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ORIGINAL RESEARCH

How Accurately Does the Information on Motor Development Collected During Health Checkups for Infants Predict the Diagnosis of Neurodevelopmental Disorders? – A Bayesian Network Model-Based Study

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Purpose: We investigated to what extent early motor development problems predict a future diagnosis of neurodevelopmental disorders (NDDs)/Early Symptomatic Syndromes Eliciting Neurodevelopmental Examinations (ESSENCE) by using a Bayesian network model (BN).

Subjects and methods: Subjects were the children who had participated in the 18- and 36-month checkups in two cities in Japan between April 2014 and March 2015. Their motor development data at the 4-, 10- and 18-month-checkups were collected with ethical consideration. The diagnosis was confirmed at the age of six, after regular assessment in all developmental areas at a neurodevelopmental clinic. The accuracy of prediction of NDD based on posterior probabilities determined using the BN was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The posterior probability (the optimal cut-off value) yielding the maximum Youden Index (sensitivity + specificity – 1) is determined with the ROC curve, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and utility index (UI) were computed.

Results: BN models showed associations between early motor items and developmental coordination disorders, borderline intelligence/intellectual disability, and speech and language disorder. The ROC curve for any NDD had an AUC of 0.735. The posterior probability with the maximal Youden Index was 0.138; at the optimal cut-off value, the sensitivity, specificity, PPV, NPV, UI+, and UI- were 0.619, 0.761, 0.250, 0.940, 0.155 and 0.715, respectively.

Conclusion: We utilized a novel approach in detailing the associations between certain early motor problems and specific NDDs. We showed that the presence of motor development problems early in development increases the probability of a future diagnosis of any NDD. Still, the sensitivity of early motor development problems as a screening tool was not high enough to be the sole instrument for detecting NDDs. The need for a broad, holistic ESSENCE perspective when looking at the course of motor development problems was stressed.

Keywords: early symptomatic syndromes eliciting neurodevelopmental clinical examinations, early screening, child health checkups, receiver operating characteristic, area under the curve, posterior probability

Background

Neurodevelopmental disorders (NDDs) affect various aspects of development, such as cognition, motor ability, language, sociability, imagination, emotion, self-regulation, and learning, leading to various learning, behavioral and emotional problems. Gillberg[1] proposed the concept of Early Symptomatic Syndromes Eliciting Neurodevelopmental Clinical Examinations (ESSENCE) and suggested that concerns (parental or specialist) persisting for at least a few months in early childhood in areas

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of (1) general development, (2) motor development, (3) responses to sensory stimuli, (4) communication/language, (5) activity/impulsiveness, (6) attention, (7) social interaction, (8) behavior, (9) mood, (10) sleep, (11) feeding, and (12) history of consciousness disturbance should always be taken "seriously" as they might likely be early signs of NDD. ESSENCE comprises autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), tic syndrome (TS), speech and language disorder (SLD), developmental coordination disorder (DCD), intellectual developmental disorder (IDD), and borderline intellectual functioning (BIF). Previous studies have shown that if there are obvious concerns in two or more of the ESSENCE areas referred to above, a comprehensive neurodevelopmental assessment and follow-up should be undertaken.[2,3] Gillberg also emphasized that clinicians and researchers should always consider the coexistence/comorbidity of NDDs (if there is one, there is likely to be at least, one more) and the sharing of early signs (such that those signs might signal, eg, ADHD, ASD, DCD – one, two or three).[1,4]

NDDs that are not detected at an early stage and are left without proper management are likely to have various psychiatric and mental health consequences.[5] In addition, NDDs have been reported to be associated with physical problems, such as obesity, chronic pain, accidents, and premature death.[6–8] The detection of NDD signs as early as possible, even before a specific diagnosis is confirmed, is a significant public/community health issue.[1]

Motor developmental problems are considered early signs of NDD,[9–16] and are assessed on one item in the ESSENCE-Questionnaire (ESSENCE-Q), which is used as a screening tool for ESSENCE.[2,17,18]

In Japan, child health checkups provide meaningful NDD screening opportunities. Relevant studies and reports have been published for health checkups of children who are older than 18 months and younger than 24 months (the "18-month-checkup") and for children who are older than three years and younger than four years (the "36-month-checkup").[19,20] Most municipal governments in Japan offer health checkups for infants aged approximately 3–4 months (the "4-month-checkup") and those aged about 9–10 months (the "10-month-checkup"). However, no studies on NDD screening have been conducted based on the data from these earlier health checkups. Motor developmental problems are relatively easy to recognize in these early health checkups for infants. If it is suggested that this is an early sign of NDD, it would be possible to initiate an appropriate intervention for NDD at an early stage, leading to an improved prognosis.

In the present study, we investigated to what extent early motor development problems predict a future diagnosis of NDDs using a Bayesian network model (BN). BN is a probabilistic graph representing a set of variables and their conditional dependencies using a directed acyclic graph (DAG). The nodes in the graph represent random variables. If an edge connects two nodes, it relates the probability of dependence from one node to the other. Each node is also assigned a Conditional Probability Table (CBT), recording its probability distribution. Using BN, the relationship between disease/disorder and clinical symptoms/signs can be expressed probabilistically.[21] For example, if the probability of a diagnosis of NDD increases when information is given about an abnormality on a motor development item in the 4-month-checkup (posterior probability) compared to the probability when such information is not given (prior probability), it can be assumed that the item contributes to the diagnosis.

Methods

Subjects and "Explanatory Variables"

This is a general population-based retrospective cohort study of 501 children (256 boys and 245 girls) and their parents who participated in the 18- and 36-month checkups in two cities (Kami and Aki) in Kochi Prefecture between April 2014 and March 2015. In Kami City, 143 (75 boys and 68 girls) of 152 eligible children (79 boys and 73 girls) (participation rate, 94%) and 150 (74 boys and 76 girls) of 158 eligible children (77 boys and 81 girls) (95%) participated in the 18- and 36 month-checkup, respectively. In Aki City, 100 (54 boys and 46 girls) of 112 eligible children (63 boys and 49 girls) (89%) and 108 (53 boys and 55 girls) of 116 eligible children (54 boys and 62 girls) (93%) in the 18- and 36-month-checkup participated, respectively. Data on children's motor development were collected with the parents' written informed consent from child development records at the 4-, 10- and 18-month-checkups. The child development records included items based on interviews with mothers by public health nurses and records of direct observation by pediatricians. Published data on typical development, along with the Japanese version of the Denver Developmental Screening Test, were used, at both sites, as references to develop the items for interviews with mothers.

"Motor development abnormalities" were identified from (1) the nurse interview items about developmental milestones that the children had not achieved at the time of the interview with their mothers, and (2) items that the

pediatricians, who performed neurological examinations during the health checkups, considered abnormal. Sex, birth weight, gestational age at birth and newborn status (the Apgar score one minute and five minutes after birth) are known to be associated with a diagnosis of NDD,[22] hence they were also included as explanatory variables in the analysis.

All explanatory variables are listed in Table 1. Note that the codes in parentheses after an item distinguish the health checkups at different months (C means checkup, and the numbers are age in months) and items (M for items based on interviews with mothers and P for items based on observation by pediatricians, followed by item number; item numbers are in the order listed in the records). The dependent variable was the diagnosis of NDD (see below).

Diagnosis of NDD

Pediatricians with extensive experience in neurodevelopmental assessment and NDDs examined each child at the final step of the 18- and 36-month-checkup. Furthermore, they detailed all records on child development since birth and reviewed the ESSENCE-

Table 1 Basic Attributes and Motor Development Items Used as Explanatory Variables

			Name of Variable	Variable Code for Motor Development-Related Items
Basic attributes			Sex [256 boys, 245 girls]	n. a.
			Birth weight [M = 3016.5, SD = 420.6] (<2500 g)*	n. a.
			Gestational age [M = 38.7, SD = 1.43] (<37 weeks)	n. a.
			Apgar score one minute after birth [M=8.7, SD=0.76] (<7)	n. a.
			Apgar score five minutes after birth [M=9.1, SD=0.56] (<7)	n. a.
Motor development	4-month-old health check-up	Item based on interviews with mothers	When you carry the child in your arms, is his/her head wobbly? ("Yes")	C4_M1
			When the child lies on his/her belly, does he/she support his/her body with his/her own arms and lift his/her head? ("No")	C4_M2
			"Does the child play with his/her hands placed close together in front of him/her?" ("No")	C4_M3
			Does the child bring his/her hands to his/her mouth? ("No")	C4_M4
			When you carry the child in your arms, do you feel that his/her body is unstable? ("Yes")	C4_M5
			When you carry the child in your arms, do you feel stiffness and hardness in his/her arms and legs? ("Yes")	C4_M6
		Neurological findings in examinations by pediatricians	Head control (The child cannot hold his/her head up to 45° when traction is applied to him/her.)	C4_P1
			Posture (opisthotonos, frog-leg posture)	C4_P2
			Muscle tone (hypotonia, hypertonia)	C4_P3
			Traction response (When traction is applied, the child stretches his/her limbs; his/her upper limbs remain stretched and his/her head does not follow.)	C4_P4
			Moro reflex (retained)	C4_P5
			Tonic neck reflex (strong asymmetrical tonic neck reflex)	C4_P6
			Vertical holding (pronation/extension of both hands; rigid extension of lower limbs)	C4_P7

(*Continued*)

Table 1 (Continued).

			Name of Variable	Variable Code for Motor Development-Related Items
			Horizontal holding (inverted U-shape, retroflexion)	C4_P8
			Prone position (The child cannot raise his/her face.)	C4_P9
			Grasping (The child keeps both hands clenched tightly, and you cannot make him/her grasp anything.)	C4_P10
	10-month-old health check-up	Item based on interviews with mothers	Does the child crawl? ("No")	C10_M1
			Does the child pull to stand independently? ("No")	C10_M2
			Does the child cruise? ("No")	C10_M3
			Does the child stand on his/her own? ("No")	C10_M4
			Does the child walk when you hold his/her hands to guide him? ("No")	C10_M5
		Neurological findings in examinations by pediatricians	Pulling to stand (The child cannot pull him/herself to stand, or even if he/she can, he/she stands on tiptoes with his/her lower limbs extended and uses only the upper part of his/her body to support his/her own weight.)	C10_P1
			Posture (The child cannot assume a sitting position and cannot crawl.)	C10_P2
			Muscle tone (insufficient hip flexion; incapable of ankle dorsiflexion; ankle clonus)	C10_P3
			Traction response (When traction is applied, the child stretches his/her limbs; his/her upper limbs remain stretched and his/her head does not follow; he/she cannot assume an ultimate sitting position.)	C10_P4
			Vertical holding (crossed extension of lower limbs; equinus; lower limbs do not touch the floor.)	C10_P5
			Parachute reflex (no forward parachute reflex; bilateral difference; hands kept clenched)	C10_P6
			Hopping reaction (no reaction)	C10_P7
			Horizontal holding (no extension/elevation of the neck/trunk; weakness of limbs)	C10_P8
			Prone position (incapable of transition from the prone position to crawling)	C10_P9
			Grasping (The child cannot grasp anything; even if you make him/her grasp something, he/she lets it fall; he/she uses the entire palm to grasp.)	C10_P10
	18-month-old health check-up	Item based on interviews with mothers	Can the child walk well? ("No")	C18_M1
			Can the child crouch down to pick up objects? ("No")	C18_M2
			Can the child walk up a staircase if you hold his/her hand lightly? ("No")	C18_M3
		Neurological findings in examinations by pediatricians	Walking (bilateral difference in step length; equinus; the child lands on his/her bottom after 2–3 steps; the child does not walk.)	C18_P1
			Gross motor skills (The child cannot walk up a staircase while you hold his/her hands to guide him/her.)	C18_P2
			Fine motor skills (The child cannot stack 2–3 blocks, pinch a small ball or scribble with a pencil even after he/she sees an example.)	C18_P3

Note: *Numbers and categories in parentheses indicate values that are considered abnormal.

Q records by the mothers, public health nurses, and psychologists. They evaluated these data to determine if more detailed neurodevelopmental examinations would be considered indicated. If deemed necessary, children underwent a secondary health checkup by a child psychiatrist with extensive clinical experience with young children. At the secondary checkup, the psychiatrist reviewed all records in detail, interviewed the mothers, and observed the children's behaviors according to the ESSENCE-Q structure. Based on the assessment results, children suspected of NDD were referred to a neurodevelopmental clinic.

All developmental areas were assessed at the neurodevelopmental clinic to confirm the diagnosis. The mothers completed the ESSENCE-Q again, and specialists completed the ESSENCE-Q based on the observation of behaviors of the children and interviews with the mothers; in addition to the information recorded at the health checkups, all developmental areas under the ESSENCE umbrella, ie, general development, motor development, reaction to sensory stimuli, communication/language, activity/impulsiveness, social interrelatedness, attention, behavior, mood, sleep, eating and history of consciousness disturbance, were evaluated.[2,3] The Kyoto Scale of Psychological Development 2001 (KSPD2001),[23] the psychometric property comparable to Bayley Scales of Infant Development second edition (BSID-II), was used to evaluate cognitive function. Diagnostic Interview for Social and Communication Disorders (DISCO-10)[24] was used to assess the development of sociability and communication. The Japanese version of the Strengths and Difficulties Questionnaire (SDQ) for parents,[25] a tool for evaluating the mental health and development in children, such as behavior, emotion, and interpersonal relationships, in terms of the effects and duration of symptoms, distress in children, disabilities in various settings, burdens on others and other aspects, was also used. Assessments with the ESSENCE-Q, KSPD2001, and SDQ were repeated every six months. In addition, ADHD-RS[26] and ASSQ[27] were used as regular assessment tools for children with hyperactivity, impulsivity, and inattention problems and those suspected to have ASD, respectively. To diagnose DCD, occupational therapists and the child psychiatrist assessed children's motor-perceptual performance based on clinical observations of behaviors such as standing, walking, throwing, and retrieving a ball. After the initial evaluation, the examinations were repeated every 1–3 months. Specialists continued unstructured clinical observations consistently over the study period. In addition, interviews with and reports from parents and nursery school/kindergarten teachers were conducted in almost every examination. The diagnosis was reviewed every six months; during every review, all the information obtained up to that point was checked and re-evaluated. The regular assessments outlined above were repeated until the child was six. After these procedures were completed, the diagnoses described were based on the diagnostic criteria for pediatric mental and neurodevelopmental disorders in the International Statistical Classification of Diseases and Related Health Problems-10/Diagnostic and Statistical Manual of Mental Disorders-IV. The diagnoses included in the analysis were ASD, ADHD, DCD, SLD, BIF/IDD, and others (including tics, reactive attachment disorder, and social anxiety disorder).

Analysis

All children were included except those with no data on motor development at all. The number of children with data available for any of the checkups was 467. Table 2 shows the numbers of eligible children, participants, and participants for whom health checkup data were available. The analysis was performed according to the steps shown in Figure 1.

Before a BN was constructed, a test of independence (Fisher's exact test) was conducted to analyze the relationships of the diagnosis of NDD with sex, birth weight, gestational age at birth, newborn status (the Apgar score one minute and five minutes after birth), and motor development-related items. The test's purpose was to compare items found to have significant relationships with the diagnosis and items included in the BN and ensure that the network included the necessary and sufficient items. The significance level was set at $p< 0.05$. Items for abnormalities found in no more than one child were excluded even if $p < 0.05$ because the statistical power was considered insufficient.

Sex and all developmental items rated by mothers regarding motor development, NDD diagnosis, and diagnosis type (BIF/IDD, ASD, ADHD, DCD, SLD, others) were taken as *candidate nodes for the BN*. The bnlearn package in R statistical software was used to construct the DAG structure and derive the CPT. Bnlearn was configured so that only explanatory variable nodes that were found to be associated with any diagnosis type by chi-square test ($p < 0.05$) were included in the DAG.

Evaluation of the Accuracy of NDD Diagnosis Prediction

The predictive accuracy of the derived BN for the diagnosis of NDD was evaluated as follows;

Table 2 Numbers of Eligible Children, Participants, and Participants for Whom Health Checkup Data Were Available

	Kami		Aki			
	18-Month-Checkup	3-Year-Checkup	18-Month-Checkup	3-Year-Checkup	Total	
Children eligible for checkups	152 (79boys)	158 (77boys)	112 (63boys)	116 (54boys)	538 (273boys)	
Participants in checkups						
Without diagnosis	130 (65boys)	133 (65boys)	91 (47boys)	90 (38boys)	444 (215boys)	501 (256boys)
With diagnosis	13 (10boys)	17 (9boys)	9 (7boys)	18 (15boys)	57 (41boys)	
Children with 4-month-checkup data available						
Without diagnosis	107 (53boys)	98 (51boys)	38 (16boys)	39 (17boys)	282 (137boys)	317 (164boys)
With diagnosis	12 (9boys)	11 (8boys)	4 (3boys)	8 (7boys)	35 (27boys)	
Children with 10-month-checkup data available						
Without diagnosis	110 (55boys)	101 (51boys)	83 (44boys)	68 (27boys)	362 (177boys)	408 (213boys)
With diagnosis	13 (10boys)	10 (8boys)	8 (6boys)	15 (12boys)	46 (36boys)	
Children with 18-month-checkup data available						
Without diagnosis	130 (65boys)	104 (54boys)	91 (47boys)	77 (31boys)	402 (197boys)	457 (237boys)
With diagnosis	13 (10boys)	16 (9boys)	9 (7boys)	17 (14boys)	55 (40boys)	
Children with data available for any of checkups						
Without diagnosis	130 (65boys)	111 (57boys)	91 (47boys)	80 (33boys)	412 (202boys)	467 (242boys)
With diagnosis	13 (10boys)	16 (9boys)	9 (7boys)	17 (14boys)	55 (40boys)	

1. The posterior probabilities of being positive for NDD diagnosis were determined using the BN.
2. These posterior probabilities were compared with the actual diagnosis results, and the sensitivity and specificity obtained when a certain posterior probability was used as a cut-off value were shown graphically as a receiver operating characteristic (ROC) curve.
3. The accuracy of prediction of NDD diagnosis based on posterior probabilities determined using the BN was evaluated using the area under the ROC curve (AUC). As a screening test, AUC > 0.7 and AUC > 0.9 indicate acceptable and very high levels of accuracy, respectively.[28–30]
4. The posterior probability (the optimal cut-off value) yielding the maximum Youden Index (sensitivity + specificity – 1) is determined with the ROC curve, and the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and utility index (UI) were computed. The UI is a measure of the clinical usefulness of screening; *positive UI* (UI+) calculated as the sensitivity × PPV and *negative UI* (UI-) calculated as the specificity × NPV are used to evaluate the "rule-in accuracy" and the "rule-out accuracy", respectively. The evaluation criteria are as follows: poor, UI± < 0.2; fair, 0.2 ≤ UI± < 0.4; moderate, 0.4 ≤ UI± < 0.6; good, 0.6 ≤ UI± < 0.8 and very good, UI± ≥ 0.8.[3,31]
5. We searched for a combination of motor development abnormalities for which the posterior probability exceeded the optimal cut-off value described above.

Ethical Considerations

The study was conducted after approval from the Institutional Review Board of the Kochi Prefectural Medical and Welfare Centre for Handicapped (No. 24–473). Written informed consent was obtained from the subjects' parents/caregivers. This study was conducted according to the principles of the Declaration of Helsinki.

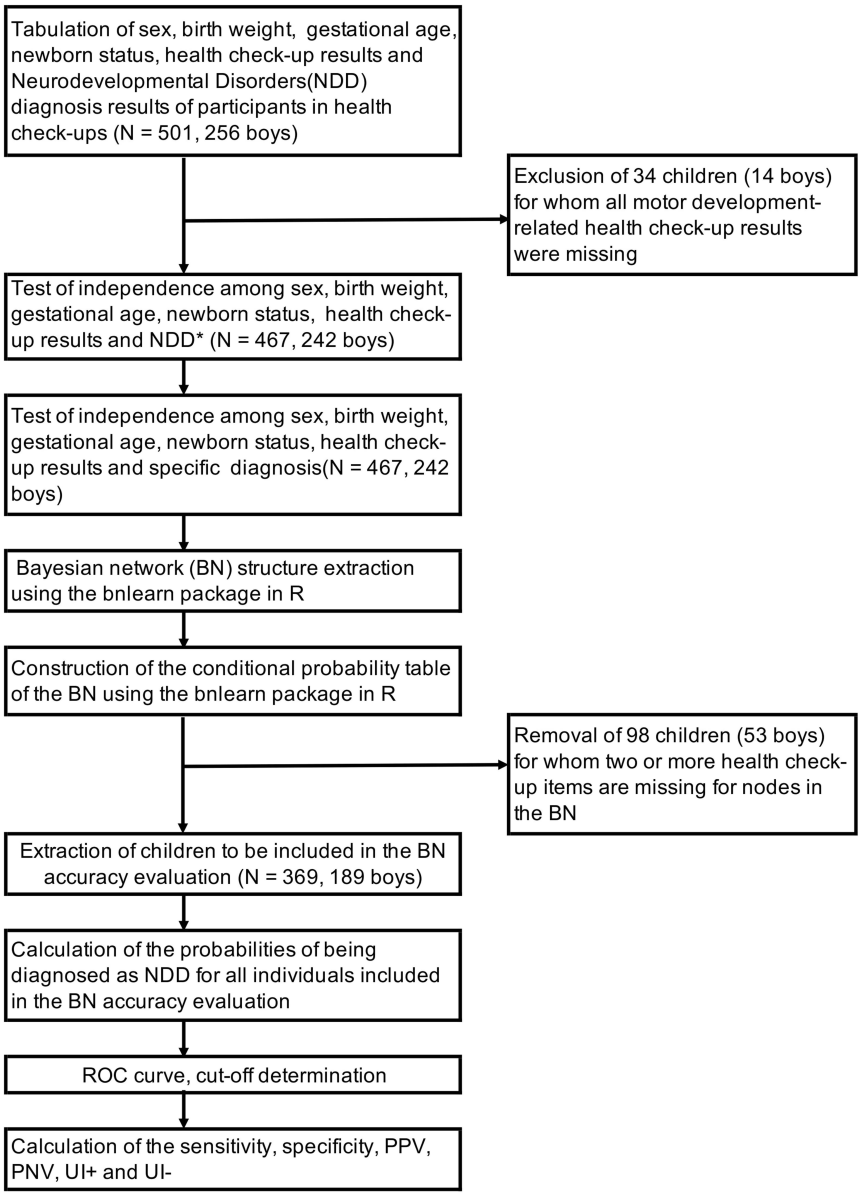

Figure 1 Flow chart showing the analysis process.
Abbreviations: ROC, receiver operating characteristic; PPV, positive predictive value; NPV, negative predictive value; UI, utility index.

Results

Table 3 shows percentage of those with normal and abnormal values for each variable. Considering the age in months at the time of the checkups, the results were largely consistent with those of previous studies.[32,33]

Diagnoses

The overall prevalence of diagnosed NDD rates in the 18-month-and 36-month-old populations was 9.1% (9.1% in Kami City and 9.0% in Aki City) and 13.6% (11.0% and 16.7%), respectively. The male: female ratio was 3.4:1 in the 18-month-old population and 2.2:1 in the 3-year-old population.

Table 4 shows the diagnoses of the children with NDD.

Table 3 Percentage of Those with Normal and Abnormal Values for Each Variable

	All Cases				Total
	Diagnosis (+)		Diagnosis (-)		
	N	%	N	%	
Sex					
Boy	41	8.2%	215	42.9%	51.1%
Girl	16	3.2%	229	45.7%	48.9%
Birth weight(wt) [g]					
wt < 2500	4	0.8%	43	8.9%	9.7%
wt ≥ 2500	52	10.7%	385	79.5%	90.3%
Gestational age(ga)					
ga < 37	4	0.8%	23	4.8%	5.6%
ga ≥ 37	51	10.6%	403	83.8%	94.4%
Apgar score one minute after birth (Ap1)					
Ap1 < 7	1	0.4%	4	1.5%	1.9%
Ap1 ≥ 7	35	13.2%	226	85.0%	98.1%
Apgar score five minute after birth (Ap5)					
Ap5 < 7	0	0.0%	0	0.0%	0.0%
Ap5 ≥ 7	23	15.3%	127	84.7%	100.0%
4-month-old health check-up Item based on interviews with mothers					
C4_M1					
Abnormal	5	1.6%	45	14.6%	16.2%
Normal	29	9.4%	229	74.4%	83.8%
C4_M2					
Abnormal	5	1.6%	26	8.4%	10.0%
Normal	29	9.4%	249	80.6%	90.0%
C4_M3					
Abnormal	6	1.9%	42	13.5%	15.4%
Normal	26	8.3%	238	76.3%	84.6%
C4_M4					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	33	10.5%	282	89.5%	100.0%
C4_M5					
Abnormal	0	0.0%	8	2.6%	2.6%
Normal	33	10.5%	272	86.9%	97.4%
C4_M6					
Abnormal	1	0.3%	13	4.2%	4.5%
Normal	30	9.6%	267	85.9%	95.5%
Neurological findings in examinations by pediatricians					
C4_P1					
Abnormal	0	0.0%	1	0.3%	0.3%
Normal	32	10.3%	279	89.4%	99.7%
C4_P2					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	33	10.5%	280	89.5%	100.0%
C4_P3					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P5					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%

(*Continued*)

Table 3 (Continued).

	All Cases				Total
	Diagnosis (+)		Diagnosis (-)		
	N	%	N	%	
C4_P6					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P7					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P8					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P9					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P10					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
C4_P11					
Abnormal	0	0.0%	0	0.0%	0.0%
Normal	35	11.1%	279	88.9%	100.0%
10-month-old health check-up Item based on interviews with mothers					
C10_M1					
Abnormal	6	1.5%	25	6.2%	7.7%
Normal	39	9.6%	335	82.7%	92.3%
C10_M2					
Abnormal	11	2.7%	47	11.6%	14.3%
Normal	35	8.6%	313	77.1%	85.7%
C10_M3					
Abnormal	18	4.4%	94	23.2%	27.6%
Normal	28	6.9%	266	65.5%	72.4%
C10_M4					
Abnormal	33	8.2%	239	59.6%	67.8%
Normal	12	3.0%	117	29.2%	32.2%
C10_M5					
Abnormal	23	5.7%	127	31.3%	36.9%
Normal	23	5.7%	233	57.4%	63.1%
Neurological findings in examinations by pediatricians					
C10_P1					
Abnormal	3	0.8%	8	2.2%	3.1%
Normal	35	9.8%	310	87.1%	96.9%
C10_P2					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P3					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P4					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%

(*Continued*)

Table 3 (Continued).

	All Cases				Total
	Diagnosis (+)		Diagnosis (-)		
	N	%	N	%	
C10_P5					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P6					
Abnormal	2	0.6%	5	1.4%	2.0%
Normal	36	10.1%	314	88.0%	98.0%
C10_P7					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P8					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P9					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
C10_P10					
Abnormal	1	0.3%	0	0.0%	0.3%
Normal	37	10.4%	318	89.3%	99.7%
18-month-old health check-up Item based on interviews with mothers					
C18_M1					
Abnormal	4	0.9%	4	0.9%	1.8%
Normal	51	11.2%	398	87.1%	98.2%
C18_M2					
Abnormal	1	0.2%	1	0.2%	0.4%
Normal	54	11.8%	401	87.7%	99.6%
C18_M3					
Abnormal	1	0.2%	9	2.0%	2.2%
Normal	53	11.7%	391	86.1%	97.8%
Neurological findings in examinations by pediatricians					
C18_P1					
Abnormal	8	1.8%	6	1.3%	3.1%
Normal	46	10.3%	387	86.6%	96.9%
C18_P2					
Abnormal	1	0.2%	5	1.1%	1.4%
Normal	49	11.1%	387	87.6%	98.6%
C18_P3					
Abnormal	1	0.2%	0	0.0%	0.2%
Normal	48	10.9%	391	88.9%	99.8%

Results from the BN

Figure 2 shows the DAG constructed using sex, health checkup results, diagnostic data, and diagnosed NDD of the subjects. Among the 10-month-checkup items, C10_M1("Does the child crawl?") was connected by arcs to C10_M2 ("Does the child grasp things to pull him/herself up to stand independently?"), C10_M3("Does the child cruise?"), C10_M5("Does the child walk when you hold his/her hands to guide him?"), and C10_P1("pulling to stand") because they had associations, and C10_P1 was connected to BIF/IDD because the former showed the strongest association with the latter. Among 18-month-checkup items, C18_M1("Can the child walk well?") was connected by arcs to C18_M2

Table 4 The Diagnoses of the Children with NDD

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

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

("Can the child crouch down to pick up objects?") and C18_P1("walking") to represent their associations, and C18_P1 and C18_M2 were connected to BIF/IDD and DCD, respectively. Associations were also found among the NDD diagnosed, and arcs connected DCD and ADHD to others and ASD, respectively. The same data were used to derive the CPT of the BN. As an example, the CPT of the BIF/IDD node is shown in Table 5. This table shows the probabilities of being negative or positive for BIF/IDD when C10_P1 and C18_P1 values are given. To evaluate the accuracy of NDD prediction by this BN, we computed the probabilities of NDD predicted from sex and health checkup results of the subjects using the BN and prepared a ROC curve, as shown in Figure 3. Notably, 98 children (53 boys and 45 girls) who had two or more missing data among the health checkup items included in the BN were excluded from the accuracy evaluation to prepare the ROC curve. This curve had an AUC of 0.735 (95% CI: 0.648–0.821). The posterior probability with the maximal Youden Index (optimal cut-off value) was 0.138; at this value, the sensitivity, specificity, PPV, NPV, UI +, and UI- were 0.619 (0.472–0.766), 0.761 (0.715–0.808), 0.250 (0.167–0.333), 0.940 (0.911–0.968), 0.155 (0.015–0.294) and 0.715 (0.679–0.752), respectively. All combinations of sex and health checkup results with posterior probabilities exceeding this cut-off value are listed in Table 6.

Discussion

The current study showed that the presence of motor development problems early in development increases the probability of a future diagnosis of any NDD, which supports the need for an ESSENCE perspective when looking at the course of delayed motor development from a different angle to previous studies.

Based on the BN results, the items associated with DCD ("Can the child walk well?" (C18_M1) and "Can the child crouch down to pick up objects?" (C18_M2)) may suggest that posture transition from walking and standing, and the development of balance function underlie the development of coordinated movement and motor dexterity.

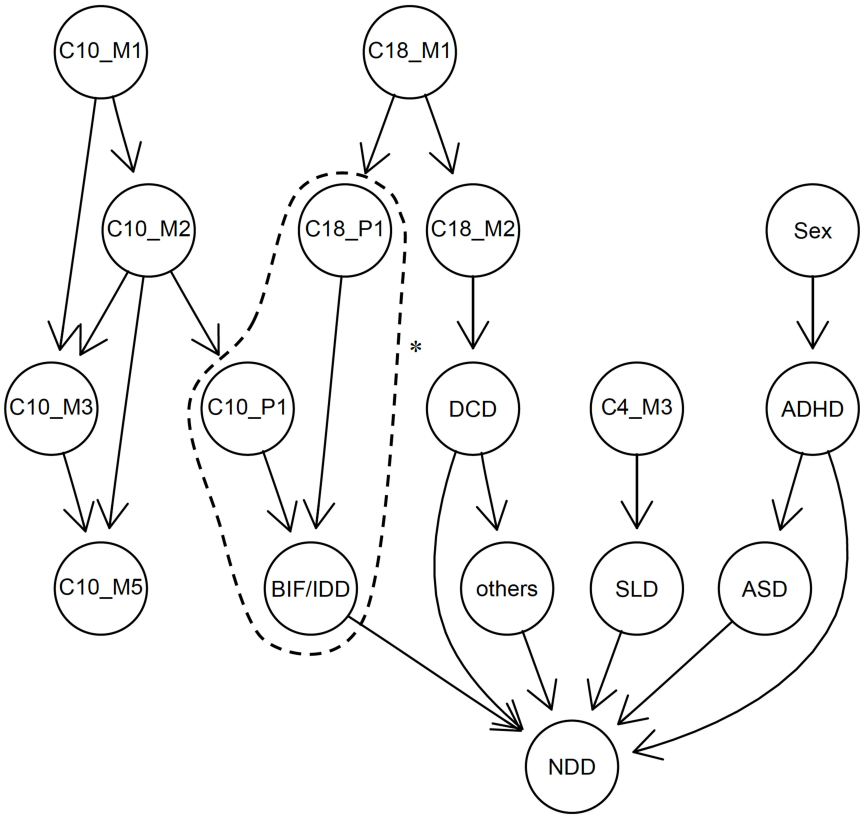

Figure 2 The constructed Bayesian network (BN). Node names starting with C denote the following health checkup items (M, items based on interviews with mothers; P, neurological findings of examinations by pediatricians).
Note: *As an example, the conditional probability table (CPT) of the BIF/IDD node corresponding to dependencies in an area enclosed by dashed lines is shown in Table 5.
Abbreviations: ADHD, attention-deficit/hyperactivity disorder; ASD, autism spectrum disorder; BIF, borderline intellectual functioning; DCD, developmental coordination disorder; IDD, intellectual developmental disorder; NDD, neurodevelopmental disorders; SLD, speech and language disorder; C4_M3, 4-month-old-checkup "Does the child play with his/her hands close together in front of him/her?"; C10_M1, 10-month-checkup "Does the child crawl?"; C10_M2, 10-month-checkup "Does the child grasp things to pull him/herself up to stand independently?"; C10_M3, 10-month-checkup "Does the child cruise?"; C10_M5, 10-month-checkup "Does the child walk when you hold his/her hands to guide him?"; C10_P1, 10-month-checkup "Pulling to stand"; C18_M1, 18-month-checkup "Can the child walk well?"; C18_M2, 18-month-checkup "Can the child crouch down to pick up objects?"; C18_P1, 18-month-checkup "Walking".

Endorsed items that might increase the posterior probability of being diagnosed with IDD/BIF were C18_M1, C18_P1 ("walking"), and all items interviewed from mothers in the 10-month-checkup except for C10_M4 ("Does the child stand on his/her own?"). This is in line with previous research suggesting an association between IDD and delayed motor development before the age of one.[34] In summary, the results could indicate that general

Table 5 Conditional Probability Table for Borderline Intellectual Functioning/Intellectual Developmental Disorder

C10_P1	C18_P1	BIF/IDD	Probability
–	–	–	0.994
–	–	+	0.006
–	+	–	0.5
–	+	+	0.5
+	–	–	1
+	–	+	0
+	+	–	0
+	+	+	1

Note: –: normal (negative), +: abnormal (positive).
Abbreviations: BIF/IDD, borderline intellectual functioning/intellectual developmental disorder; C10_P1, 10-month-old health check-up "Pulling to stand"; C18_P1, 18-month-old health check-up "Walking".

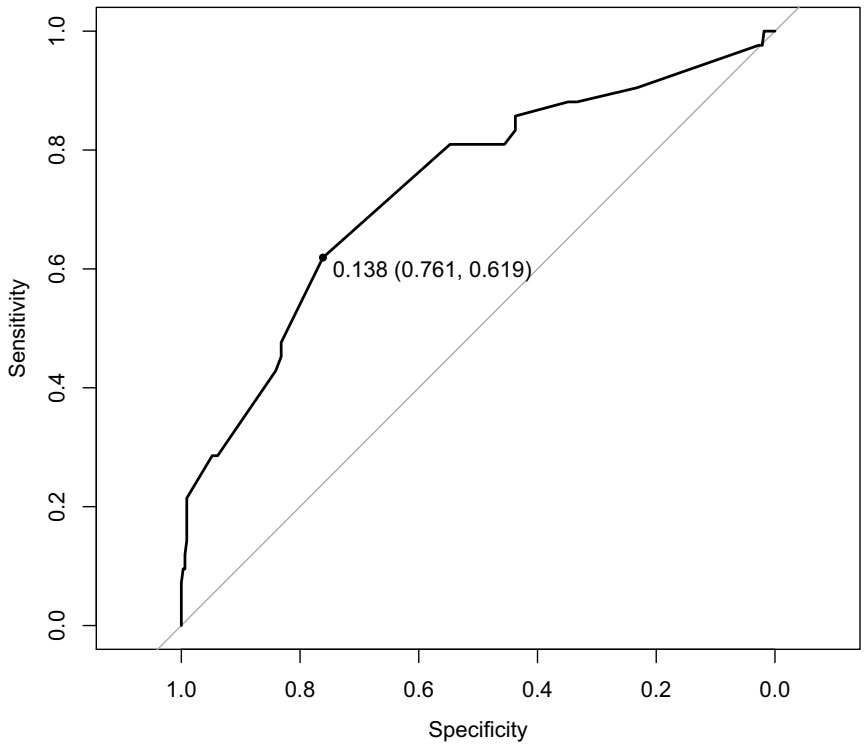

Figure 3 Receiver operating characteristic curve when the constructed Bayesian network is applied to the analysis set (N = 369). The value on the curve is the cutoff value (specificity, sensitivity) at the maximal Youden Index.

intellectual development assessments should be considered necessary whenever motor development abnormalities are suspected at the 10-month-checkup.

The item associated with SLD ("Does the child play with his/her hands close together in front of him/her?" (C4_M3)) may suggest an association between motor control development and language development, as has been demonstrated in previous research. However, the diagnosis of ASD was found to have no association with

Table 6 Combinations Where the Posterior Probability of Neurodevelopmental Disorders is Above the Cut-Off Value

Sex (Male)	**+**	**x**	**x**	**+**	**x**	**x**	**+**
C4_M3	+	+	x	+	+	x	+
C10_M1	x	x	x	x	x	x	x
C10_M2	x	x	x	x	x	x	x
C10_M3	x	x	x	x	x	x	x
C10_M5	x	x	x	x	x	x	x
C10_P1	x	x	x	x	x	x	x
C18_M1	x	x	x	x	x	x	x
C18_M2	x	x	x	+	+	+	x
C18_P1	+	+	+	x	x	x	x
NDD posterior probability	≥ 0.568	≥ 0.543	≥ 0.531	≥ 0.415	≥ 0.383	≥ 0.362	≥ 0.180

Note: +: positive, -: negative, x: either positive or negative.

Abbreviations: C4_M3, 4-month-old health check-up "Does the child play with his/her hands close together in front of him/her?"; C10_M1, 10-month-old health check-up "Does the child crawl?"; C10_M2, 10-month-old health check-up "Does the child grasp things to pull him/herself up to stand independently?"; C10_M3, 10-month-old health check-up "Does the child cruise?"; C10_M5, 10-month-old health check-up "Does the child walk when you hold his/her hands to guide him?"; C10_P1, 10-month-old health check-up "Pulling to stand"; C18_M1, 18-month-old health check-up "Can the child walk well?"; C18_M2, 18-month-old health check-up "Can the child crouch down to pick up objects?"; C18_P1, 18-month-old health check-up "Walking".

delayed motor development. In a systematic review, Lim et al[35] reported a result of a meta-analysis showing a significant association between the diagnosis of ASD and abnormal motor development in the first 18 months of life. However, there were variations among the different studies. In most studies included in their review, structured scales with established validity and reliability were used to evaluate motor development. The motor development-related items used in the health checkups here have not been standardized, which may have influenced the outcome. The later diagnosis of ADHD was also found to have no association with delayed motor development.

Further studies will be necessary to establish a clearer picture. Of the 11 cases diagnosed with SLD, three had SLD only, seven had SLD and ADHD, and one had SLD and ASD. Speculatively, in these cases of SLD and other NDD comorbidities, the association between motor developmental problems and ADHD or ASD may be mediated by language delay.[36]

The ROC curve had an AUC of 0.735, which means that NDD screening based on problems in motor development had acceptable, albeit much less than perfect, accuracy. However, the sensitivity with the optimum cut-off value was 0.619, which is not sufficiently high for a screening tool. The UI- value was 0.715, and the rule-out accuracy was also inadequate. This indicates that, while an abnormality among the motor development-related items in a health checkup suggests that the child would be at risk of an NDD and requires careful follow-up, the absence of abnormalities among the motor development-related items does not necessarily mean that the child is free of the risk of NDD and still may require examinations in all areas of development included under the ESSENCE umbrella. Given the paucity of data and a relatively high frequency of missing values, combinations giving the posterior probabilities exceeding the cut-off value shown in Table 6 should be carefully interpreted. Nevertheless, the following finding that when motor development is compromised under the age of one, careful follow-up on various developmental aspects, including non-motor aspects, would still be considered valid.

The novelty and strength of this study is the use of BNs to quantify the effects of motor development problems on the diagnosis of NDD in the form of the posterior probability. However, a considerable number of missing values in the data used in this study may have had a major impact on the results. Given that the data used were originally not recorded for research, it is possible that no values were recorded just because no abnormalities were found in these items. Nonetheless, we had to treat them as missing values because no data was recorded.

Conclusion

The study showed that motor development problems early in development increased the probability of a future diagnosis of any of the NDDs, but was not sufficiently sensitive as a screening tool for NDDs. The need for a broad, holistic ESSENCE perspective when looking at the course of motor development problems was emphasized.

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Disclosure

All authors declare that they have no conflicts of interest in this work.

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