
DCD + Tics+social anxiety disorder	1 (1 girl)	DCD: 45, Tics: 45, social anxiety disorder: 46	–
NDD (precise diagnosis unknown)	3 (2 boys)	unknown	One boy and one girl had previously been diagnosed with an ESSENCE disorder before the evaluation. The relevant medical institution did not provide information for one boy.
Total	57 (41 boys)		

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIF, borderline intellectual functioning; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; IDD, intellectual developmental disorder; NDD, neurodevelopmental disorder; RAD, reactive attachment disorder; SD, standard deviation; SLD, speech and language disorder.

1. The posterior probability of a positive NDD diagnosis, given the presence or absence of a problem for each item node, was determined using BN.
2. The sensitivity and specificity were determined and graphed when a certain posterior probability was used as the cutoff value, and a receiver operating characteristic (ROC) curve was drawn. In subsequent analyses, the data from 34 children who were missing all checkup items included in the BN were excluded.
3. The area under the curve (AUC) value of the ROC curve was used to assess the prediction accuracy of NDD diagnosis using the posterior probability calculated using the BN. As a screening test, an AUC >0.7 indicates acceptable accuracy, whereas an AUC >0.9 indicates very high accuracy.[19–21]
4. The posterior probability of maximising the Youden Index (sensitivity + specificity − 1) in the ROC curve was determined as the optimum cutoff value. Subsequently, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and utility index (UI) at that value were determined. The UI measures the clinical utility of screening, with rule-in accuracy being positive UI (UI +) calculated as sensitivity × PPV. Negative UI (UI −), calculated as specificity × NPV, assesses rule-out accuracy. The criteria for evaluation are: less than 0.2 is poor, between 0.2 and 0.4 is fair, between 0.4 and 0.6 is moderate, between 0.6 and 0.8 is good, and higher than 0.8 is very good.[12,22]
5. All combinations of values for all items were enumerated, and the posterior probability of an NDD was derived for each value combination using the BN. From these results, we enumerated all combinations of values of items such that the posterior probability of NDD exceeded 0.5. In addition, we found all sets of

TABLE 5 Variables used for Bayesian network construction.

Type of information	Variable	Code in the figure[a]	Fisher's Exact Test[b]
Demographic information	Sex	Sex	Any NDD**, ASD*, ADHD*
Pregnancy-related abnormalities	Maternal smoking	B1	–
Delivery-related information	Meconium-stained amniotic fluid	B2	Any NDD*, ADHD*
Neonatal conditions	Apgar score at 1 min	B3	Any DD*
Items obtained from interviews with the mothers at 4-month checkups	*Does your baby play with their hands together in front of them?*	C4_M1	SLD*
	Does your baby turn their head when you call to them?	C4_M2	Others*
Items obtained from interviews with the mothers at 10-month checkups	*Does your child crawl?*	C10_M1	BIF/IDD*
	Does your child hold on and stand by themselves?	C10_M2	BIF/IDD*
	Does your child walk while holding onto things?	C10_M3	BIF/IDD**
	Does your child walk when held by both hands?	C10_M4	BIF/IDD**
	Does your child look at the parent when you say "no"?	C10_M5	Any NDD**, DCD**
	Does your child imitate the pronunciation of their parents?	C10_M6	Any NDD**, ASD*, ADHD*, SLD*
	Does your child imitate gestures such as waving?	C10_M7	Any NDD**, BIF/IDD**, ASD**, ADHD*, DCD*
	Does your child imitate their parents?	C10_M8	Any NDD**, BIF/IDD**, ADHD*, SLD**
Neurological examinations at 10-month checkups	Pull-up standing	C10_P1	BIF/IDD**
Items obtained from interviews with the mothers at 18-month checkups	*Can your child walk well?*	C18_M1	Any NDD**, BIF/IDD**
	Can your child squat and lift objects?	C18_M2	BIF/IDD*, DCD*
	Does your child scribble with a pencil?	C18_M3	Any NDD*, ASD*, SLD**
	Do you worry that your child's eye contact or eye movements are unusual?	C18_M4	Any NDD**, ADHD*
	Can your child say at least one meaningful word?	C18_M5	Any NDD**, BIF/IDD*, SLD*
	Does your child play well with other children?	C18_M6	Others*
	Can your child drink water from a cup?	C18_M7	BIF/IDD*, DCD*
	Does your child eat meals by themselves?	C18_M8	Any NDD**, BIF/IDD*, ASD*
	Is your child a picky eater?	C18_M9	BIF/IDD*
Neurological examinations at 18-month checkups	Gait	C18_P1	Any NDD**, BIF/IDD**
	Speech and language development	C18_P2	Any NDD**, BIF/IDD**, ASD**, DCD**, SLD**
	Social interaction	C18_P3	Any NDD**, BIF/IDD**, ASD**, ADHD*, DCD**
	Hyperactivity	C18_P4	Any NDD**, BIF/IDD**, ADHD*
	Interest in surrounding environment	C18_P5	Any NDD**, BIF/IDD**, ASD**, ADHD*, DCD*, SLD*

Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIF, borderline intellectual functioning; DCD, developmental coordination disorder; ESSENCE, early symptomatic syndromes eliciting neurodevelopmental clinical examinations; IDD, intellectual developmental disorder; NDD, neurodevelopmental disorder; RAD, reactive attachment disorder; SD, standard deviation; SLD, speech and language disorder.

[a]"B" and "C" in the codes stand for birth and check-up, respectively. "M" and "P" stand for mothers and paediatricians, respectively.

[b]Independence tests were conducted between each item in Tables 1–3 and NDD diagnoses (any NDD, ADHD, ASD, BIF/IDD, DCD, SLD, and Others). This table includes all items with a significant relationship ($p < 0.05$) to the diagnoses. The tests did not find a relationship between the item coded as B1 and the diagnoses, but the Bayesian network structure learning identified a relationship with "Others."

*$p < 0.05$, **$p < 0.01$.

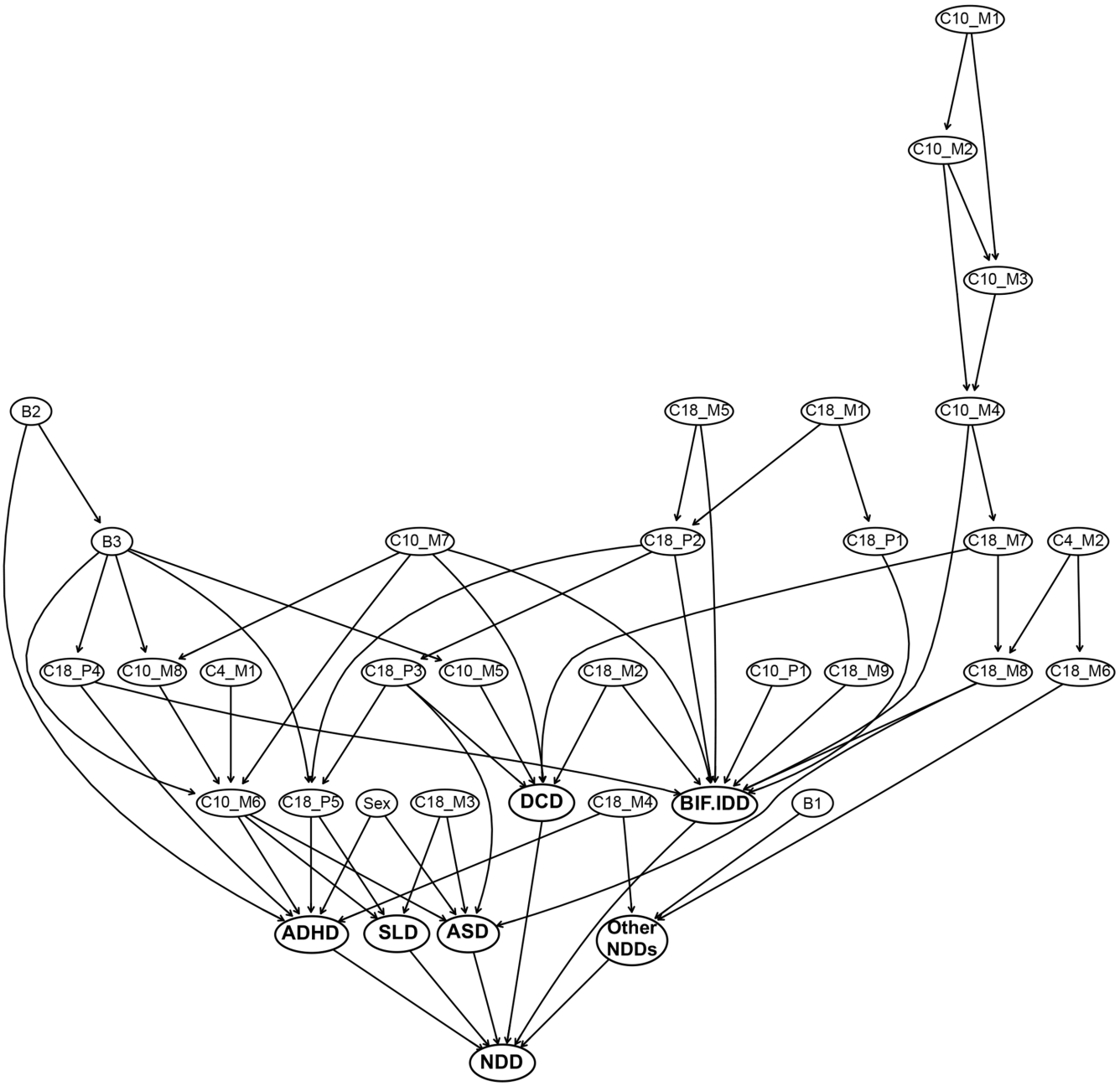

FIGURE 2 The directed acyclic graph of the constructed Bayesian network. The codes in the nodes are explained in Table 5 (brief explanations are provided herein). B1, maternal smoking; B2, meconium-stained amniotic fluid; B3, Apgar score (1 min); C4_M1, plays with their hands; C4_M2, turns their head when called; C10_M1, crawls; C10_M2, holds on and stands by themselves; C10_M3, walks while holding onto things; C10_M4, walks when held by both hands; C10_M5, looks at the parent when they say "no"; C10_M6, imitates the pronunciation of their parents; C10_M7, imitates gestures such as waving; C10_M8, imitates their parents; C10_P1, pull-up standing; C18_M1, walks well; C18_M2, squats and lifts objects; C18_M3, scribbles with a pencil; C18_M4, unusual eye contact or movements; C18_M5, says at least one meaningful word; C18_M6, plays well with other children; C18_M7, drinks water from a cup; C18_M8, eats meals by themselves; C18_M9, picky eater; C18_P1, gait; C18_P2, speech and language development; C18_P3, social interaction; C18_P4, hyperactivity; C18_P5, interest in surrounding environment. ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIF, borderline intellectual functioning; DCD, developmental coordination disorder; IDD, intellectual developmental disorder; NDD, neurodevelopmental disorder; SLD, speech and language disorder.

items for which the posterior probability exceeded 0.5 when all items in a set were abnormal, regardless of the values of the other items. Identifying such a set of items is considered helpful in clinical practice.

The prediction accuracy evaluation described above was repeated four times by changing the items providing evidence in Step 1 above. The items that provided evidence for the following four cases were:

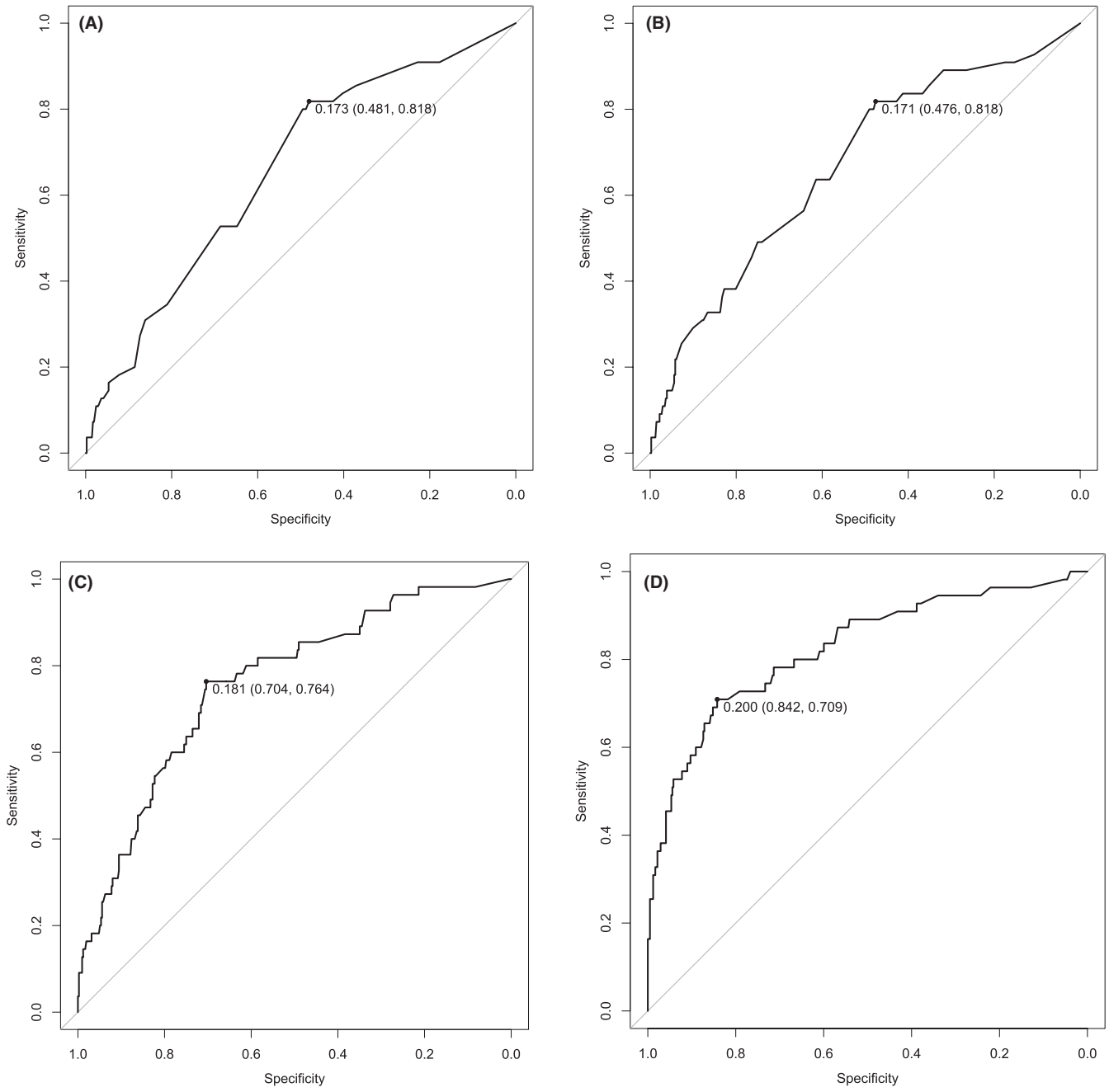

FIGURE 3 ROC curves for NDD diagnosis predicted by Bayesian network using four different sets of checkup items. The points on the curves indicate the Youden Index (specificity and sensitivity in parentheses). (A) Items before 4-month checkup. (B) Items before and at 4-month checkup. (C) Items before and at 10-month checkup. (D) Items before and at 18-month checkup. NDD, neurodevelopmental disorder; ROC, receiver operating characteristic.

- Items with values that were available before 4-month checkups (demographic information, pregnancy-related abnormalities, delivery-related abnormalities, and neonatal conditions).
- Items with values that were available at 4-month checkups and before the checkups.
- Items with values that were available at 10-month checkups and before the checkups.
- Items with values that were available at 18-month checkups and before the checkups.

2.5 | Ethical considerations

This study was conducted following the principles of the Declaration of Helsinki, with the approval of the Institutional Review Board of the Kochi Prefectural Rehabilitation and Welfare Centre (No. 24–473). Furthermore, written informed consent was obtained from the parents or caregivers of the individuals before participation. More specifically, at the checkups, the document explaining the research was included in the municipal checkup guide sent out in advance. If

TABLE 6 Comparison of prediction accuracy across different checkup ages.

	Before 4-month checkups	4-month checkups	10-month checkups	18-month checkups
AUC[a]	0.659 (0.584–0.734)	0.669 (0.592–0.747)	0.758 (0.691–0.825)	0.825 (0.759–0.891)
Sensitivity	0.818 (0.716–0.920)	0.818 (0.716–0.920)	0.765 (0.651–0.876)	0.709 (0.589–0.829)
Specificity	0.481 (0.432–0.529)	0.476 (0.428–0.524)	0.704 (0.660–0.748)	0.842 (0.807–0.877)
PPV	0.174 (0.128–0.220)	0.172 (0.127–0.218)	0.256 (0.189–0.323)	0.375 (0.282–0.468)
NPV	0.952 (0.923–0.981)	0.951 (0.922–0.981)	0.957 (0.934–0.980)	0.956 (0.935–0.977)
UI +[b]	0.142 (0.046–0.238)	0.141 (0.046–0.237)	0.196 (0.081–0.310)	0.266 (0.132–0.400)
UI −[b]	0.457 (0.410–0.505)	0.453 (0.405–0.500)	0.674 (0.639–0.709)	0.805 (0.779–0.832)

Note: Values in parentheses indicate the 95% confidence interval.

Abbreviations: AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value; UI +, positive utility index; UI −, negative utility index.

[a]AUC >0.7: acceptable accuracy, AUC >0.9: very high accuracy.

[b]UI <0.2: poor, 0.2 ≤UI <0.4: fair, 0.4 ≤UI <0.6: moderate, 0.6 ≤UI <0.8: good, UI ≥0.8: very good.

TABLE 7 All combinations of values of items available before a 4-month checkup where the posterior probability of neurodevelopmental disorder always exceeds 0.5.

Item	Value[a]	Meaning of item
Sex		*Sex*
B1		*Maternal smoking*
B2	+	*Meconium-stained amniotic fluid*
B3	+	*Apgar score at 1 minute*

[a]"+" indicates positive. Blank indicates any value (i.e., positive or negative).

parents do not want to participate in the research, they could offer their refusal at the reception desk on the day of the checkups. In addition, at the neurodevelopmental clinics, a verbal and written explanation was given individually at the time of the first medical examination, and only the medical information of those who had signed a consent form was used as data.

3 | RESULTS

3.1 | Diagnoses (Table 4)

As we used the same sample as in a previous study,[10] the same table for diagnosing NDDs in that study applies to the current study. In the 18-month-old and 36-month-old populations, the prevalence of diagnosed NDD rates was 9.1% (with 9.1% observed in Kami City and 9.0% in Aki City) and 13.6% (with 11.0% and 16.7% observed in Kami City and Aki City), respectively. In addition, data analysis revealed that the male-to-female ratio was 3.4:1 and 2.2:1 in the 18-month-old and 3-year-old populations, respectively.

3.2 | Fisher's exact test and BN construction

The fourth column of Table 5 presents Fisher's exact test results for each variable concerning the presence or absence of a diagnosis of any NDD and each diagnosis included in the analysis. Figure 2 shows the constructed DAG. Table 5 shows the variables used for construction. Items included as nodes in the DAG among the demographic information, pregnancy-related abnormalities, delivery-related abnormalities, and neonatal status were sex, maternal smoking, meconium-stained amniotic fluid, and 1 min Apgar score.

3.3 | Predictive accuracy of NDD diagnosis

Figure 3A shows ROC curves when using the items before the 4-month checkup, yielding an AUC of 0.659 (95% confidence interval [CI]: 0.584–0.734). The posterior probability with the maximal Youden Index (optimal cutoff value) was 0.173. At this value, the sensitivity, specificity, PPV, NPV, UI +, and UI − were 0.818 (0.716–0.920), 0.481 (0.432–0.529), 0.174 (0.128–0.220), 0.952 (0.923–0.981), 0.142 (0.046–0.238), and 0.457 (0.410–0.505), respectively.

Figure 3B shows the ROC curves when using the items before and at the 4-month checkup, yielding an AUC of 0.669 (95% CI: 0.592–0.747). The posterior probability with the maximal Youden Index (optimal cutoff value) was 0.171. At this value, the sensitivity, specificity, PPV, NPV, UI +, and UI − were 0.818 (0.716–0.920), 0.476

TABLE 8 All combinations of values of items available before and at a 4-month checkup where the posterior probability of neurodevelopmental disorder always exceeds 0.5.

Item	Value[a]			Meaning of item
Sex		+	+	*Sex*
B1	+			*Maternal smoking*
B2	+	+	+	*Meconium-stained amniotic fluid*
B3		+		*Apgar score at 1 min*
C4_M1			+	*Does your baby play with their hands together in front of them?*
C4_M2	+	+	+	*Does your baby turn their head when you call to them?*

[a]"+" indicates positive. Blank indicates any value (i.e., positive or negative).

TABLE 9 All combinations of values of items available before and at a 10-month checkup where the posterior probability of neurodevelopmental disorder always exceeds 0.5.

Item	Value[a]															Meaning of item
Sex		+	+	+	+	+				+	+	+		+	+	*Sex*
B1							+		+		+		+	+	*Maternal smoking*
B2	+	+	+				+			+	+		+	+		*Meconium-stained amniotic fluid*
B3		+		+	+		+	+	+	+		+				*Apgar score at 1 min*
C4_M1											+		+	+	+	*Does your baby play with their hands together in front of them?*
C4_M2			+	+		+	+	+	+	+			+	+	+	*Does your baby turn their head when you call to them?*
C10_M1																*Does your child crawl?*
C10_M2																*Does your child hold on and stand by themselves?*
C10_M3																*Does your child walk while holding onto things?*
C10_M4												+				*Does your child walk when held by both hands?*
C10_M5																*Does your child look at the parent when you say "no"?*
C10_M6	+			+	+	+			+			+				*Does your child imitate the pronunciation of their parents?*
C10_M7											+	+	+	+	+	*Does your child imitate gestures such as waving?*
C10_M8											+		+	+	+	*Does your child imitate their parents?*
C10_P1		+	+		+	+	+	+	+		+		+		+	*Pull-up standing*

[a]"+" indicates positive. Blank indicates any value (i.e., positive or negative).

TABLE 10 Excerpts from the combinations of values of items available before and at a 18-month checkup where the posterior probability of neurodevelopmental disorder always exceeds 0.5.

Item	Value[a]																										
Sex	+						+	+	+	+																	
C18_M1																											
C18_M2		+	+				+				+	+	+														
C18_M3							+	+	+	+	+	+	+	+	+	+	+	+	+								
C18_M4	+		+	+	+	+																			+	+	
C18_M5								+						+	+							+	+	+	+	+	
C18_M6		+		+					+							+	+	+				+	+	+			+
C18_M7																											
C18_M8					+						+			+		+			+		+					+
C18_M9																											
C18_P1										+									+	+		+		+			+
C18_P2																											
C18_P3						+						+					+										
C18_P4													+		+			+		+				+		+	
C18_P5	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

Values of the checkup items not shown in this table are all blank.

[a]"+" indicates positive. Blank indicates any value (i.e., positive or negative).

(0.428–0.524), 0.172 (0.127–0.218), 0.951 (0.922–0.981), 0.141 (0.046–0.237), and 0.453 (0.405–0.500), respectively.

Figure 3C shows ROC curves when using the items before and at the 10-month checkup, yielding an AUC of 0.758 (95% CI: 0.691–0.825). The posterior probability with the maximal Youden Index (optimal cutoff value) was 0.181. At this value, the sensitivity, specificity, PPV, NPV, UI +, and UI − were 0.765 (0.651–0.876), 0.704 (0.660–0.748), 0.256 (0.189–0.323), 0.957 (0.934–0.980), 0.196 (0.081–0.310), and 0.674 (0.639–0.709), respectively.

Figure 3D shows the ROC curves when using the items before and at the 18-month checkup, yielding an AUC of 0.825 (95% CI: 0.759–0.891). The posterior probability with the maximal Youden Index (optimal cutoff value) was 0.200. At this value, the sensitivity, specificity, PPV, NPV, UI +, and UI − were 0.709 (0.589–0.829), 0.842 (0.807–0.877), 0.375 (0.282–0.468), 0.956 (0.935–0.977), 0.266 (0.132–0.400), and 0.805 (0.779–0.832), respectively.

To allow comparison of prediction accuracy across checkup ages, these values for accuracy are summarised in Table 6.

Tables 7–10 detail the combinations of values for each item when the posterior probability of an NDD exceeded 0.5. However, Table 10 only shows the following excerpts. There were 189 combinations for which the posterior probability of NDD exceeded 0.5 when values were given as evidence for all items up to the 18-month checkup. Owing to space limitation and clinical usefulness, Table 10 lists all 47 combinations of item values for the 18-month checkup, leading to posterior probabilities exceeding 0.5, regardless of the item values up to the 10-month checkup.

4 | DISCUSSION

Prior research has highlighted the importance of early identification and intervention for NDDs in infants and young children to support long-term outcomes.[2–5] However, early detection remains challenging at an early age. In the current paper, we used Bayesian network analysis of data from routine health checkups to identify important early predictors for later NDDs. Pregnancy-related abnormalities,[7–9] delivery-related abnormalities, and neonatal conditions and early ESSENCE-related traits,[2] according to interviews from mothers and clinician evaluation, were explored as longitudinal predictors. Several novel findings were obtained along with corroboration of prior research.

4.1 | Items included in the DAG

Male sex and maternal smoking during pregnancy, known NDD risks, were supported by this study.[23,24] Meconium-stained amniotic fluid, previously inconsistently linked to ASD,[25,26] was associated with a higher probability of ASD and other NDDs in this study, warranting further investigation including problems derived from

																					Meaning of item
				+	+	+	+														*Sex*
																					Can your child walk well?
																					Can your child squat and lift objects?
				+	+	+	+	+	+	+	+	+	+	+						+	*Does your child scribble with a pencil?*
		+	+															+	+		*Do you worry that your child's eye contact or eye movements are unusual?*
								+													*Can your child say at least one meaningful word?*
+	+														+	+	+				*Does your child play well with other children?*
				+	+				+	+								+	+	+	*Can your child drink water from a cup?*
				+		+	+		+		+	+	+		+	+	+				*Does your child eat meals by themselves?*
+		+			+	+					+	+	+		+	+	+		+		*Is your child a picky eater?*
+	+	+	+					+						+					+	+	*Gait*
							+				+		+		+		+		+	+	*Speech and language development*
								+						+						+	*Social interaction*
	+		+						+	+		+	+			+	+	+			*Hyperactivity*
+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+	*Interest in surrounding environment*

meconium-stained amniotic fluid (e.g., foetal aspiration syndrome and neonatal infections) and NDDs. Unlike prior research showing an NDD risk with low 5 min Apgar scores was associated with a risk of NDD,[27] no significant association was found in the present study, possibly due to the small number of cases with abnormal values. However, low 1 min Apgar scores did increase NDD risk. Despite the consensus on low 1 min Apgar scores not posing a problem if a patient recovers after 5 min, further detailed studies on NDDs may be necessary.

Two items from maternal interviews at the 4-month checkups were included in the DAG, possibly reflecting the challenge of accurate assessments at this stage. Eight items from 10-month maternal interviews were included in the BN, possibly due to the increased reliability of assessments made by mothers at this developmental stage. These items related to motor development, imitation, and response to others, suggesting their importance as NDD risk factors. The paediatricians' findings from the same period adopted an item on "pull-up standing" for the BN. "Pull-up standing", as a precursor to standing and walking, may thus be an important milestone in motor development confirming prior research.[28,29]

At 18-month checkups, nine items from maternal interviews and six from paediatricians were included in the BN. These items encompassed general intellectual, motor, language or communication, social development, and feeding domains, all under the umbrella of the concept of ESSENCE. According to Gillberg,[2] ESSENCE is not intended to replace more detailed NDD diagnosis/−es. Instead, the concept serves as an umbrella term for all the early onset neurodevelopmental syndromes that always require careful multidisciplinary assessment and long-term follow-up. In very young children, in particular, ESSENCE may be the only "label" that is suitable until a more definite diagnosis/−es can be made, and in this sense the current findings confirm early ESSENCE problems as predictors of future NDDs.

4.2 | Prediction accuracy evaluation

The AUC based on the ROC curve was 0.659 for items available before the 4-month checkups and 0.669 for items available at and before the 4-month checkups, neither of which met the acceptable accuracy criteria (AUC >0.7). This result implies that early prediction of NDD risk is impossible with any degree of validity or that currently collected DR-PHNs up to 4 months are insufficient. In contrast, the AUC for items available at and before the 10-month checkups was 0.758, meeting the accuracy criteria, with sensitivity and specificity both higher than 0.7 but a UI− of 0.674. This indicates that while screening for cases needing follow-up is possible at 10 months, excluding risk-free cases is not fully valid. The AUC for items available at and before the 18-month checkups was 0.825, with sensitivity and specificity exceeding 0.7 and

a UI− of 0.805, suggesting effective screening and exclusion of risk-free cases at this stage.

4.3 | Combinations of items with posterior probabilities exceeding the cutoff value

The analysis identified a specific combination of factors, B2 (meconium-amniotic fluid) and B3 (1-min Apgar score), with a posterior probability exceeding 50% before the 4-month checkup. Moreover, all combinations up to the 4-month checkup with a posterior probability exceeding 50% included B2 and C4_M2 ("Does your baby turn their head when you call to them?"). In addition, every combination of factors up to the 10-month checkup with a minimum posterior probability exceeding 0.5 had positive abnormal findings in at least one of B2 (meconium-amniotic fluid), B3 (1 min Apgar score), C4_M2 ("Does your baby turn their head when you call to them?"), and C10_P1 (pull-up standing). These findings underscore the significance of considering meconium-amniotic fluid and the 1 min Apgar score as potential risk factors for future NDDs. The response to the mother's voice may indicate social communication and attention development, particularly in the absence of hearing issues. Early recognition of social and attention problems in infancy, with timely intervention, holds promise for improving prognoses. In addition, the inclusion of pull-up standing at the 10-month checkup in our study on motor development further emphasises its potential as an early indicator of NDD.

In the context of the 47 potential combinations of factors up to the 18-month checkup, where the posterior probability exceeded 50%, regardless of previous results up to the 10-month checkup, C18_M3 ("Does your child scribble with a pencil?") was present in 55.3% of them. Moreover, C18_P5 (interest in the surrounding environment) was a consistent component in all these combinations. Even if earlier checkups did not identify any developmental issues, the presence of problems in fine motor development, such as hand dexterity or social communication, at the 18-month checkup necessitates vigilant monitoring of the child's developmental progress, considering the risk of NDDs. This conclusion fares well with findings by Øien et al.,[30] revealing that children who are later diagnosed with ASD tend to exhibit delays at 18 months in core social and communication areas as well as fine motor skills even though some screen negative on standard parent ratings scales of autism, such as the M-CHAT.

A limitation of our study is the inability to assess the risk of NDD for items with no or minimal abnormal values in the study sample. In addition, variations in the number of responses available for different items introduced differences in the analysis. Future analyses will involve additional samples, ensuring a more comprehensive understanding and validation of the obtained results to enhance the robustness of our findings.

All data used in this study were collected in the daily work of PHNs in municipalities in Japan. Therefore, the findings from this study can be applied to future infant mental health activities in the community.

5 | CONCLUSION

This study is the first systematic analysis of DR-PHNs for early NDD detection. We assessed DR-PHNs' predictive accuracy for NDD diagnoses using a BN and identified items linked to NDDs. The results showed acceptable predictive accuracy up to the 10-month checkup, with combinations having a minimum posterior probability >0.5. The findings support the feasibility and significance of early detection and monitoring of children at risk for NDDs. Our study highlights the accuracy in excluding cases not at risk during the 18-month checkup. Furthermore, we identified specific items that warrant ongoing monitoring from this point onward to track the developmental trajectory of children at risk for NDD.

AUTHOR CONTRIBUTIONS

Yuhei Hatakenaka: Conceptualization; methodology; investigation; resources; writing – original draft; project administration; funding acquisition; data curation. **Koutaro Hachiya:** Conceptualization; methodology; software; formal analysis; writing – review and editing; visualization; data curation. **Jakob Åsberg Johnels:** Writing – review and editing; validation. **Christopher Gillberg:** Writing – review and editing; supervision; validation.

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CONFLICT OF INTEREST STATEMENT

The authors report no conflicts of interest in this work.

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