Association of fetal eye movement density with sleeping and developmental problems in 1.5-year-old infants

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Eye movement density (EMD) is an evaluation index of rapid eye movements observed during sleep. This study aimed to investigate the association of fetal EMD with sleeping and developmental problems in infancy. We observed 60 normal singleton pregnancies (gestational age 28–37 weeks) using ultrasonography for 1 h. Fetal eye movements were counted, and EMD was calculated. Participants answered questionnaires regarding their child’s sleep and development 1.5 years after their delivery. The outcomes of an infant’s sleep were night awakening (yes or no), bedtime (before or after 22:00), and nighttime sleep duration (< 9 or ≥ 9 h). An infant’s development was evaluated using the Child Behavior Checklist (CBCL) T-score. We found that decreased fetal EMD was associated with increased night awakening at the age of 1.5 years (odds ratio 0.84, 95% confidence interval 0.69–1.00 per unit decrease in EMD). However, fetal EMD was not associated with bedtime or nighttime sleep duration. In addition, fetal EMD was independently associated with the total problems T-score of the CBCL at the age of 1.5 years in the multivariate model (p = 0.047). In conclusion, fetal EMD may be associated with sleep and developmental problems in infants.

Results
The baseline characteristics and outcomes of the 60 included cases are shown in Table 1. The mean gestational age at fetal EM data acquisition was 33.4 weeks (28–37 weeks). The average fetal EMD was 9.8/min (standard deviation [SD], 3.2; range 4.2–21.0).

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Association between fetal EMD and infant sleep problems. The numbers and proportions of cases with each sleep outcome are as follows: 36 cases (60%) with night awakening, 11 cases (20%) with a bedtime after 22:00, and 22 cases (37%) with nighttime sleep duration of ≤ 9 h (Table 2).

Fetal EMD was significantly associated with night awakening at the age of 1.5 years (odds ratio [OR] 0.84, 95% confidence interval [CI] 0.69–1.00, p = 0.046). Even after adjusting for maternal age, children's birth weight, and parity (0 or ≥ 1), the association did not change (aOR 0.84, 95% CI 0.69–1.00, p = 0.049). On the other hand, fetal EMD was not associated with the other two sleep outcomes, a bedtime after 22:00 and a short nighttime sleep duration.
The stratified analysis showed a significant association between fetal EMD measured from 33 to 37 gestational weeks and infant night waking (OR 0.80, 95% CI 0.61–0.99, \(p = 0.044\) in the multivariate model). Conversely, fetal EMD measured from 28 to 32 gestational weeks was not associated with infant night waking.

A sensitivity analysis wherein the “birth weight” covariate was replaced with “gestational weeks at birth” showed no change in the above significant association (Supplementary Table S1).

**Association of fetal EMD and developmental problems.** We used the Japanese version of the Child Behavior Check List/1½–5 (CBCL) to evaluate the infants’ developmental problems when they turned 1.5 years old.

The logistic regression model did not show any significant association between fetal EMD and whether the CBCL T-scores for total, internalizing, and externalizing problems were above the cutoff points. The results were similar in both the univariate and multivariate models (Table 3). The results of the stratified analysis by the timing of measurement of fetal EMD were also the same.

Linear regression univariate models showed that CBCL T-scores tended to increase as fetal EMD decreased. This was observed in T-scores for total, internalizing, and externalizing problems. However, the differences were not statistically significant (Table 4). After adjusting for maternal age, children’s birth weight, and parity (0 or ≥ 1), fetal EMD was significantly associated with the total problems CBCL T-score (\(\beta = -0.69, 95\% \text{ CI} -1.36 \text{ to } -0.01, \ p=0.047\)). The internalizing and externalizing problem T-scores were not associated with fetal EMD before and after adjustment.

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Table 3. Association between fetal EMD and infant CBCL abnormality. EMD, eye movement density; OR, odds ratio; aOR, adjusted odds ratio; CI, confidence interval; GWs, gestational weeks. *Adjusted for maternal age at delivery, parity, and child’s birth weight. **All ORs or aORs are per 1/min increasing fetal EMD.

| No. of answers | No. of outcome | Univariate model | Multivariate model* |
|----------------|---------------|------------------|---------------------|
|                | %             | OR 95% CI        | \(p\) value | aOR 95% CI | \(p\) value |
| **Total score**|               |                  |          |           |            |
| All population | 60            | 18 30            | 0.98     | 0.81–1.16 | 0.829      | 0.98 | 0.81–1.17 | 0.828 |
| Examined between 28 and 32 GWs | 23 8 35 | 1.25 0.85–1.93  | 0.278 | 1.42 | 0.88–2.58 | 0.183 |
| Examined between 33 and 37 GWs | 37 10 27 | 0.93 0.72–1.15 | 0.520 | 0.92 | 0.71–1.15 | 0.480 |
| **Internalizing score** |         |                  |          |           |            |
| All population | 60            | 4 7              | 0.82     | 0.51–1.16 | 0.337      | 0.79 | 0.45–1.16 | 0.316 |
| Examined between 28 and 32 GWs | 23 4 17 | 0.94 0.55–1.53 | 0.796 | 0.89 | 0.49–1.50 | 0.680 |
| Examined between 33 and 37 GWs | 37 0 0 | n.a | n.a | n.a | n.a |
| **Externalizing score** |         |                  |          |           |            |
| All population | 60            | 16 27            | 0.96     | 0.78–1.15 | 0.649      | 0.94 | 0.76–1.14 | 0.555 |
| Examined between 28 and 32 GWs | 23 4 17 | 1.12 0.68–1.88 | 0.657 | 1.09 | 0.61–1.99 | 0.767 |
| Examined between 33 and 37 GWs | 37 12 32 | 0.88 0.68–1.09 | 0.270 | 0.87 | 0.66–1.09 | 0.257 |

Table 4. Association of fetal EMD and CBCL T-scores. EMD, eye movement density; \(\beta\), partial regression coefficient; CI, confidence interval; GWs, gestational weeks. *Adjusted for maternal age at delivery, parity, and child’s birth weight.

| No. of answers | Average | Range | Univariate model | Multivariate model* |
|----------------|---------|-------|------------------|---------------------|
|                | \(\beta\) | 95% CI | \(p\) value | \(\beta\) | 95% CI | \(p\) value |
| **Total score**|         |       |                |              |          |            |
| All population | 60 53.9 | 30–66 | -0.64          | -1.32 to 0.03 | 0.062 | -0.69 | -1.36 to 0.01 | 0.047 |
| Examined between 28 and 32 GWs | 23 55.5 | 38–66 | 0.32 | -1.08 to 1.73 | 0.635 | 0.17 | -1.39 to 1.73 | 0.825 |
| Examined between 33 and 37 GWs | 37 52.9 | 30–66 | -0.82 | -1.68 to 0.04 | 0.062 | -0.82 | -1.69 to 0.05 | 0.064 |
| **Internalizing score** |         |       |                |              |          |            |
| All population | 60 49.5 | 38–63 | -0.58          | -1.21 to 0.05 | 0.071 | -0.60 | -1.24 to 0.05 | 0.068 |
| Examined between 28 and 32 GWs | 23 52.0 | 38–63 | 0.13 | -0.35 to 0.60 | 0.578 | 0.11 | -0.42 to 0.65 | 0.654 |
| Examined between 33 and 37 GWs | 37 47.9 | 38–59 | -0.69 | -1.43 to 0.05 | 0.067 | -0.70 | -1.47 to 0.07 | 0.072 |
| **Externalizing score** |         |       |                |              |          |            |
| All population | 60 54.6 | 36–70 | -0.60          | -1.26 to 0.07 | 0.077 | -0.64 | -1.30 to 0.01 | 0.052 |
| Examined between 28 and 32 GWs | 23 54.7 | 43–65 | 0.20 | -1.03 to 1.43 | 0.742 | 0.06 | -1.23 to 1.35 | 0.925 |
| Examined between 33 and 37 GWs | 37 54.5 | 36–70 | -0.87 | -1.76 to 0.01 | 0.053 | -0.86 | -1.74 to 0.01 | 0.054 |
The stratified analysis did not show any significant association between CBCL T-scores and a specific period of gestation. However, the results of the second group (33–37 gestational weeks) more closely reflected the overall results compared to the first group (28–32 gestational weeks).

The above significant association persisted even in sensitivity analyses wherein the "birth weight" covariate was replaced with "gestational weeks at birth" (Supplementary Tables S2 and S2).

Discussion

This study prospectively investigated the association between fetal EMD measured at 28–37 gestational weeks and sleeping and developmental problems in 1.5-year-old infants. This study showed that lower fetal EMD during the fetal EM period was associated with a higher risk of night awakening. Fetal EMD was not associated with whether the CBCL T-scores were above the cutoff points, but lower fetal EMD was associated with higher T-score for total problems in CBCL.

REM sleep develops during the fetal period and is observed from about 30 weeks of gestation. REM sleep occupies a large proportion of sleep in full-term neonates, but this gradually decreases with REM activity. The present study showed the association between low REM activity during the late fetal period and night awakening at the age of 1.5 years.

Studies with similar results have been reported in premature infants. Decreased EMs and EMD during REM sleep have been reported in premature infants grown to term compared to full-term infants. Premature infants were also reported to have more nocturnal awakenings than full-term infants after the neonatal period. One hypothesis that may explain these findings is that early exposure to the extrauterine environment disturbs normal sleep development in premature infants. This is supported by reports that the postnatal environment affects the brain function and structure of premature infants in the neonatal intensive care unit. However, altered functional connectivity in the fetal brain was also observed before birth in premature infants. Thus, the intrauterine environment may also have a significant influence on fetal development. Moreover, this influence may continue to affect postnatal neural development. The results of this study suggest that the difference in REM sleep development during the fetal period may also affect postnatal sleep development, even in full-term infants.

In the present study, REM activity during the fetal period was associated with only night awakenings among sleep outcomes in children at 1.5 years of age. A study performed in mice supported this association by describing a common origin of cells that regulate REM/non-REM sleep and wakefulness. This suggests that the factor that affects REM sleep may also affect sleep-wakening.

There have been no reported studies on the association of fetal EM activity with developmental problems after birth. However, the association between REM activity and developmental outcomes has been reported in premature infants at 6 months of age. REM sleep plays an important role in neurological development through synaptogenesis and pruning. Therefore, low REM activity during the fetal period may affect development after birth.

CBCL is a developmental screening test that is reportedly associated with the diagnosis of autism; studies show that both sensitivity and specificity of CBCL for diagnosing autism spectrum disorder are approximately 60–80%. Children with autism spectrum disorder tend to show REM sleep abnormalities, including a decreased quantity of REM sleep and a lower number of REMs during the REM period. Low REM activity during the fetal period may be a prognostic factor and may help identify children who are at high risk for developmental disorders after birth. It may also facilitate early intervention, which is crucial in improving neurodevelopmental outcomes in autism spectrum disorder. In this study, we used sleep and developmental problems in 1.5-year-old infants as the outcome because these problems may also be a precursor to developmental disorders in the future. However, further studies are necessary to investigate whether fetal EMD will be associated with future developmental disorders such as autism.

The associations between fetal EMD and infant outcomes in the present study were insufficient to set the cutoff points for predicting infant outcomes. Fetal EMD was associated with CBCL T-scores, but not with whether these were above the cutoff points. Therefore, the relationship between fetal EMD and infant development observed in this study was very weak, and it could not be concluded whether fetal EMD was an appropriate index for predicting postnatal development problems. In our previous study, fetal EMD did not significantly change within 28–37 gestational weeks. Hence, fetal EMD was measured within this period. However, in this study, fetal EMD measured at 33–37 gestational weeks was observed to be more closely associated with infant outcomes than fetal EMD measured at 28–32 gestational weeks.

The duration of the fetal EM and NEM period increases starting at around 30 weeks of gestation. The same phenomenon has been reported in preterm infants with the same postconceptional age. Since the development of fetal sleep continues beyond the 30th week of pregnancy, it is considered reasonable that EMD in the late fetal period is more closely associated with postnatal sleep and development. In our study, the developmental outcomes were determined from results of a screening questionnaire performed in the postnatal period. Although we could not identify a concrete relationship between fetal EMD and postnatal developmental outcomes, our findings highlight the need to further investigate how fetal EMD may be associated with the clinical diagnosis of developmental disorders. Future studies should explore whether including larger cohorts, measuring fetal EMD only in the late fetal period, and assessing outcomes (developmental disorders) at later stages in life (in older infants) impact this association. Additionally, it may be useful to combine fetal EMD with other clinically known high-risk factors such as parental age.

This study has several limitations. It was conducted in a single institution and had a small sample size. In addition, information about the outcomes in infancy was not available for about half of the original cohort, mainly because of no response to questionnaires. Information about each patient's family socio-economic status and environment after birth, such as nursery school attendance or the mother's job, was also not considered.
Therefore, we could not fully adjust for factors that may affect infant sleep and development. Also, outcome information for the 1.5-year-old children was acquired from questionnaires completed by their mothers, making results relatively subjective. Conversely, a strong point of this study is that it is the first to describe an association between fetal EMD with sleep and development during infancy.

In conclusion, differences in fetal REM activity in the third trimester may be associated with sleeping and developmental problems in early infancy.

Methods

Ethics. This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethics Committee of Kyushu University Hospital (No. 27-51). A written informed consent was obtained from all participants.

Study participants. To investigate fetal EMs, we conducted 1-h ultrasonography examinations 232 times in 156 cases between 2013 and 2019. We sent questionnaires about infant sleep and development to parents 1.5 years after their delivery. Out of the 156 cases, 96 cases were excluded due to the following reasons: unfollowable or no response to questionnaires (n = 79), transferred to other hospital before delivery (n = 2), examined only before 28 weeks gestation (n = 7), examined only after 38 weeks gestation (n = 4), birth before 34 weeks gestation (n = 1), and effective observation time was less than 48 minutes (n = 3). The remaining 60 cases were included in the analysis (Fig. 1). In cases where observation was conducted multiple times, we selected the data with the longer effective observation time.

Data acquisition. Patients were placed in a supine position in a quiet room, allowing them to change positions freely. The procedure was performed between 13:00 and 16:00 at least 2 h after food ingestion. Fetal EMs were observed for 60 min at a frame rate of 30 frames/s or higher using transabdominal two-dimensional sonography (APLIO 500 TUS-A500; TOSHIBA, Japan) with a 3.5-MHz convex transducer (PVT375BT Probe). The video data were recorded in an MP4 format digital video file on an SD card.

Calculation of fetal EMD. The effective observation time was defined as the time when the fetal EMs could be determined. We excluded 3 cases with data whose effective observation times were ≤ 80% (48 min) from the analysis because accurate measurement of EMD could not be ensured. We counted the fetal EMs (Supplementary Video) and created time-series data of each EM using the video recorded. Each minute was examined, and the periods during which EMs occurred were defined as EM periods. EMD was calculated as the total number of EMs divided by the EM period (minutes). These definitions were the same as in our previous paper.

Outcome 1: Infant sleep problems. Information regarding each 1.5-year-old infant’s sleep habits was acquired from the questionnaire sent to their mothers. The questionnaire was prepared by modifying the Brief Infant Sleep Questionnaire and included questions about bedtime, total sleep duration during the night, and nocturnal awakening. Children with autism spectrum disorder report a long sleep latency and frequent nocturnal awakenings. They also tend to wake up earlier and take a longer nap than neurotypical children. Based on these studies, we focused on three points. The first point was night awakening, defined as whether infants usually woke during the night as the outcome. The second point was the infant’s bedtime. A bedtime later than 22:00 was defined as late. The third point was sleep duration during the night (between 20:00 and 7:59). A sleep dura-
tion of ≤ 9 h was deemed unusual. The cutoff points of sleep duration during night and bedtime were determined by referring to the quartile points of the study population.

Outcome 2: Infant's developmental problems. We used the Japanese version of the Child Behavior Check List/1½–5 (CBCL) to evaluate an infant’s developmental problems when they turned 1.5 years old. The CBCL is widely used to evaluate emotional/behavioral problems of children\(^{15}\), and the version used in the present study has been validated\(^{16}\). It consists of 100 items on specific behavior problems scored from 0 (not true at all) to 2 (completely true). The scores per item are added to yield a total problems score and two broadband scores (internalizing and externalizing problems). Internalizing problems comprised attention problems and aggressive problems subscale measures. Externalizing problems comprised attention problems and aggressive problems subscale measures. All scores and subscales are a standardized T-score (mean = 50, SD = 10), and 60 is set as the cutoff score for each domain\(^{15}\). The outcomes in this study were defined by whether T-scores were above or below the cutoff points for each CBCL domain. We also used the T-scores as outcomes.

Covariates. Information about maternal age at delivery, gestational weeks at birth, children's birth weight, whether or not the infant was small for gestational age, parity (0 or ≥ 1), and infant sex were collected via medical records. We choose these factors as covariates because these were reported as risk factors for developmental disorders\(^{8,39}\). Since the number of analysis subjects was limited, we selected three covariates (maternal age, children's birth weight, and parity) with large correlation coefficients for infant outcomes for main multivariate analysis.

Statistical analysis. JMP 14 (SAS Institute Inc., Cary, NC, USA) was used for all analyses. The statistical significance was set at 0.05. Descriptive statistical analyses were performed using means and SD, or numbers and percentages.

To explore the association of fetal EMD and sleeping outcomes, we used a logistic regression model and estimated the OR for each sleeping outcome and 95% CIs. We then used multivariate logistic regression models adjusted for maternal age at delivery, children's birth weight, and parity (0 or ≥ 1) to estimate the adjusted OR (aOR) and 95% CI.

In the same way as above, we also examined the association between fetal EMD and whether the CBCL scores in total, internalizing, and externalizing problems were above the cutoff points. In addition, we used linear regression models to analyze the association between fetal EMD and sleep outcomes. The same covariates were selected in the multivariate models used to analyze the association between fetal EMD and sleep outcomes.

We also performed stratified analysis to investigate the period associated with each infant outcome. We divided the cases into those measured at 28–32 gestational weeks (n = 23) and those at 33–37 gestational weeks (n = 37).

In addition, we performed sensitivity analyses by replacing the "birth weight" covariate with "gestational weeks at birth" in the multivariate models.

Data availability
The data that support the findings of this study are available from the corresponding author upon reasonable request.

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References
1. De Vries, J. I. P. & Fong, B. F. Normal fetal motility: An overview. *Ultrasound Obstet. Gynecol.* 27, 701–711 (2006).
2. Inoue, M. *et al.* Functional development of human eye movement in utero assessed quantitatively with real-time ultrasound. *Am. J. Obstet. Gynecol.* 155, 170–174 (1986).
3. Okai, T., Kozuma, S. & Shinozuka, Y. A study on the development of sleep-wakefulness cycle in the human fetus. *Early Hum. Dev.* 29, 391–396 (1992).
4. Koyanagi, T. *et al.* Ontogenesis of ultradian rhythm in the human fetus, observed through the alternation of eye movement and no eye movement periods. *J. Reprod. Infant Psychol.* 11, 129–134 (1993).
5. Mirrman, M., Maas, Y. G. H. & Ariagno, R. L. Development of fetal and neonatal sleep and circadian rhythms. *Sleep Med. Rev.* 7, 321–334 (2003).
6. Schroeder, L. A. *et al.* Reduced rapid eye movement density in Parkinson disease: A polysomnography-based case-control study. *Sleep 39*, 2133–2139 (2016).
7. Marzano, C., de Simoni, E., Tempesta, D., Ferrara, M. & de Gennaro, L. Sleep deprivation suppresses the increase of rapid eye movement density across sleep cycles. *J. Sleep Res.* 20, 386–394 (2011).
8. Darchia, N., Campbell, I. G. & Feinberg, I. Rapid eye movement density is reduced in the normal elderly. *Sleep 26*, 973–977 (2003).
9. Reynolds, A. M. *et al.* Sleep problems in 2- to 5-year-olds with autism spectrum disorder and other developmental delays. *Pediatrics 143* (2019).
10. Humphreys, J. S. *et al.* Sleep patterns in children with autistic spectrum disorders: A prospective cohort study. *Arch. Dis. Child.* 99, 114–118 (2014).
11. Richdale, A. L. & Prior, M. R. The sleep/wake rhythm in children with autism. *Eur. Child Adolesc. Psychiatry* 4, 175–186 (1995).
12. Tanguay, P. E., Ornitz, E. M., Forsythe, A. B. & Ritvo, E. R. Rapid eye movement (REM) activity in normal and autistic children during REM sleep. *J. Autism Child. Schizophr.* 6, 275–288 (1976).
13. Ornitz, E. M. *et al.* The EEG and rapid eye movements during REM sleep in normal and autistic children. *Electroencephalogr. Clin. Neurophysiol.* 26, 167–175 (1969).
14. Okawa, H. et al. Eye movement activity in normal human fetuses between 24 and 39 weeks of gestation. PLoS ONE 12, 1–12 (2017).
15. Yasuko, F. & Toshiya, M. Standardization of a Japanese version of the child behavior checklist for ages 1 1/2-5 and the caregiver-teacher report form. Jpn. J. Child Adolesc. Psychiatry 58, 107–123 (2017).
16. Ednick, M. et al. A review of the effects of sleep during the first year of life on cognitive, psychomotor, and temperament development. Sleep 32, 1449–1458 (2009).
17. Scher, M. S., Steppe, D. A., Dahl, R. E., Asthana, S. & Guthrie, R. D. Comparison of EEG sleep measures in healthy full-term and preterm infants at matched conceptional ages. Sleep 15, 442–448 (1992).
18. Huang, Y. S., Paiwa, T., Hsu, J. F., Kuo, M. C. & Guilleminault, C. Sleep and breathing in premature infants at 6 months post-natal age. BMC Pediatr. 14, 1–6 (2014).
19. Anders, T. F. & Keener, M. Developmental course of nighttime sleep-wake patterns in full-term and premature infants during the first year of life. J. Sleep Res 8, 173–192 (1995).
20. Als, H. et al. Early experience alters brain function and structure. Pediatrics 113, 846–857 (2004).
21. Soleimani, F. et al. Do NICU developmental care improve cognitive and motor outcomes for preterm infants? A systematic review and meta-analysis. BMC Pediatr. 20, 1–16 (2020).
22. Thomason, M. E. et al. Weak functional connectivity in the human fetal brain prior to preterm birth. Sci. Rep. 7, 1–10 (2017).
23. Hayashi, Y. et al. Cells of a common developmental origin regulate REM/non-REM sleep and wakefulness in mice. Science 350, 957–962 (2015).
24. Arditi-Babchuk, H., Feldman, R. & Eidelman, A. I. Rapid eye movement (REM) in premature neonates and developmental outcome at 6 months. Infant Behav. Dev. 32, 27–32 (2009).
25. Wolfe, K. & Ralls, F. M. Rapid eye movement sleep and neuronal development. Curr. Opin. Pulm. Med. 25, 555–560 (2019).
26. Li, W., Ma, L., Yang, G. & Gan, W. REM sleep selectively prunes and maintains new synapses in development and learning. Nat. Neurosci. 20, 27–43 (2017).
27. Limberg, K., Gruber, K. & Noterdaeme, M. The German version of the Child Behavior Checklist 1.5–5 to identify children with a risk of autism spectrum disorder. Autism 21, 368–374 (2017).
28. Cho, H. N. & Ha, E. H. A validation study of the Korean Child Behavior Checklist 15–5 in the diagnosis of autism spectrum disorder and non-autism spectrum disorder. J. Korean Acad. Child Adolesc. Psychiatry 30, 9–16 (2019).
29. Harvdahl, K. A., van Tetedtcher, S., Huerta, M., Lord, C. & Bishop, S. L. Utility of the Child Behavior Checklist as a screener for autism spectrum disorder. Autism Res. 9, 33–42 (2016).
30. Ooi, Y. P., R规避ora, L., Ang, R. P., Woo, B. & Fung, D. S. S. Identification of autism spectrum disorders using the child behavior checklist in Singapore. J. Autism Dev. Disord. 41, 1147–1156 (2011).
31. Teng, Y. et al. Association between sleep timing, obesity, diabetes: The Hispanic Community Health Study/Study of Latinos (HCHS/SOL) Cohort Study. Sleep 40, 1–8 (2017).
32. Buckley, A. W. et al. Rapid eye movement sleep percentage in children with autism compared with children with developmental delay and typical development. Arch. Pediatr. Adolesc. Med. 164, 1032–1037 (2010).
33. Devnani, P. A. & Hegde, A. U. Autism and sleep disorders. J. Pediatr. Neurosci. 10, 304–307 (2015).
34. Limoge, E., Mottron, L., Bolduc, C., Berthiaume, C. & Godbout, R. Atypical sleep architecture and the autism phenotype. Brain 128, 1049–1061 (2005).
35. Landa, R. J. Efficacy of early interventions for infants and young children with, and at risk for, autism spectrum disorders. Int. Rev. Psychiatry 30, 25–39 (2018).
36. Fisher, A., Van Jaarsveld, C. H. M., Llewellyn, C. H. & Wardle, J. Genetic and environmental influences on infant sleep. Pediatrics 129, 1091–1096 (2012).
37. Holmes, C., Levy, M., Smith, A., Pinne, S. & Neese, P. A model for creating a supportive trauma-informed culture for children in preschool settings. J. Child Fam. Stud. 24, 1650–1659 (2015).
38. Gardener, H., Spiegelman, D. & Buka, S. L. Perinatal and neonatal risk factors for autism: A comprehensive meta-analysis. Pediatrics 128, 344–355 (2011).
39. Hua, J. et al. The prenatal, perinatal and neonatal risk factors for children’s developmental coordination disorder: A population study in mainland China. Res. Dev. Disabil. 35, 619–625 (2014).

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S.M.: Conceptualization, Methodology, Investigation, Project administration, Writing—original draft. K.N.: Data Curation, Formal analysis, Investigation, Visualization, Writing—original draft. K.M.: Data Curation, Investigation, Writing—review and editing. H.O.: Data Curation, Investigation, Writing—review and editing. Y.F.: Resources, Writing—review and editing. K.K.: Writing—review and editing.

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