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Infants' early recovery from sleep disturbance is associated with a lower risk of developmental delay in the Japan Environment and Children's Study

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To examine whether patterns, such as the timings of onset or recovery from sleep disturbance, are associated with later developmental problems, including autism spectrum disorder (ASD). Mothers participating in the Japan Environment and Children's Study with a child aged 3 years were included in the analyses. Children were assessed for short sleep and frequent awakenings at 1 month, 6 months, and 1 year of age. Developmental problems were evaluated at 3 years of age based on ASD diagnosis and developmental delay, using the Japanese translation of the Ages and Stages Questionnaire (ASQ) 3rd edition. Sleep disturbance patterns were classified by onset age, and developmental problem risks were examined based on onset/recovery ages. Among 63,418 mother-infant dyads, 0.4% of infants were later diagnosed with ASD, and 14.4% had abnormal scores on any ASQ domains. The later the onset of short sleep, the lower the risk of abnormal ASQ scores (RR of short sleep onset at 1 year: 1.41; 6 months: 1.52; 1 month: 1.57). The earlier the infants recovered from short sleep persistence, the lower the risk of developmental delay (RR of remittance of sleep problems identified at 1 month by 6 months: 1.07; 1 year: 1.31; not before 1 year: 1.57). Although not all patterns were significant, later short sleep onset and earlier recovery were associated with lower ASD risk. These findings may have significant implications for future interventions in infant development.

Keywords Sleep disturbance, ASD, ASQ, Pediatrics

Infants spend a significant portion of their early life sleeping, profoundly affecting their development through maturation of the central nervous system[1]. Infant healthy sleep has been linked to better cognitive and motor development as well as executive function[2]. A study using the general infant developmental screening tool, the Ages and Stages Questionnaire (ASQ), revealed that infants' frequent awakenings at 6 months were associated

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with lower ASQ scores at 18 months and 3 and 5 years[3]. Furthermore, research on specific infant development indicates that longer night-time sleep is associated with better cognitive problem-solving skills[4] and better executive function performance[5,6]. Conversely, insufficient night-time sleep in infants has been associated with poor fine motor development[7] and social-emotional problems[8]. Longer and more consistent night-time and total sleep trajectories and a short daytime sleep trajectory in early childhood have been associated with better cognition at the ages of 2 and 4.5 years[9]. Thus, a relationship exists between infant sleep disturbance and development.

Autism spectrum disorder (ASD) is a neurodevelopmental disorder associated with sleep disturbances, including those occurring in infants[10]. An previous study reported that the nationwide 5-year lifetime cumulative incidence of ASD was 2.75% in Japan[11]. ASD is characterized by social communication deficits and restrictive and repetitive sensorimotor behaviors[12]. In their study, Nguyen et al. demonstrated an association between frequent awakenings at 12 months of age and an increased risk of ASD symptoms 1 year later[13]. In addition, Schreck et al. found that shorter sleep each night predicted higher total autism scores on the Gilliam Autism Rating Scale in children aged 5–12[14]. Our previous longitudinal study also found that more daytime sleep than night-time sleep at 1 month was associated with the diagnosis of ASD at 3 years of age[15]. The results of these studies suggest that sleep disturbance in infants predicts future ASD diagnoses.

Despite the demonstrated associations between sleep disturbances and developmental problems, such as ASD, the relationship between the timings of onset or recovery from sleep disturbances and later developmental problems has not yet been determined. Understanding these associations could offer insights into the possible interventions in infants with sleep disturbances to mitigate their impact and reduce the risk of later developmental challenges. Therefore, this study aimed to examine whether the timings of onset or recovery from sleep disturbance are associated with later developmental problems, including ASD, using data from a large, longitudinal cohort study in Japan.

Results

Of the 103,060 registered pregnancies, data from 63,418 eligible mother-infant dyads were analyzed (Fig. 1). A total of 271 (0.4%) infants were diagnosed with ASD. Those with abnormal scores on any of the five ASQ domains were 9159 (14.4%), and those per domain were 2315 (3.7%) in communication, 2631 (4.2%) in gross motor skills, 4483 (7.1%) in fine motor skills, 4396 (7.0%) in problems-solving, and 1922 (3.0%) in personal-social characteristics. Table 1 shows the baseline characteristics of the infants based on the patterns according to when a short sleep duration was detected. In total, 19,059 (30.1%) had persistent short sleep from 1 month to 1 year of age. Table 2 shows the baseline characteristics of the infants based on the patterns according to when frequent night-time awakenings were observed. Among them, 6684 (10.5%) had frequent night-time awakenings at 1 month, 6 months, or 1 year of age.

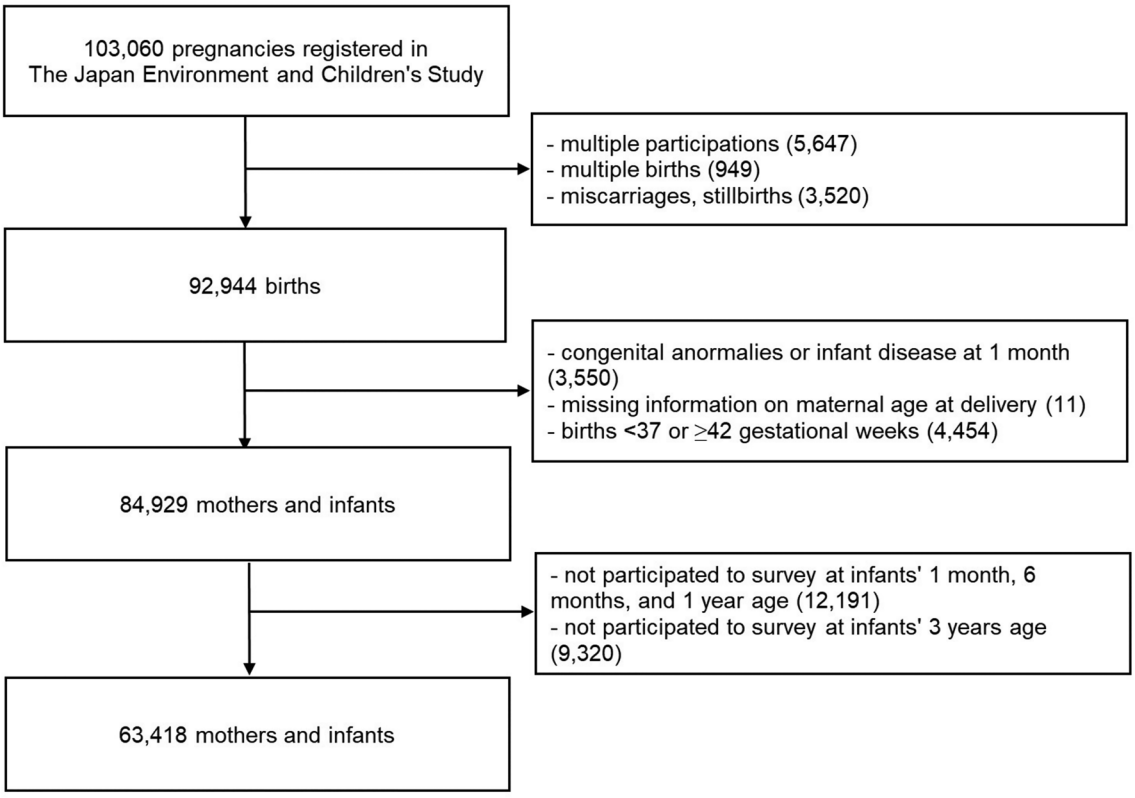

Figure 1. Flow diagram of the selection process of study participants.

	Short sleep patterns									
1 month of age			–	–	–	–	**SS**	**SS**	**SS**	**SS**
6 months of age			–	–	**SS**	**SS**	–	–	**SS**	**SS**
1 year of age	**Total**		–	**SS**	–	**SS**	–	**SS**	–	**SS**
	n	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
No. of women	63,418		44,359	1753	4373	721	10,061	525	1352	274
Age at delivery (years)										
< 25	5010	7.9	7.5	8.0	8.6	11.4	8.4	13.7	10.7	13.9
25–29	17,251	27.2	27.4	22.8	28.3	20.5	27.6	22.5	26.2	24.1
30–34	23,150	36.5	37.0	36.9	34.2	32.6	36.0	33.0	34.3	33.6
≥ 35	18,007	28.4	28.1	32.3	29.0	35.5	28.0	30.9	28.9	28.5
Smoking habits										
Never smoked	38,829	61.3	61.5	60.6	62.5	61.3	60.5	58.2	61.3	59.9
Ex-smokers who quit before pregnancy	14,865	23.5	23.8	22.7	22.0	20.4	23.3	21.4	22.7	18.3
Smokers during early pregnancy	9615	15.2	14.7	16.7	15.5	18.3	16.2	20.4	16.0	21.9
Alcohol consumption										
Never drank	21,993	34.7	34.6	34.5	33.3	32.9	35.6	36.8	34.4	40.5
Ex-drinkers who quit before pregnancy	11,390	18.0	18.2	18.8	17.3	19.1	17.4	17.3	16.6	17.5
Drinkers during early pregnancy	29,980	47.3	47.2	46.8	49.4	48.0	47.0	45.9	49.0	42.0
Parity										
0	28,766	45.5	42.5	44.5	52.0	53.6	52.6	57.0	60.8	63.9
≥ 1	34,432	54.5	57.5	55.5	48.0	46.4	47.4	43.1	39.2	36.1
Gestational age at delivery (week)										
37	6041	9.5	9.2	9.8	8.2	9.3	11.4	11.2	10.4	12.4
38	14,532	22.9	22.7	20.8	21.2	20.8	25.2	24.2	23.0	25.2
39	18,776	29.6	29.8	29.1	30.6	29.0	28.6	27.8	29.1	26.6
40	17,830	28.1	28.4	30.2	28.5	28.7	26.5	27.2	27.1	23.0
41	6239	9.8	9.9	10.2	11.5	12.2	8.4	9.5	10.4	12.8
Educational background (years)										
< 13	20,697	32.9	32.4	35.8	32.8	38.7	32.9	41.3	35.4	43.9
≥ 13	42,263	67.1	67.6	64.2	67.2	61.3	67.1	58.7	64.7	56.1
Household income (million Japanese yen/year)										
< 6	42,713	71.9	71.4	71.8	72.7	75.1	73.3	79.0	72.1	77.1
≥ 6	16,673	28.1	28.6	28.2	27.3	24.9	26.7	21.1	27.9	22.9
Postpartum depressive symptoms 1 month after delivery were assessed by Edinburgh postnatal depression scale										
No (score < 8)	54,317	86.7	87.7	85.7	83.3	80.9	85.3	79.5	82.5	75.0
Depressive (score ≥ 9)	8366	13.4	12.3	14.3	16.7	19.1	14.7	20.5	17.5	25.0
Small for gestational age										
No	58,632	92.8	92.8	92.7	93.3	92.5	92.7	90.1	91.6	90.5
Yes	4566	7.2	7.2	7.3	6.7	7.5	7.3	9.9	8.4	9.5
Infant sex										
Boys	32,306	50.9	50.9	53.2	53.2	55.8	49.5	46.9	51.9	54.7
Girls	31,112	49.1	49.1	46.8	46.8	44.2	50.5	53.1	48.2	45.3
Feeding status at 1 month after birth										
Exclusive breastfeeding	33,926	54.6	56.0	51.6	53.0	53.3	51.0	49.9	49.8	48.9
Partial breastfeeding or formula feeding	28,170	45.4	44.0	48.4	47.1	46.7	49.0	50.1	50.2	51.1

Table 1. Baseline characteristics according to infant short sleep patterns in the Japan Environment and Children's Study (2011–2014). The dashes in the columns of sleep patterns in the table indicate a healthy sleep state. *SS:* short sleep. *Subgroup totals do not equal the overall number because of missing data.

Risk ratios of developmental problems based on the age of onset of short sleep

Appendix 1 shows the association between the age patterns during which short sleep was observed and later developmental problems. Infants who had a short sleep at 6 months and 1 year of age (risk ratio [RR] 2.65, 95% confidence interval [CI] 1.24–5.67), at 1 month of age only (RR 1.45, 95% CI 1.05–1.99), or at 1 month, 6 months, and 1 year of age (RR 4.08, 95% CI 1.56–10.54) were associated with a risk of later diagnosis of ASD. Those with short sleep at any age were associated with a risk of later developmental delays in any domain of the ASQ, compared to those without.

	Night-time awakenings patterns									
1 month of age			–	–	–	–	**AW**	**AW**	**AW**	**AW**
6 months of age			–	–	**AW**	**AW**	–	–	**AW**	**AW**
1 year of age	**Total**		–	**AW**	–	**AW**	–	**AW**	–	**AW**
	n	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**	**(%)**
No. of women	63,418		56,734	1179	1141	208	3751	161	194	50
Age at delivery (years)										
< 25	5010	7.9	8.2	4.6	5.6	2.9	6.5	5.0	3.6	2.0
25–29	17,251	27.2	27.3	26.0	27.7	25.5	26.5	23.6	26.3	18.0
30–34	23,150	36.5	36.4	38.2	39.2	41.8	36.5	44.1	40.2	34.0
≥ 35	18,007	28.4	28.2	31.2	27.5	29.8	30.6	27.3	29.9	46.0
Smoking habits										
Never smoked	38,829	61.3	61.3	63.9	62.4	65.2	60.7	64.0	57.8	74.0
Ex-smokers who quit before pregnancy	14,865	23.5	23.3	24.3	26.3	24.2	24.6	26.7	29.7	20.0
Smokers during early pregnancy	9615	15.2	15.4	11.8	11.3	10.6	14.7	9.3	12.5	6.0
Alcohol consumption										
Never drank	21,993	34.7	34.9	35.5	31.8	30.8	33.5	34.8	30.6	26.0
Ex-drinkers who quit before pregnancy	11,390	18.0	17.9	20.9	18.8	17.8	18.7	16.2	18.1	20.0
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Parity										
0	28,766	45.5	46.1	42.8	46.5	39.3	38.3	35.6	37.5	34.0
≥ 1	34,432	54.5	53.9	57.2	53.5	60.7	61.7	64.4	62.5	66.0
Gestational age at delivery (week)										
37	6041	9.5	9.4	10.4	8.6	11.5	10.8	10.6	11.3	14.0
38	14,532	22.9	22.6	25.0	22.5	23.1	26.4	28.6	26.8	30.0
39	18,776	29.6	29.6	29.8	28.4	26.9	30.9	31.7	28.9	26.0
40	17,830	28.1	28.4	26.1	30.9	29.8	25.1	19.3	23.2	16.0
41	6239	9.8	10.1	8.7	9.6	8.7	6.8	9.9	9.8	14.0
Educational background (years)										
< 13	20,697	32.9	33.2	29.4	29.5	29.3	31.5	23.8	24.0	32.0
≥ 13	42,263	67.1	66.8	70.6	70.6	70.7	68.5	76.3	76.0	68.0
Household income (million Japanese yen/year)										
< 6	42,713	71.9	72.0	72.6	69.3	69.8	72.3	69.7	72.1	79.2
≥ 6	16,673	28.1	28.1	27.5	30.7	30.2	27.7	30.3	27.9	20.8
Postpartum depressive symptoms 1 month after delivery were assessed by the Edinburgh postnatal depression scale										
No (score < 8)	54,317	86.7	86.7	86.3	84.4	85.4	87.2	86.8	83.4	75.5
Depressive (score ≥ 9)	8366	13.4	13.3	13.7	15.6	14.6	12.8	13.2	16.6	24.5
Small for gestational age										
No	58,632	92.8	92.8	92.6	94.6	94.7	92.5	92.5	91.2	90.0
Yes	4566	7.2	7.2	7.4	5.4	5.3	7.5	7.5	8.9	10.0
Infant sex										
Boys	32,306	50.9	50.4	55.1	60.7	58.7	53.5	62.7	59.8	66.0
Girls	31,112	49.1	49.6	44.9	39.4	41.4	46.5	37.3	40.2	34.0
Feeding status at 1 month after birth										
Exclusive breastfeeding	33,926	54.6	53.3	66.2	61.6	67.2	66.2	73.9	69.8	72.0
Partial breastfeeding or formula feeding	28,170	45.4	46.7	33.8	38.4	32.8	33.8	26.1	30.2	28.0

Table 2. Baseline characteristics according to infant night-time awakenings patterns in the Japan Environment and Children's Study (2011–2014). The dashes in the columns of sleep patterns in the table indicate a healthy sleep state. AW: night-time awakening. *Subgroup totals do not equal the overall number because of missing data.

Risk ratios of developmental problems based on the age of onset of frequent night-time awakenings

Appendix 2 shows the association between the age patterns during which frequent night-time awakenings were observed and the later developmental problems. Many patterns did not show statistical results because of the small number of participants who had night-time awakenings. However, infants who began to have frequent awakenings at 1 and 6 months of age were associated with a risk of being later diagnosed with ASD (RR 4.01; 95%

CI 1.30–12.34). Infants who had frequent awakenings at only 1 year of age (RR 1.31, 95% CI 1.15–1.48) and at only 1 month and 1 year of age (RR 1.63, 95% CI 1.22–2.17) were associated with a risk of later developmental delays in any domain of the ASQ, compared to those without.

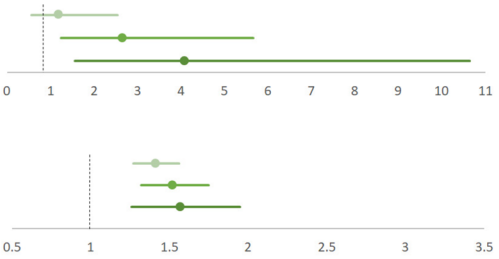
Risk ratios of developmental problems based on the persistence and remittance of short sleep

Figure 2 shows a portion of Appendices 1 and 2 rearranged in the order of scenarios 1 and 2 concerning the short sleep patterns. The upper tables and figures indicate the risks of later developmental problems regarding the short sleep onset age patterns. Although not all patterns were significant, the later the age at which short sleep was observed, the lower the risk of later ASD diagnosis (RR of short sleep onset at 1 year: 1.19; 6 months: 2.65; 1 month: 4.08). This trend was also similar for the risk of later ASQ abnormal score (RR of short sleep onset at 1 year: 1.41; 6 months: 1.52; 1 month: 1.57). Regarding the five domains of the ASQ, communication (RR of short sleep onset at 1 year: 1.22; 6 months: 1.88; 1 month: 1.96) and personal-social characteristics (RR of short sleep onset at 1 year: 1.38; 6 months: 1.61; 1 month: 1.73) showed similar trends in association with the onset of short sleep as shown in Fig. 3.

The bottom tables and figures indicated the risks of later developmental problems regarding the age patterns of recovery from persistent short sleep. Although not all patterns were significant, the earlier the age at which short sleep was recovered, the lower the risk of later ASD diagnosis (RR of short sleep recovery at 6 months: 1.45; 1 year: 1.47; no recovery before 1 year of age: 4.08). This trend was also similar for the risk of later ASQ abnormal score (RR of short sleep recovery at 6 months: 1.07; 1 year: 1.31; no recovery before 1 year of age: 1.57). Regarding the five ASQ domains, communication (RR of short sleep recovery at 6 months: 1.15; 1 year: 1.34; no recovery before 1 year of age: 1.96), fine-motor skills (RR of short sleep recovery at 6 months: 1.11; 1 year: 1.28; no recovery before 1 year of age: 1.82), and personal-social characteristics (RR of short sleep recovery at 6 months: 1.14; 1 year: 1.41; no recovery before 1 year of age: 1.73) showed similar trends in association with recovery from a short sleep, as shown in Fig. 3.

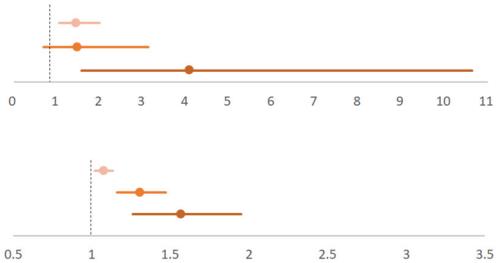
Scenario 1. Risk ratios of developmental problems on later onset of short sleep

Short-sleep patterns			No. of participants	No. of outcome		Adjusted*		
1m	6m	1y			%	RR	95% CI	
Autism Spectrum Disorders								
–	–	–	44,359	165	0.4	Reference		
–	–	SS	1,753	8	0.5	1.19	0.56	2.55
–	SS	SS	721	7	1.0	2.65	1.24	5.67
SS	SS	SS	274	4	1.5	4.08	1.56	10.64
Total score of Ages and Stages Questionnaire (abnormal score for any 1 of the 5								
–	–	–	44,359	5,982	13.5	Reference		
–	–	SS	1,753	339	19.3	1.41	1.27	1.56
–	SS	SS	721	164	22.8	1.52	1.32	1.75
SS	SS	SS	274	67	24.5	1.57	1.26	1.95



Scenario 2. Risk ratios of developmental problems on early recovery from short sleep

Short-sleep patterns*			No. of participants	No. of outcome		Adjusted*		
1m	6m	1y			%	RR	95% CI	
Autism Spectrum Disorders								
–	–	–	44,359	165	0.4	Reference		
SS	–	–	10,061	54	0.4	1.45	1.05	1.99
SS	SS	–	1,352	8	0.6	1.47	0.70	3.12
SS	SS	SS	274	4	1.5	4.08	1.56	10.64
Total score of Ages and Stages Questionnaire (abnormal score for any 1 of the 5								
–	–	–	44,359	5,982	13.5	Reference		
SS	–	–	10,061	1,504	15.0	1.07	1.02	1.13
SS	SS	–	1,352	263	19.5	1.31	1.16	1.47
SS	SS	SS	274	67	24.5	1.57	1.26	1.95



* Adjusted for infant sex, small for gestational age, feeding status at one-month after birth, maternal age at delivery, smoking habits, alcohol consumption, gestational age at birth, parity, educational background, household income, postpartum depressive symptoms at one-month.

Figure 2. Risk ratios of developmental problems (assessed with ASD diagnosis/total score of ASQ) at 3 years of age in relation to later onset of/early recovery from persistent short sleep (caregiver-reported) in the Japan Environment and Children's Study. The upper two tables and figures show the risk ratios of developmental problems (ASD and total score of ASQ) in relation to the later onset of short sleep. The two tables and figures at the bottom show the risk ratios in relation to early recovery from a short sleep. The lighter green color in the graph indicates patterns of later onset of short sleep and the lighter orange color indicates patterns of early recovery from short sleep. *ASD* autism spectrum disorder, *ASQ* Ages and Stages Questionnaire, *CI* confidence interval, *RR* risk ratio, *SS* short sleep. The dashes in the short-sleep patterns indicate healthy sleep.

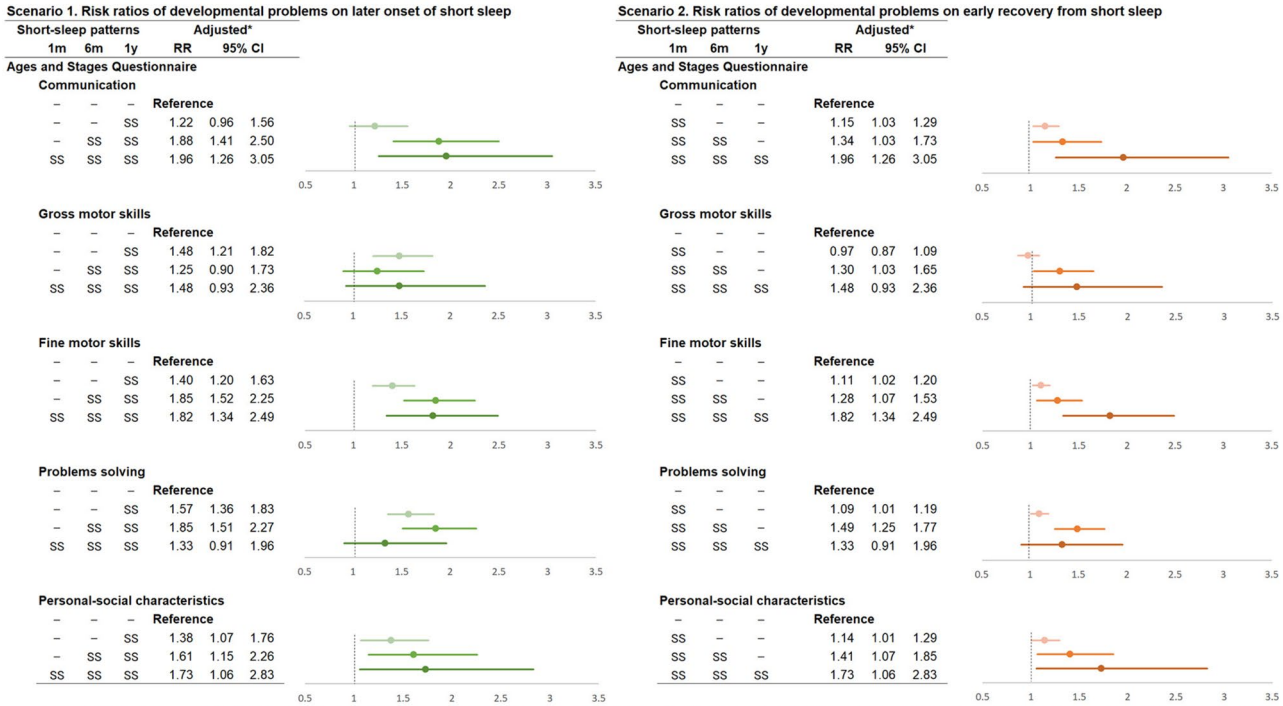


Figure 3. Risk ratios of developmental problems (assessed with the five domains of ASQ) at 3 years of age in relation to later onset of/ early recovery from persistent short sleep (caregiver-reported) in the Japan Environment and Children's Study. The data on the left show the risk ratios of developmental problems assessed with the five domains of ASQ in relation to the later onset of short sleep. The tables and figures on the right side show the risk ratios in relation to early recovery from a short sleep. The lighter green color in the graph indicates patterns of later onset of short sleep, and the lighter orange color indicates patterns of early recovery from short sleep. *CI* confidence interval, *RR* risk ratio, *SS* short sleep. The dashes in the short-sleep patterns indicate healthy sleep.

Discussion

This is the first longitudinal study on the risks of developmental problems based on patterns of sleep disturbance onset and recovery. As assessed using the ASQ score, infants whose onset of short sleep was observed earlier showed a higher risk of later developmental problems. Conversely, those whose short sleep was observed at 1 month of age and who recovered at 6 months had a lower risk of later developmental delays than those who recovered at 1 year. These associations were particularly similar for the "communication" and "personal–social characteristics" domains of the ASQ. Although not statistically significant, similar risk patterns were observed in relation to the diagnosis of ASD by age 3.

Our findings revealed that infants whose onset of short sleep was earlier were more likely to have developmental delays by 3 years. A similar trend was observed in association with ASD diagnosis. These findings suggest that infants who experience short sleep at 1 month that persists until 1 year old are at a higher risk of developmental problems such as ASD later in life than those with short sleep persisting until 6 months. This result is consistent with previous studies showing the association between longitudinal nocturnal sleep duration and developmental problems[9,16,17]. This association may be bi-directorial. Infants with ASD have genetic features related to sleep disturbances, such as polymorphisms in clock genes and genes involved in melatonin production[18].

In addition, early recovery from persistent short sleep was associated with a lower likelihood of developing developmental problems by 3 years of age than later recovery. Although not statistically significant, a similar trend of RR was observed in association with ASD diagnosis. This suggests that a shorter period of short sleep reduces the risk of developmental problems, which is consistent with the aforementioned findings. While previous studies have identified an association between sleep disturbance and developmental problems[13,14], our study specifically highlighted the association between a longer sleep disturbance and an increased risk of developmental problems. This latter finding is particularly important because it implies that early improvement in sleep disturbance may potentially mitigate developmental problems and symptoms, including ASD.

When examining the ASQ domains individually, we observed associations between short sleep and the "communication" and "personal–social characteristics" traits, which are common in children with ASD as outlined in the diagnostic and statistical manual of mental disorders[19]. These results align with the findings of the present study, linking sleep disturbance to the diagnosis of ASD. Furthermore, ASD may increase the likelihood of having social and communication problems when infants have sleep disturbances[20]. Nevertheless, this association may sometimes not be observed owing to caregiver observation limitations in detecting subtle motor signs[21]. However, further research is required to clarify this relationship.

This study has several limitations. First, the sleep disturbance assessment relied on caregiver reports on a single day, which may have been insufficient. Reports on infant sleep quality may have been overestimated when there was no behavioral evidence of poor sleep. In addition, the frequency of night-time awakening may have been underestimated because infants may have awakened briefly without crying or alerting their caregivers[22]. Second, outcomes related to a child's development, including ASD diagnosis, relied on caregiver self-reports. Because the present study analyzed data followed until 3 years of age, we could not categorize children diagnosed after 3 years of age into the ASD group. Thus, the ASD rate in this study might be underestimated since it is lower than that in a previous study[11]. Third, owing to the large sample size, even small differences in outcomes may be statistically significant. Fourth, in our study, the criteria for measuring sleep disturbance in 1-month-old infants are different from those in 6-month-old and 1-year-old infants. Our previous research has shown that even at 1 month of age, nighttime sleep duration trends to increase[15,23,24], making it important to use nighttime sleep duration as a criterion for sleep disturbance. However, no established evidence exists for nighttime sleep duration in 1-month-old infants. Therefore, in this study, we used the criterion that daytime sleep duration is longer than nighttime sleep duration to measure sleep disturbance in 1-month-old infants. Despite these limitations, this study contributes significantly to understanding the longitudinal association between sleep disturbances and developmental problems, such as ASD using a substantial sample size.

In conclusion, this study suggests that the later onset or early recovery period of sleep disturbances in infancy reduces the risk of later developmental problems, including ASD. The finding that early recovery from sleep disturbances is associated with a reduced risk of developmental problems is particularly encouraging and may have significant implications for future interventions of these issues. Moreover, this finding serves as a crucial indicator for future studies on infant development.

Methods

Study design and participants

This longitudinal cohort study used data from the Japan Environment and Children's Study (JECS), a nationwide prospective birth cohort study, registered in the University Hospital Medical Information Network Clinical Trials Registry (UMIN000030786). The study protocol and profile for which have been reported previously[25,26]. The JECS enrolled approximately 100,000 pregnant women and their children who had long-term follow-ups. Recruitment was conducted at 15 Regional Centers between January 2011 and March 2014. Those with multiple participations, multiple births, miscarriages or stillbirths, congenital anomalies, missing information on maternal age at delivery, birth at <37 or ≥ 42 gestational weeks, unanswered questions on infant sleep disturbance at 1 month, 6 months, and 1 year of age, and unanswered questions on ASQ and ASD diagnosis by 3 years of age, were excluded (Fig. 4). Preterm births were excluded since they are associated with ASD[27].

The JECS protocol was reviewed and approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (No. 100910001) and the Ethics Committees of all participating institutions. All procedures were performed in accordance with relevant guidelines/regulations and with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Procedure

Caregivers completed self-administered questionnaires during the first, second, or third trimester of pregnancy and at 1 month, 6 months, 1 year, and 3 years postpartum. The infants' medical record transcripts at birth were also collected.

Assessment of infant sleep quality

We assessed infant sleep quality at 1 month, 6 months, and 1 year of age, considering it abnormal if they had short sleep and/or frequent awakenings. To gather this information, we asked caregivers regarding the infant's sleep patterns and how often the infant woke up during the previous day (from 12:00 a.m. to 11:30 p.m., at 30-min intervals), and scored accordingly. For 1-month-old infants, we defined short sleep as meeting the following conditions: daytime sleep duration (between 8:00 a.m. and 7:59 p.m.) was longer than night-time sleep duration (between 8:00 p.m. and 7:59 a.m.). This dichotomization was chosen because 1-month-old infants typically have a longer night-time sleep pattern than during the day[24]. At 6 months and 1 year of age, short sleep duration was defined as <8 h of night-time sleep, as it falls below the night-time sleep range at 6 months (8.0–10.4 h) or 12 months (8.0–11.0 h)[28]. Regarding the frequency of awakenings, we defined unusual awakening frequency as infant awakening between 8:00 p.m. and 7:59 a.m. more frequent than average; ≥ 5 times at 1 month of age (range 2–4 times[28–30]), ≥ 4 times at 6 months (range 1–3.5 times[28–30]), or ≥ 3 times at 1 year (range 1.0–2.62[28,30]).

Developmental problems

We defined the children's developmental problems based on the diagnosis of ASD and the abnormal ASQ scores at 3 years old. ASD diagnosis information was collected based on caregiver responses regarding whether their child had been diagnosed with ASD (e.g., autism, pervasive developmental disorder, or Asperger syndrome) by the age of 3 years. In addition, we assessed the children's developmental delays using the validated Japanese translation of the ASQ 3rd edition[31]. This tool measures developmental disorders in five domains: communication, gross motor skills, fine motor skills, problem-solving, and personal-social characteristics. The cut-off points for each domain are 41.55 for communication, 39.26 for gross motor skills, 27.91 for fine motor skills, 30.03 for problem-solving, and 29.89 for personal-social characteristics. The scores below the cut-off point for any one of the five domains were defined as an abnormal score on the ASQ[31].

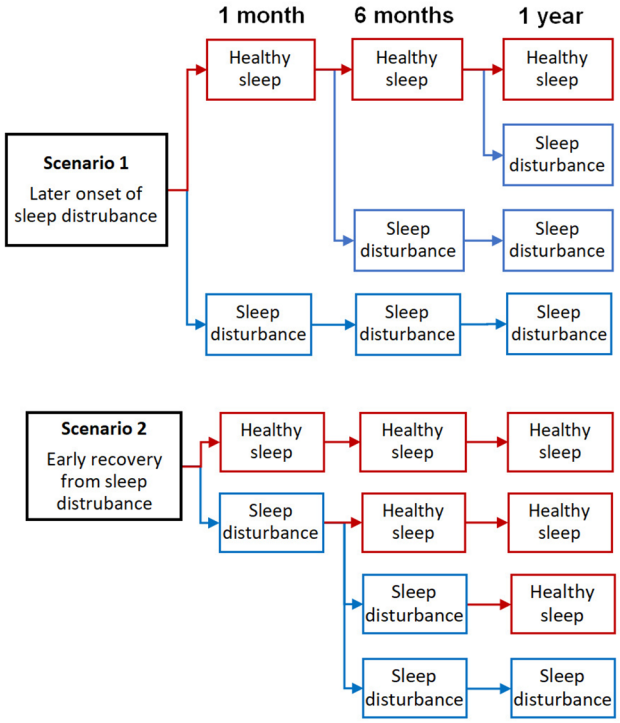


Figure 4. Two scenarios of sleep disturbances and age patterns. The figure shows the patterns of sleep disturbances and ages (1 month, 6 months, and 1 year of age) based on the later onset of sleep disturbances (scenario 1) and the early recovery from the sleep disturbances (scenario 2). The red boxes indicate healthy sleep status and the blue boxes indicate sleep disturbance (short sleep or night-time awakening). In the Poisson regression analysis, the pattern of healthy sleep at all ages from 1 month to 1 year was set as a reference to examine the risk ratios for scenarios 1 and 2.

Covariates

The covariates adjusted in the regression models were assessed based on the previous studies[15,23,32–35]. They included infant sex, small for gestational age (< 10th percentile of birth weight for gestational age standards[36]), breastfeeding status at 1 month postpartum, and gestational age at delivery, in addition to maternal age at delivery, smoking habits, alcohol consumption, parity, educational attainment, household income, and postpartum depressive symptoms at 1 month postpartum (Edinburgh Postnatal Depression Scale score[37–39] ≥ 9).

Statistical analysis

First, we descriptively analyzed all data based on patterns of the sleep disturbances (night-time awakening or short sleep) and the onset (1 month, 6 months, and 1 year) when the sleep disturbances were observed. We then performed the Poisson regression analyses to estimate the RRs of ASD diagnosis and ASQ scores for each pattern. We set two scenarios to address our study objectives. Scenario 1 aimed to identify the lower risk of later onset of sleep disturbance (scenario 1 in Fig. 2). Here, we compared a pattern of persistent sleep disturbance with patterns of sleep disturbances that began later in infancy. Scenario 2 aimed to identify the lower risk of early recovery from sleep disturbance (scenario 2 in Fig. 2). In this scenario, we compared a pattern of persistent sleep disturbance with patterns of recovery from sleep disturbance in early infancy. To accomplish this, we selected and sorted all sleep patterns in order of later onset sleep disturbances and later recovery from the disturbances. We then examined their associations with developmental problems at 3 years old, setting the reference on the pattern of persistent healthy sleep. We included all covariates in the regression model for RR assessment. All analyses were performed using STATA version 16.1 (StataCorp LLC, College Station, TX, USA). The dataset used in this study was the jecs-ta-20190930 dataset, which was released in October 2019.

Data availability

Data are unsuitable for public deposition due to ethical restrictions and the legal framework of Japan. It is prohibited by the Act on the Protection of Personal Information (Act No. 57 of 30 May 2003, amendment on 9 September 2015) to deposit the data containing personal information publicly. Ethical Guidelines for Medical and Health Research Involving Human Subjects enforced by the Japan Ministry of Education, Culture, Sports, Science and Technology and the Ministry of Health, Labour and Welfare also restrict the open sharing of epidemiologic data. All inquiries about access to data should be sent to: jecs-en@nies.go.jp. The person responsible for handling inquiries sent to this e-mail address is Dr. Shoji F. Nakayama, JECS Programme Office, National Institute for Environmental Studies.

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Author contributions
Study concept and design: S.M.; Statistical analyses: T.M.; Drafting of the manuscript and approval of the final content: K.K., S.M., and T.M.; Critical revision of the manuscript for important intellectual content: All authors; Manuscript review: All authors.

Competing interests
The authors declare no competing interests.

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