Circumstances and factors of sudden infant deaths during sleep in Japan

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Methods: Forensic pathology sections from eight universities participated in the selection of subjects from 2013 to 2018. Data obtained from the checklist form were analyzed based on information at postmortem.
Results: There were 259 SUDI cases consisting of 145 male infants and 114 female infants with a mean birth weight of 2888 ± 553 and 2750 ± 370 g, respectively. Deaths most frequently occurred among infants at 1 month of age (18%). According to population data as the control, the odds ratio (95% confidence interval) of mother’s age ≤19 years was 11.1 (6.9–17.7) compared with ages 30–39. The odds ratio for the fourth- and later born infants was 5.2 (3.4–7.9) compared with the frequency of first-born infants. The most frequent time of day for discovery was between 7 and 8 o’clock, and the time difference from the last seen alive was a mean of 4.1 h. Co-sleeping was recorded for 61%, and the prone position was found for 40% of cases at discovery. Mother’s smoking habit exhibited an odds ratio of 4.5 (2.9–5.8).
Conclusion: This study confirmed the trends that have been observed for sudden infant death syndrome; particularly, very high odds ratios were evident for teenage mothers and later birth order in comparison with those in other developed countries. Neglect was suspected in some cases of the prolonged time to discovery of unreactive infants. To our knowledge, this is the first report of an extensive survey of SUDI during sleep in Japan.
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The detailed review of our article is appreciated. The comments by the reviewer have been helpful in allowing us to revise the manuscript. The authors have attempted to address the questions raised as separate pages. According to the raised comments, the manuscript has been rewritten extensively to a revised version. Alterations are indicated as track changes in the revised manuscript.

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Circumstances and factors of sudden infancy deaths during sleep in Japan

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Abstract

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**Conclusion:** This study confirmed the trends that have been observed for sudden infant death syndrome; particularly, very high odds ratios were evident for teenage mothers and later birth order in comparison with those in other developed countries. Neglect was suspected in some cases of the prolonged time to discovery of unreactive infants. To our knowledge, this is the first report of an extensive survey of SUDI during sleep in Japan.
**Introduction**

Sudden infant death syndrome (SIDS) is the possible cause-of-death for sudden infant death during sleep, in which all known identifiable conditions that might engender sudden and unexpected death must be excluded by postmortem examinations. However, several pathologists have changed their diagnostic preferences since 2004 primarily because of the difficult distinction of SIDS from accidental asphyxia or natural diseases such as arrhythmias and metabolic disorders. [1-3] Reluctance to use the term has decreased the number globally over the years. [4-6] In Japan, around 0.5 per 1,000 livebirths (LBs) of annual SIDS rate was recorded in the 1990s, but recent diagnostic numbers have decreased to fewer than 0.1. [7]

Currently, another broad term has become popular, i.e., sudden unexpected death in infancy (SUDI) or sudden unexpected infant death (SUID). Although SUDI/SUID originally has been used as an umbrella term for the initial presentation of explained or unexplained infant deaths, it is interpreted to include several categories such as SIDS (R95), ill-defined and unknown cause of mortality (R99), and accidental suffocation or strangulation in bed (W75). [8] Several attempts have been made to categorize SUDI/SUID, but the terminology and classification have not yet been defined clearly. [9]

In recent years, a protocol of investigation items has been standardized. [10,11] For instance, in the U.S., the Centers for Disease Control and Prevention published guidelines and a reporting form, which is designated as the SUID Investigation Reporting Form. [12] In Japan, a list of items to be investigated is used as a similar checklist form in cases of infant death. [13] A system is in operation for clinicians and pathologists to ascertain circumstances and to investigate background factors.
Information from death scene investigation (DSI) acquired by experts is indispensable to fill out the form. [14] Furthermore, the maternity passbook, which records information about the mother and the child during pregnancy as well as after childbirth, is beneficial. We previously analyzed forensic autopsy cases of sudden infant deaths after vaccination using this passbook. [15]

While the childcare environment differs according to region and time, there are few epidemiological data describing infant deaths during sleep in Japan. [16] Takatsu et al. [17] exhibited the trends of SUID cases from 1982 to 2006. This population-based retrospective study was conducted to investigate the latest trends of sleep-related SUDI cases using the checklist form including the maternity passbook at multiple centers.

Methods

SUDI cases during sleep were recruited from autopsy files for the period of 6 years from 2013 to 2018 to obtain a statistically significant number. Inclusion criteria for cases were age not less than 1 week and not more than 12 months, and the collapse occurring during sleep in an unexpected manner. Based on the cause and manner of death, infant deaths were grouped as follows: (1) infants who died of SIDS, (2) infants who died of other natural diseases, (3) infants who died of accidental injuries, (4) infants who died of non-accidental injuries, and (5) infants with unexplained manner of death. [18] The term ‘unexplained’ implies insufficient evidence of the causative disease or event. [9] In this study, we selected cases of groups (1) and (5) and those of suspected accidental suffocation during sleep even though pathological diagnosis with natural disease of group (2).
Postmortem examinations included histology, toxicology, biochemistry, virology, and bacteriology. [19,20] Tests for assessing inherited metabolic disorders were conducted nationwide in the routine examination for newborns. [21] Genetic testing for arrhythmic disorders was also conducted for cases examined in this study. [22] Data used for analysis consisted of DSI information, therapeutic information in emergency care, and maternity passbook. The checklist form, consisting of 41 items, was filled in initially by each center. Then the lists were transferred to one site to confirm unclear issues and aggregate the data.

The forensic pathology sections of the following eight universities participated in this study: Kitasato University School of Medicine, Mie University School of Medicine, Kyoto University Graduate School of Medicine, Hyogo College of Medicine, Kobe University Graduate School of Medicine, Graduate School of Medical Science Kyushu University, Graduate School of Biomedical Sciences Nagasaki University, and Tokai University School of Medicine. The areas of these facilities cover six prefectures without regional bias in the country. Further, the covered area contained approximately 14% of the entire population resides, and this percentage was applied to calculate the annual rate per 1000. Every sudden infant death had been autopsied, but there could have been some deaths that had not received autopsy outside major centers in Japan, whose exact number remained unknown. Although DSI was performed by the police for all cases, not all items were optimal, particularly, for the sleep environment such as sleep surface, wrapping, and clothing. The principal investigator obtained approval for this retrospective study from the Institutional Review Board for Clinical Research, Tokai University. This study was also approved by the respective ethical committees of the faculties as a collaborative study. All data were fully anonymized before the
analyzing investigators accessed them. The study protocol was disclosed to the public at
the website.

The number of 263 cases were originally registered to this project. We checked each
candidate case carefully at a meeting, and selected subjects in which terminal events
remained at speculation irrespective of the diagnosis in the death certificate. Among
them, 4 cases were eliminated from the reasons of not found in sleep environment \(n = 3\) and expected course of terminal heart failure \(n = 1\). The original causes of death \(n = 259\) were SIDS and suspicious SIDS in 94 cases (36%), unexplained in 75 cases
(29%), potential asphyxia in bed in 51 cases (20%), and other natural causes in 39 cases
(15%). Suspected causes of asphyxia were supposed to be due to accidental overlay and
swallowing in bed. Inflammation of the airway, including bronchitis, accounted for 22
cases, comprising the largest group among “others.” Pathological findings do not
always reflect the terminal event. Pathologists tend to favor any apparent
histological findings as the cause of death whether it was fatal or not. Despite of such
histological evidence, the pathologists reconsidered that these cases might also be
regarded as sleep-related SUDI because of co-sleeping, in which coexistent factors may
have served as contributors in causing death.

In forensic pathology, most of infant deaths are SUDI. Since we had a small number
of non-SUDI cases that were suitable for the control, we used national population data
as a substitute for the control cases in a comparison with the present data. The statistical
data of LBs recorded during 2013–2018 in the Japanese population at the National
Institute of Population and Social Security Research (http://www.ipss.go.jp/p-info/)
were used as the control. Prevalence information of regular tobacco consumption was
available at Japan Tobacco Inc. as a questionnaire survey performed in 2016
Logistic regression analyses based on population data were performed to determine the associations of independent variables as estimated using the odds ratio and confidence interval (CI). For significant differences, the $p$ value was calculated using chi-square tests. Statistical analyses were conducted using BellCurve in Excel, ver. 3.20 (Social Survey Research Information Co., Tokyo, Japan).

**Results**

A total of 259 cases were collected at multiple centers for the 6-year period. The circumstances and factors were investigated using the checklist form filled with information at postmortem.

The annual frequency of SUDI during sleep was estimated to approximately 0.31 per 1000 LBs. However, the value could be slightly underestimated because of the possibility that some cases could have been out of management by these facilities.

Table 1 presents the number of subjects according to sex, birth weight, gestation week, maternal age, parity and maternal smoking habit along with the population data. Table 2 summarizes the odds ratios (95% CI) and $p$ values in terms of the related factors.

| Factors                      | No. (%) of No. (%) of LBs* | Approx. annual |
|------------------------------|-----------------------------|----------------|
### SUDI rate per 1000 LBs

| Sex        | Male                | Female              | Total                |
|------------|---------------------|---------------------|----------------------|
|            | 145 (56%)           | 114 (44%)           | 259 (100%)           |
|            | 3,015,822 (51%)     | 2,864,653 (49%)     | 5,880,475 (100%)     |
| Male       | 0.34                | 0.28                | 0.31                 |
| Female     | 23 (21%)            | 85 (79%)            | 108 (100%)           |
| Total      | 304,624 (11%)       | 2,559,683 (89%)     | 2,864,307 (100%)     |
| Birth weight: | < 2,500                | ≥ 2,500            |                      |
| Male       | 21 (15%)            | 116 (85%)           | 137 (100%)           |
| Female     | 21 (15%)            | 116 (85%)           | 137 (100%)           |
| Total      | 21 (15%)            | 116 (85%)           | 137 (100%)           |
| Birth weight: | < 2,500                | ≥ 2,500            |                      |
| Male       | 304,624 (11%)       | 2,762,747 (92%)     | 3,015,245 (100%)     |
| Female     | 23 (21%)            | 85 (79%)            | 108 (100%)           |
| Total      | 304,624 (11%)       | 2,762,747 (92%)     | 3,015,425 (100%)     |

### Gestation week

| Gestation week | < 37 | ≥ 37 | Total |
|----------------|------|------|-------|
| Male           | 31 (13%) | 324,829 (6%) | 324,860 (6%) |
| Female         | 31 (13%) | 324,829 (6%) | 324,860 (6%) |
| Total          | 62 (13%) | 649,658 (12%) | 656,220 (12%) |

### Maternal age at delivery (years)

| Maternal age at delivery (years) | 18-19 | 20-24 | 25-29 | 30-34 | 35-39 | 40-44 | ≥ 45 | Total |
|----------------------------------|------|------|------|------|------|------|------|-------|
| Male                             | 21 (9%) | 63 (26%) | 58 (24%) | 53 (22%) | 43 (17%) | 7 (3%) | 0 | 245 (100%) |
| Female                           | 31 (13%) | 324,829 (6%) | 324,860 (6%) | 324,883 (6%) | 324,960 (6%) | 324,997 (6%) | 0 | 324,997 (6%) |
| Total                            | 52 (13%) | 387,692 (9%) | 387,722 (9%) | 387,836 (9%) | 387,923 (9%) | 387,994 (9%) | 0 | 387,994 (9%) |

### Parity

| Parity | 1 | 2 | 3 | 4 | ≥ 5 | Total |
|--------|---|---|---|---|-----|-------|
| Male   | 77 (31%) | 93 (38%) | 46 (19%) | 20 (8%) | 10 (4%) | 246 (100%) |
| Female | 77 (31%) | 93 (38%) | 46 (19%) | 20 (8%) | 10 (4%) | 246 (100%) |

### Maternal Smoking habit

| Maternal Smoking habit | Non-smoker | 1,983 (89%) | Smoker | 254 (11%) | Total | 2,237 (100%) |
|------------------------|------------|------------|--------|------------|-------|-------------|

*: Japanese population data represent the sum of LBs during 2013 to 2018.

**Table 2 Odds ratios (95% CI) and p values of SUDI cases to population data**

| Factors     | Odds ratio | p value |
|-------------|------------|---------|
| Male        | 1.2 (0.9–1.5) | p = .13 |
| Female (ref. group) | 1.0 |         |

172*: Japanese population data represent the sum of LBs during 2013 to 2018.

173

174 Table 2 Odds ratios (95% CI) and p values of SUDI cases to population data
|                          | Male                      | Female                   |
|--------------------------|---------------------------|--------------------------|
| Birth weight             |                           |                          |
| < 2,500                  | 2.0 (1.3–3.2)             | 2.3 (1.4–3.6)            |
| ≥ 2,500 (ref. group)     | 1.0                       | 1.0                      |
| Gestation week           |                           |                          |
| < 37                     | 2.6 (1.8–3.8)             |                          |
| ≥ 37 (ref. group)        | 1.0                       |                          |
| Maternal age at delivery |                           |                          |
| ≤ 19                     | 11.1 (6.9–17.7)           |                          |
| 20–29                    | 2.1 (1.6–2.8)             |                          |
| 30–39 (ref. group)       | 1.0                       |                          |
| ≥ 40                     | 0.8 (0.4–1.7)             |                          |
| Parity                   |                           |                          |
| ≤ 19                     | 1.0                       |                          |
| 2–3                      | 1.7 (1.3–2.3)             |                          |
| ≥ 40                     | 5.1 (3.4–7.8)             |                          |
| Maternal smoking habit   |                           |                          |
| Non-smoker (ref. group)  | 1.0                       |                          |
| Smoker                   | 4.1 (2.9–5.8)             |                          |

**Age**

Fig 1 shows the age distribution at the time of death. It was observed that deaths most frequently occurred in infants at 1 month of age, consisting of 45 cases (18%). The number was found to decrease with age. Deaths occurring within 6 months after birth accounted for 180 cases (72%).

**Fig 1. Age distribution of SUDI infants during sleep (n = 259) examined in this study.** Key indicates the birth order of infants, in which the column is divided into four groups of the first-born infants (blank), the second- and third-born ones (gray), more than the fourth-born ones (black), and unknown ones (diagonal).
Birth weight and gestation weeks

The mean (± S.D.) birth weight of SUDI infants was 2885 ± 556 g for male subjects (n = 137) and 2763 ± 466 g for female subjects (n = 108). These birth weights were lower by 191 g (6%) and 227 g (8%), respectively, than the national mean birth weights of 3076 g for males and 2990 g for females recorded in 2017. The incidence of low birth weight infants was significantly higher than the control group in both sexes. For low birth weight infants, the odds ratio of over 2.0 was observed in both the male and female groups. Infants of premature birth were found to be 2.6 times more likely to die from SUDI than those of mature birth.

Maternal age and birth order

The odds ratio of incidence of infant death of mothers whose age ≤19 years was the highest at 11.1 compared with mothers aged 30–39 years, and that for mothers aged 20–29 years was 2.1, which showed significant differences. This finding indicated that mothers of a younger age, especially teenage, should be considered as the most important risk factor for the occurrence of SUDI during sleep.

In terms of the birth-order distribution, there were 31% of first-born infants, 38% of second-born infants, 19% of third-born infants, 8% of fourth-born infants, 2% (6 cases) of fifth-born infants, 1% (3 cases) of sixth-born infants, and 0.4% (1 case) of seventh-born infant. The odds ratio to the fatal frequency among the first-born infants clearly indicated that later birth order constituted an important risk factor. Moreover, as shown in Figure 1, there were more first-born infant deaths within 2 months in age (38/92) than those after 3 months (39/154) (p < 0.001).
Time of discovery and sleeping position

Fig 2A shows the distribution of the time of day when an unresponsive infant was found. There were 30 cases (12%) found between 7 and 8 o’clock a.m., which was the most frequent time. A large peak was evident between 6 and 9 o’clock in the morning.

Fig 2B depicts that the duration between the last time the infant was found alive and the time of discovery of being unresponsive \((n = 222)\), which varied widely from approximately 10 min to 13 h. The mean duration was \(4.1\pm2.7\) h. The collapse was discovered within 6 h in the majority of cases \((n = 184, 83\%)\).

Table 3 presents the child sleeping position when the collapse was discovered. The prone position in late SUDI infants accounted for 40% of cases, and there were 19% of cases with the prone position even in 0 to 2-month-old subjects who cannot roll over.
| Position | Total (0–11 month) | 0–2 month |
|----------|--------------------|-----------|
| Supine   | 117 (52%)          | 60 (72%)  |
| Prone    | 89 (40%)           | 16 (19%)  |
| Side     | 16 (7%)            | 7 (9%)    |
| Others   | 2 (1%)             | 0         |
| Total    | 224 (100%)         | 83 (100%) |

**Maternal smoking habit**

The descriptions in the maternity passbook entries are considered to reflect the smoking habits before and during the early phase of pregnancy. We attempted to obtain the smoking rate of the mothers of SUDI cases. A significant risk of SUDI was evident with an odds ratio of 4.5 compared with the general rate. Although there were limited cases wherein the information related to the number of cigarettes \( n = 30 \) was available, the mean number was 11 cigarettes/day.

**Discussion**

Since we had a small number of control cases that were suitable for a case-control study, the national population data was used as a substitute for the reference. In addition, there was a limitation that data were not fully available for each item because of the retrospective approach. The analysis might be accompanied by potential imprecision, however the high odd ratios were evident in low birth weight, premature birth, teenage mothers, later birth order infants and maternal smoking habit.
These results of the present investigation of sleep-related SUDI cases were consistent with risk factors such as the smoking habit of parents in the large epidemiological surveys of SIDS. [23] However, some differences were evident. The peak age of death is generally 2 months in SIDS surveys, [4,24] but that among the present SUDI infants was 1 month of age. We thought that the difference should be caused by that a particularly higher risk was evident among teenage mothers than that found in an earlier study [25], and that more first-born infants were dead during 0–2 months of age.

The most frequent birth order associated with infant death due to SUDI during sleep was the second birth order. Blair et al. [26] reported that SIDS was most frequent among first-born children in the UK, although it was earlier presumed to be frequent in large families. Data from Taiwan indicate that the first-, second-, and third- and later born children account for 36%, 40%, and 24% of SIDS, respectively. [27] The distribution in the present study was more similar to that reported in Taiwan.

Traditional bedding of cotton mat, known as futon, on the floor is common in Japan. Therefore, it is more appropriate to use the term co-sleeping (sharing a sleeping surface) than bed-sharing. Such co-sleeping is a common style of sleep. Tokutake et al. [17] reported that 84% of mothers practice co-sleeping, of whom half also practice breastfeeding. The father was found to be the first responder in up to 20% of cases, and in most of these cases the father also co-slept and discovered the infant death upon awakening. The risk of SIDS among infants who co-sleep was found to be significantly high in several earlier studies. [28,29] Nevertheless, the effects of co-sleeping on the occurrence of SUDI, if any, could not be evaluated in this study because of a variety of co-sleeping styles and the absence of good control subjects.

It is a traditional practice in Japan to lay infants in the supine position. However,
40% of infants were found in the prone position, of which frequency was higher than that reported in an earlier study. [17] Li et al. [30] reported that 60% of SIDS infants were found in the prone position in the United States. It is possible that turning over by infants during sleep is a causal factor. However, approximately 28% of 0 to 2-month-old infants who were unable to turn over were found in the prone and side positions. They might have been placed in the prone position or been breastfed during co-sleeping, but the original position was not recorded sufficiently at DSI.

A striking finding was the prolonged time to discovery. In nine cases, it spent more than 10 hours to find the unreactive infants. No apparent infanticide was involved in all subjects, however neglect by parents was suspected in a couple of cases from circumstances at DSI. We think that the time difference should be an important indicator to suspect careless infant rearing.

A relationship between the occurrence of SIDS and the smoking habit of parents has been found in Japan. [31] In the present investigation, the incidence of pregnant mother’s smoking among SUDI cases was 34%. This incidence in the general female population was reported as 11%, which also resulted in the high odds ratio of 4.5 in this study. According to Anderson et al., [32] the incidence of SUDI more than doubles when a parent is smoking during the period of pregnancy. The odds ratio increases along with the number of cigarettes up to 20. It is evident that infants co-sleeping with someone who smokes exhibit the highest risk for SUDI. [33]

Pasquale-Styles et al. [34] reported that asphyxia and suffocation occur more than presumed in many situations such as bed-sharing, overlay, wedging, prone position, obstruction of the nose and mouth, and coverage of the head. Postmortem findings alone are not generally sufficient to explain the cause of these deaths. Consequently, the
diagnoses often lack consistency. [3,4,7] To avoid preventable any types of SUDI, including SIDS, such various causes of accidental suffocation, and unexplained causes, it is important to identify high risk factors from the study based on the wide variety of cases. [17] In addition, there exists a difficulty of the current situation in Japan, particularly in DSI that is performed by police officers who are not well trained. Garstang et al. [24] indicated that police-led DSI does not comply with practical information. After a new law related to child health was enacted in 2018, child death reviews will be introduced to the society in the near future. These reviews in combination with multiple agencies will be helpful in investigating the sleeping environments of infants in detail.

In conclusion, we conducted an effective epidemiological analysis of sleep-related SUDI using the checklist form. This approach has revealed the present critical features prevailing in the country. This report displayed the latest trends of SUDI in Japan.

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References

1. Krous HF, Beckwith JB, Byard RW, Rognum TO, Bajanowski T, Corey T, et al. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. Pediatrics. 2004;114:234-238.

2. Malloy MH, MacDorman M. Changes in the classification of sudden unexpected infant deaths: United States, 1992-2001. Pediatrics. 2005;115:1247-1253.

3. Camperlengo LT, Shapiro-Mendoza CK, Kim SY. Sudden infant death syndrome: diagnostic practices and investigative policies, 2004. Am J Forensic Med Pathol. 2012;33:197-201.

4. Moon RY. Task Force on Sudden Infant Death Syndrome. SIDS and other sleep related infant deaths: expansion of recommendations for a safe infant sleeping environment. Pediatrics. 2011;128:1030-1039.

5. Fleming PJ, Blair PS, Pease A. Sudden unexpected death in infancy: aetiology, pathophysiology, epidemiology and prevention in 2015. Arch Dis Child. 2015;100:984-988.

6. Matthews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. Natl Vital Stat Rep. 2015;64:1-30.

7. Taylor BJ, Garstang J, Engelberts A, Obonai T, Cote A, Freemantle J, et al. International comparison of sudden unexpected death in infancy rates using a newly proposed set of cause-of-death codes. Arch Dis Child. 2015;100:1018-1023.

8. Goldstein RD, Blair PS, Sens MA, Shapiro-Mendoza CK, Krous HF, Rognum TO, et al. Inconsistent classification of unexplained sudden deaths in infants and children hinders surveillance, prevention and research: recommendations from the 3rd International Congress on Sudden Infant and Child Death. Forensic Sci Med
Shapiro-Mendoza CK, Camperlengo L, Ludvigsen R, Cottengim C, Anderson RN, Andrew T, et al. Classification system for the Sudden Unexpected Infant Death Case Registry and its application. Pediatrics. 2014;134:e210-9.

Corey TS, Hanzlick R, Howard J, Nelson C, Krous H. A functional approach to sudden unexplained infant deaths. Am J Forensic Med Pathol. 2007;28:271-277.

Bennett T, Martin LJ, Heathfield LJ. Global trends in the extent of death scene investigation performed for sudden and unexpected death of infant (SUDI) cases: A systematic review. Forensic Sci Int. 2019;301:435-444.

Centers for Disease Control and Prevention. Sudden Unexplained Infant Death Investigation Reporting Form 2007. www.cdc.gov/sids/pdf/suidiform2-1-2010.pdf. Accessed 1 Nov 2019.

Guideline for SIDS diagnosis, ver. 2. Ministry of Health, Labour and Welfare, Japan. (in Japanese), 2012. http://www.mhlw.go.jp/bunya/kodomo/sids_guideline.html of subordinate document. Accessed 2 Nov 2019.

Erck Lambert AB, Parks SE, Camperlengo L, Cottengim C, Anderson RL, Covington TM, et al. Death scene investigation and autopsy practices in sudden unexpected infant deaths. J Pediatr. 2016;174:84-90.

Osawa M, Nagao R, Kakimoto Y, Kakiuchi Y, Satoh F. Sudden infant death after vaccination: Survey of forensic autopsy files. Am J Forensic Med Pathol. 2019;40:232-237.

Takatsu A, Shigeta A, Sakai K, Abe S. Risk factors, diagnosis and prevention of sudden unexpected infant death. Leg Med. 2007;9:76-82.
17. Tokutake C, Haga A, Sakaguchi K, Samejima A, Yoneyama M, Yokokawa Y, et al. Infant suffocation incidents related to co-sleeping or breastfeeding in the side-lying position in Japan. Tohoku J Exp Med. 2018; 246:121-130.

18. Matthews T, McDonnell M, McGarvey C, Loftus G, O'Regan M. A multivariate "time based" analysis of SIDS risk factors. Arch Dis Child. 2004;89:267-271.

19. Howatson AG. The autopsy for sudden unexpected death in infancy. Curr Diagn Pathol. 2006;12:173-183.

20. Kakimoto Y, Seto Y, Ochiai E, Satoh F, Osawa M. Cytokine elevation in sudden death with respiratory syncytial virus: A Case Report of 2 Children. Pediatrics. 2016;138:e20161293.

21. Yamamoto T, Mishima H, Mizukami H, Fukahori Y, Umehara T, Murase T, et al. Metabolic autopsy with next generation sequencing in sudden unexpected death in infancy: Postmortem diagnosis of fatty acid oxidation disorders. Mol Genet Metab Rep. 2015;5:26-32.

22. Osawa M, Inaoka Y, Ochiai E, Hasegawa I, Satoh F. Variable single C repetitive tract in KCNQ1: Postmortem molecular testing in a sudden and unexpected death. Exp Clin Cardiol. 2014;20:927-930.

23. Moon RY, Hauck FR. Risk Factors and Theories In: Duncan JR, Byard RW, editors. SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future. Adelaide (AU): University of Adelaide Press; 2018.

24. Garstang J, Ellis C, Sidebotham P. An evidence-based guide to the investigation of sudden unexpected death in infancy. Forensic Sci Med Pathol. 2015;11:345-357.

25. Colson ER, Willinger M, Rybin D, Heeren T, Smith LA, Lister G, et al. Trends and factors associated with infant bed sharing, 1993-2010: the National Infant Sleep
26. Blair PS, Sidebotham P, Berry PJ, Evans M, Fleming PJ. Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the UK. *Lancet*. 2006;367:314-319.

27. Chang HP, Li CY, Chang YH, Hwang SL, Su YH, Chen CW. Sociodemographic and meteorological correlates of sudden infant death in Taiwan. *Pediatr Int*. 2013;55:11-16.

28. Hauck FR, Herman SM, Donovan M, Iyasu S, Merrick Moore C, Donoghue E, et al. Sleep environment and the risk of sudden infant death syndrome in an urban population: the Chicago Infant Mortality Study. *Pediatrics*. 2003;111:1207-1214.

29. Blair PS, Sidebotham P, Pease A, Fleming PJ. Bed-sharing in the absence of hazardous circumstances: is there a risk of sudden infant death syndrome? An analysis from two case-control studies conducted in the UK. *PLoS One*. 2014;9:e107799.

30. Li L, Fowler D, Liu L, Ripple MG, Lambros Z, Smialek JE. Investigation of sudden infant deaths in the State of Maryland (1990-2000). *Forensic Sci Int*. 2005;148:85-92.

31. Tanaka T, Kato N. Evaluation of child care practice factors that affect the occurrence of sudden infant death syndrome: Interview conducted by public health nurses. *Environ Health Prev Med*. 2001;6:117-120.

32. Anderson TM, Lavista Ferres JM, Ren SY, Moon RY, Goldstein RD, Ramirez JM, et al. Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. *Pediatrics*. 2019;143:e20183325.

33. James C, Klenka H, Manning D. Sudden infant death syndrome: bed sharing with
mothers who smoke. Arch Dis Child. 2003;88:112-113.

34. Pasquale-Styles MA, Tackitt PL, Schmidt CJ. Infant death scene investigation and the assessment of potential risk factors for asphyxia: a review of 209 sudden unexpected infant deaths. J Forensic Sci. 2007;52:924-929.
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Circumstances and factors of sleep-related sudden infancy deaths in Japan

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Abstract

Background: Sudden unexpected death in infancy (SUDI) comprises both natural and unnatural causes of death. However, a few epidemiological surveys have investigated SUDI in Japan.

Objective: This retrospective study was conducted to investigate the recent trends of circumstances and risk factors of sleep-related SUDI cases.

Methods: Forensic pathology sections from eight universities participated in the selection of subjects from 2013 to 2018. Data obtained from the checklist form were analyzed based on information at postmortem.

Results: There were 259 SUDI cases consisting of 145 male infants and 114 female infants with a mean birth weight of 2888 ± 553 and 2750 ± 370 g, respectively. Deaths most frequently occurred among infants at 1 month of age (18%). According to population-based analyses, the odds ratio (95% confidence interval) of mother’s age ≤19 years was 11.1 (6.9–17.7) compared with ages 30–39. The odds ratio for the fourth- and later born infants was 5.2 (3.4–7.9) compared with the frequency of first-born infants. The most frequent time of day for discovery was between 7 and 8 o’clock. Co-sleeping was recorded for 61%, and the prone position was found for 40% of cases at discovery. Mother’s smoking habit exhibited an odds ratio of 4.5 (2.9–5.8).

Conclusion: This study confirmed the trends that have been observed for sudden infant death syndrome; particularly, very high odds ratios were evident for teenage mothers and later birth order in comparison with those in other developed countries. The child of a young mother tended to die within 2 months of age. To our knowledge, this is the first report of an extensive survey of sleep-related SUDI in Japan.
Introduction

Sudden infant death syndrome (SIDS) is the possible cause-of-death for sudden infant death during sleep, in which all known identifiable conditions that might engender sudden and unexpected death must be excluded by postmortem examinations. However, several pathologists have changed their diagnostic preferences since 2004 primarily because of the difficult distinction of SIDS from accidental asphyxia or natural diseases such as arrhythmias and metabolic disorders. [1-3] Reluctance to use the term has decreased the number globally over the years. [4-6] In Japan, around 1,000 cases of SIDS were recorded in the 1990s, but recent diagnostic numbers have decreased to fewer than 100 cases per year. [7]

Currently, another broad term has become popular, i.e., sudden unexpected death in infancy (SUDI) or sudden unexpected infant death (SUID). Although SUDI/SUID originally has been used as an umbrella term for the initial presentation of explained or unexplained infant deaths, it is interpreted to include several categories such as SIDS (R95), ill-defined and unknown cause of mortality (R99), and accidental suffocation or strangulation in bed (W75). [8] Several attempts have been made to categorize SUDI/SUID, but the terminology and classification have not yet been defined clearly. [9]

In recent years, a protocol of investigation items has been officially standardized. [10,11] For instance, in the U.S., the Centers for Disease Control and Prevention published guidelines and a reporting form, which is designated as the SUID Investigation Reporting Form. [12] In Japan, a list of items to be investigated is used as a checklist form in cases of infant death. [13] A system is in operation for clinicians and pathologists to ascertain circumstances and to investigate background factors.
Information from death scene investigation (DSI) acquired by experts is indispensable to fill out the form. [14] Furthermore, the maternity passbook, which records information about the mother and the child during pregnancy as well as after childbirth, is beneficial. We previously analyzed forensic autopsy cases of sudden infant deaths after vaccination using this passbook. [15]

While the childcare environment differs according to region and time, there are few epidemiological data describing infant deaths during sleep in Japan. [16,17] This population-based retrospective study was conducted to investigate the recent trends of sleep-related SUDI using the checklist form at multiple centers.

Methods

Deaths of sleep-related SUDI cases were extracted from autopsy files for the period of 6 years from 2013 to 2018. Inclusion criteria for cases were age not more than 12 months and the collapse occurring during sleep in an unexpected manner. Based on the cause and manner of death, infant deaths were grouped as follows: (1) infants who died of SIDS, (2) infants who died of other natural diseases, (3) infants who died of accidental injuries, (4) infants who died of non-accidental injuries, and (5) infants with unexplained manner of death. [18] The term ‘unexplained’ implies insufficient evidence of the causative disease or event. [9] In this study, we selected cases of groups (1) and (5) and those of suspected accidental suffocation during sleep.

Postmortem examinations included histology, toxicology, biochemistry, virology, and bacteriology. [19,20] Tests for assessing inherited metabolic disorders were conducted nationwide in the routine examination for newborns. [21] Genetic testing for
arrhythmic disorders was also conducted for cases examined in this study. [22] Data used for analysis consisted of DSI information, therapeutic information in emergency care, and maternity passbook. The checklist form, consisting of 41 items, was filled in initially by each center. Then the lists were transferred to one site to confirm unclear issues and aggregate the data.

The forensic pathology sections of the following eight universities participated in this study: Kitasato University School of Medicine, Mie University School of Medicine, Kyoto University Graduate School of Medicine, Hyogo College of Medicine, Kobe University Graduate School of Medicine, Graduate School of Medical Science Kyushu University, Graduate School of Biomedical Sciences Nagasaki University, and Tokai University School of Medicine. The areas of these facilities cover six prefectures in which approximately 14% of the entire population resides, and this percentage was applied to calculate the annual rate per 1000. Every sudden infant death had been autopsied, but there could have been some deaths that had not received autopsy outside major centers in Japan, whose exact number remained unknown. Although DSI was performed by the police for all cases, not all items were optimal, particularly, for the sleep environment such as sleep surface, wrapping, and clothing. The principal investigator obtained approval for this retrospective study from the Institutional Review Board for Clinical Research, Tokai University. This study was also approved by the respective ethical committees of the faculties as a collaborative study.

The original causes of death (n = 259) were SIDS and suspicious SIDS in 94 cases (36%), unexplained in 75 cases (29%), potential asphyxia in bed in 51 cases (20%), and other causes in 39 cases (15%). We investigated each candidate case carefully at a meeting, and selected subjects in which terminal events remained at speculation irrespective of the diagnosis in the death certificate. Among them, 4 cases were eliminated from the reasons of not found in sleep environment (n = 3) and expected course of terminal heart failure (n = 1). The …
irrespective of the diagnosis in the death certificate. Suspected causes of asphyxia were supposed to be due to accidental overlay and swallowing in bed. Inflammation of the airway, including bronchitis, accounted for 22 cases, comprising the largest group among “others.” Despite such histological evidence, the pathologists reconsidered that these cases might also be regarded as sleep-related SUDI because of co-sleeping, in which coexistent factors may have served as contributors in causing death.

The statistical data of live births recorded during 2013–2018 in the Japanese population at the National Institute of Population and Social Security Research (http://www.ipss.go.jp/p-info/) were used as the control. Prevalence information of regular tobacco consumption was available at Japan Tobacco Inc. as a questionnaire survey performed in 2016 (https://www.jti.co.jp/investors/press_releases/2016/0728_01.html). The numbers of smokers and nonsmokers in the 20s and 30s of female volunteers were used for the control.

Logistic regression analyses based on population data were performed to determine the associations of independent variables as estimated using the odds ratio and confidence interval (CI). For significant differences, the p value was calculated using chi-square tests. Statistical analyses were conducted using BellCurve in Excel, ver. 3.20 (Social Survey Research Information Co., Tokyo, Japan).

Results

A total of 259 cases were collected at multiple centers for the 6-year period. The circumstances and factors were investigated using the checklist form filled with
information at postmortem.

The annual frequency of sleep-related SUDI was estimated to approximately 0.3 per 1000 births. However, the value could be slightly underestimated because of the possibility that some cases could have been out of management by these facilities.

Table 1 presents the number of subjects according to sex, birth weight, gestation week, maternal age, parity and maternal smoking habit along with the population data.

Table 2 summarizes the odds ratios (95% CI) and p values in terms of the related factors.

The factors were also analyzed for two groups, i.e., the early group in which death occurred within 2 months of age (n = 98) and the late group in which death occurred after 3 months (n = 161).

### Table 1: Number of infants of SUID subjects and live births

| Factors          | No. of SUID | No. of live births | Approx. annual rate per 1000 | No. of early/late |
|------------------|-------------|--------------------|------------------------------|-------------------|
| **Sex**          |             |                    |                              |                   |
| Male             | 145 (56%)   | 53/92              | 3,015,822                    | 0.34              |
| Female           | 114 (44%)   | 45/69              | 2,864,653                    | 0.28              |
| Total            | 259 (100%)  | 98/141             | 5,880,475                    | 0.31              |
| **Birth weight** |             |                    |                              |                   |
| Male < 2,500     | 21 (15%)    | 3/48               | 252,678                      | 0.59              |
| Male ≥ 2,500     | 116 (85%)   | 18/68              | 2,762,747                    | 0.30              |
| Total            | 137 (100%)  | 21/146             | 3,015,425                    | 0.32              |
| Female < 2,500   | 23 (21%)    | 9/14               | 304,624                      | 0.54              |
| Female ≥ 2,500   | 85 (79%)    | 36/49              | 2,559,683                    | 0.24              |
| Total            | 108 (100%)  | 45/63              | 2,864,307                    | 0.27              |
| **Gestation week** |         |                    |                              |                   |
| < 37             | 31 (13%)    | 8/23               | 324,829                      | 0.68              |
| ≥ 37             | 203 (87%)   | 84/119             | 5,546,995                    | 0.26              |
### Table 2

| Factors                               | Total (0–11 month) | Early (0–2 month) | Late (3–11 month) |
|---------------------------------------|--------------------|-------------------|-------------------|
| **Sex**                               |                    |                   |                   |
| Male                                  | 1.2 (0.9–1.5), p = 0.13 | 1.1 (0.8–1.7), p = 0.58 | 1.3 (0.9–1.7), p = 0.14 |
| Female (ref. group)                   | 1.0                | 1.0               | 1.0               |
| **Birth weight**                      |                    |                   |                   |
| Male < 2,500                           | 2.0 (1.3–3.2), p = 0.003 | 0.7 (0.2–2.2), p = 0.52 | 2.9 (1.7–4.9), p < 0.001 |
| Male ≥ 2,500 (ref. group)             | 1.0                | 1.0               | 1.0               |
| Female < 2,500                         | 2.3 (1.4–3.6), p < 0.001 | 2.1 (1.0–4.1), p = 0.042 | 2.4 (1.3–4.3), p = 0.003 |

*: Japanese population data represent the sum of live births during 2013 to 2018.

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### Maternal age at delivery (years)

| Age group | Count (%) | Live births | Live births (%) |
|-----------|-----------|-------------|-----------------|
| ≤ 19      | 21 (9%)   | 12/9        | 2.22            |
| 20-24     | 63 (26%)  | 18/45       | 0.90            |
| 25-29     | 58 (24%)  | 26/42       | 0.27            |
| 30-34     | 53 (22%)  | 46/48       | 0.18            |
| 35-39     | 43 (17%)  | 19/24       | 0.23            |
| 40-44     | 7 (3%)    | 3/4         | 0.16            |
| ≥ 45      | 0         | 8,268       |                 |

### Parity

| Parity | Count (%) | Live births | Live births (%) |
|--------|-----------|-------------|-----------------|
| 1      | 77 (31%)  | 38/39       | 0.20            |
| 2      | 93 (38%)  | 26/67       | 0.31            |
| 3      | 46 (19%)  | 20/26       | 0.43            |
| 4      | 20 (8%)   | 5/4        | 0.91            |
| ≥ 5    | 10 (4%)   | 4/6         | 1.41            |

### Maternal Smoking habit

| Smoking habit | Count (%) | Live births | Live births (%) |
|---------------|-----------|-------------|-----------------|
| Non-smoker    | 106 (66%) | 44/62       | 1.98            |
| Smoker        | 55 (34%)  | 14/41       |                 |

### Total

| Total (100%) | Live births | Live births (%) |
|--------------|-------------|-----------------|
| 234 (100%)   | 92/142      | 5,871,824       |
| 5,22         | 0.28        |
| 245 (100%)   | 93/152      | 5,880,468       |
| 5,23         | 0.30        |

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Age

Fig 1 shows the age distribution at the time of death. It was observed that deaths most frequently occurred in infants at 1 month of age, consisting of 45 cases (18%). The number was found to decrease with age. Deaths occurring within 6 months after birth accounted for 180 cases (72%).

Fig 1. Age distribution of sleep-related SUDI infants (n = 259) examined in this study. Key indicates the birth order of infants, in which the column is divided into four groups of the first-born infants (blank), the second- and third-born ones (gray), more than the fourth-born ones (black), and unknown ones (diagonal).

Birth weight and gestation weeks

| Gestation week | Birth weight (g) | p-value 1 | p-value 2 |
|----------------|------------------|-----------|-----------|
| ≥ 2,500 (ref. group) | 1.0 | 1.0 |
| < 37 (1.8–3.8), p < 0.001 | 1.6 (0.8–3.4), p = 0.18 | 3.3 (2.1–5.2), p < 0.001 |
| ≥ 37 (ref. group) | 1.0 |

| Maternal age at delivery (years) | Birth weight (g) | p-value 1 | p-value 2 |
|---------------------------------|------------------|-----------|-----------|
| ≤ 19 (6.9–17.7), p < 0.001 | 11.1 (6.9–17.7), p < 0.001 | 7.4 (3.7–14.9), p < 0.001 |
| 20–29 (1.6–2.8), p < 0.001 | 2.1 (1.4–3.5), p < 0.001 | 2.1 (1.5–2.9), p < 0.001 |
| 30–39 (ref. group) | 1.0 | 1.0 |
| ≥ 40 (0.4–1.7), p = 0.56 | 0.8 (0.4–1.7), p = 0.96 | 0.7 (0.3–2.0), p = 0.51 |

| Parity | Birth weight (g) | p-value 1 | p-value 2 |
|--------|------------------|-----------|-----------|
| 1 (ref. group) | 1.0 | 1.0 | 1.0 |
| 2–3 | 1.7 (1.3–2.3), p < 0.001 | 2.1 (1.5–2.9), p < 0.001 |
| ≥ 4 | 3.1 (3.4–7.8), p < 0.001 | 2.5 (3.4–7.8), p = 0.001 |

| Maternal smoking habit | Birth weight (g) | p-value 1 | p-value 2 |
|------------------------|------------------|-----------|-----------|
| Non-smoker (ref. group) | 1.0 | 1.0 | 1.0 |
| Smoker | 4.1 (2.9–5.8), p < 0.001 | 4.7 (3.7–6.1), p < 0.001 |

Commented [大澤 資樹]: SUDI infants during sleep.
The mean (± S.D.) birth weight of SUDI infants was 2885 ± 556 g for male subjects and 2763 ± 466 g for female subjects. These birth weights were lower by 191 g (6%) and 227 g (8%), respectively, than the national mean birth weights of 3076 g for males and 2990 g for females recorded in 2017. The percentage of low birth weight infants was significantly higher than the control group in both sexes. For low birth weight infants, the highest odds ratio of 2.9 was observed in the late male group.

Infants of premature birth were found to be 2.6 times more likely to die from SUDI than those of mature birth. The late group also showed higher odds ratio than the early group.

Maternal age and birth order

The odds ratio of incidence of infant death of mothers whose age ≤19 years was the highest at 11.1 compared with mothers aged 30–39 years, and that for mothers aged 20–29 years was 2.1, which showed significant differences. Furthermore, the child of a teenage mother tended to die within 2 months of age, compared with other generations (12/21 to 81/225, p = 0.04). This finding indicated that mothers of a younger age, especially teenage, should be considered as the most important risk factor for the occurrence of sleep-related SUDI during sleep.

In terms of the birth-order distribution, there were 31% of first-born infants, 38% of second-born infants, 19% of third-born infants, 8% of fourth-born infants, 2% (6 cases) of fifth-born infants, 1% (3 cases) of sixth-born infants, and 0.4% (1 case) of seventh-born infant. The odds ratio to the fatal frequency among the first-born infants clearly indicated that later birth order constituted an important risk factor. Moreover, as shown in Figure 1, there were more first-born infants in the early group (38/92) than in the late group.
the late group (39/154) \((p < 0.001)\).

Time of discovery and sleeping position

Fig 2A shows the distribution of the time of day when an unresponsive infant was found. There were 30 cases (12%) found between 7 and 8 o’clock a.m., which was the most frequent time. A large peak was evident between 6 and 9 o’clock in the morning.

Fig 2B depicts that the duration between the last time the infant was found alive and the time of discovery of being unresponsive \((n = 222)\), which varied widely from approximately 10 min to 13 h. The mean duration was 4.1±2.7 h. The collapse was discovered within 6 h in the majority of cases \((n = 184, 83\%)\).

The first responder \((n = 252)\), who discovered the unresponsive infant, was the mother in 188 cases (75%), followed by the father in 49 cases (19%), a grandmother in 8 cases (3%), a childminder in 2 cases (1%), and others in 6 cases (2%).

Co-sleeping was recorded for 143 cases (61%) among a total of 230 available cases.

Table 3 presents the child sleeping position when the collapse was discovered. The prone position in late SUDI infants accounted for 40% of cases, and there were 19% of cases with the prone position in the early group.

Table 3 Sleep position at the scene

Commented [大澤 資樹46]: infant deaths within 2 months in age (38/92) than those after 3 months (39/154)

Commented [大澤 資樹47]: even in 0 to 2-month-old subjects who cannot roll over
Maternal smoking habit

The descriptions in the maternity passbook entries are considered to reflect the smoking habits before and during the early phase of pregnancy. We attempted to obtain the smoking rate of the mothers of SUDI cases. A significant risk of SUDI was evident with an odds ratio of 4.5 compared with the general rate. Although there were limited cases wherein the information related to the number of cigarettes \( n = 30 \) was available, the mean number was 11 cigarettes/day.

Discussion

Results of the present investigation of sleep-related SUDI cases were consistent with risk factors such as the smoking habit of parents in the large epidemiological surveys of SIDS. [23] However, some differences were evident. The peak age of death is generally 2 months in SIDS surveys, [4,24] but that among the present SUDI infants was 1 month of age. A particularly higher risk was observed among teenage mothers than that found in an earlier study. [25] Moreover, the mothers tended to lose their infants at age 0–2
The most frequent birth order associated with infant death due to sleep-related SUDI was the second birth order. Blair et al. [26] reported that SIDS was most frequent among first-born children in the UK, although it was earlier presumed to be frequent in large families. Data from Taiwan indicate that the first-, second-, and third- and later born children account for 36%, 40%, and 24% of SIDS, respectively. [27] The distribution in the present study was more similar to that reported in Taiwan.

Traditional bedding of cotton mat, known as futon, on the floor is common in Japan. Therefore, it is more appropriate to use the term co-sleeping (sharing a sleeping surface) than bed-sharing. Co-sleeping is a common style of sleep. [17] reported that 84% of mothers practice co-sleeping, of whom half also practice breastfeeding. The father was found to be the first responder in up to 20% of cases, and in most of these cases the father also co-slept and discovered the infant death upon awakening. The risk of SIDS among infants who co-sleep was found to be significantly high in several earlier studies. [28,29] Nevertheless, the effects of co-sleeping on the occurrence of SUDI, if any, could not be evaluated in this study because of the absence of good control subjects.

It is a traditional practice in Japan to lay infants in the supine position. However, 40% of infants were found in the prone position, of which frequency was higher than that reported in an earlier study. [17] Li et al. [30] reported that 60% of SIDS infants were found in the prone position in the United States. It is possible that turning over by infants during sleep is a causal factor. However, approximately 28% of infants in the early group who were unable to turn over were found in the prone and side positions. They might have been placed in the prone position or been breastfed during co-sleeping.
but the original position was not recorded sufficiently at DSI.

A relationship between the occurrence of SIDS and the smoking habit of parents has been found in Japan. [31] In the present investigation, the incidence of pregnant mother’s smoking among SUDI cases was 34%. This incidence in the general female population was reported as 11%, which also resulted in the high odds ratio of 4.5 in this study. According to Anderson et al., [32] the incidence of SUDI more than doubles when a parent is smoking during the period of pregnancy. The odds ratio increases along with the number of cigarettes up to 20. It is evident that infants co-sleeping with someone who smokes exhibit the highest risk for SUID.[33]

Pasquale-Styles et al. [34] reported that asphyxia and suffocation occur more than presumed in many situations such as bed-sharing, overlay, wedging, prone position, obstruction of the nose and mouth, and coverage of the head. Postmortem findings alone are not generally sufficient to explain the cause of these deaths. Consequently, the diagnoses often lack consistency. [3,4,7] In addition, there exists a difficulty of the current situation in Japan, particularly in DSI that is performed by police officers who are not well trained. Garstang et al. [24] indicated that police-led DSI does not comply with practical information. After a new law related to child health was enacted in 2018, child death reviews will be introduced to the society in the near future. These reviews in combination with multiple agencies will be helpful in investigating the sleeping environments of infants in detail.

In conclusion, we conducted an effective epidemiological analysis of sleep-related SUDI using the official checklist form. This approach has revealed the present critical features prevailing in the country. This report is the first of an extensive study of SUDI in Japan.

Commented: A striking finding was the prolonged time to discovery. In nine cases, it spent more than 10 hours to find the unreactive infants. No apparent infanticide was involved in all subjects, however neglect by parents was suspected in a couple of cases from circumstances at DSI. We think that the time difference should be an important indicator to suspect careless infant rearing.

Commented: SUDI

Commented: To avoid preventable any types of SUDI, including SIDS, such various causes of accidental suffocation, and unexplained causes, it is important to identify high risk factors from the study based on the wide variety of cases. [17] In addition, ...

Commented: deleted

Commented: displayed the latest trends
Acknowledgements

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References

1. Krous HF, Beckwith JB, Byard RW, Rognum TO, Bajanowski T, Corey T, et al. Sudden infant death syndrome and unclassified sudden infant deaths: a definitional and diagnostic approach. Pediatrics. 2004;114:234-238.

2. Malloy MH, MacDorman M. Changes in the classification of sudden unexpected infant deaths: United States, 1992-2001. Pediatrics. 2005;115:1247-1253.

3. Camperlengo LT, Shapiro-Mendoza CK, Kim SY. Sudden infant death syndrome: diagnostic practices and investigative policies. 2004. Am J Forensic Med Pathol. 2012;33:197-201.

4. Moon RY. Task Force on Sudden Infant Death Syndrome. SIDS and other sleep related infant deaths: expansion of recommendations for a safe infant sleeping environment. Pediatrics. 2011;128:1030-1039.

5. Fleming PJ, Blair PS, Pease A. Sudden unexpected death in infancy: aetiology, pathophysiology, epidemiology and prevention in 2015. Arch Dis Child. 2015;100:984-988.

6. Matthews TJ, MacDorman MF, Thoma ME. Infant mortality statistics from the 2013 period linked birth/infant death data set. Natl Vital Stat Rep. 2015;64:1-30.

7. Taylor BJ, Garstang J, Engelberts A, Obonai T, Cote A, Freemantle J, et al. International comparison of sudden unexpected death in infancy rates using a newly proposed set of cause-of-death codes. Arch Dis Child. 2015;100:1018-1023.

8. Goldstein RD, Blair PS, Sens MA, Shapiro-Mendoza CK, Krous HF, Rognum TO, et al. Inconsistent classification of unexplained sudden deaths in infants and children hinders surveillance, prevention and research: recommendations from the 3rd International Congress on Sudden Infant and Child Death. Forensic Sci Med
9. Shapiro-Mendoza CK, Camperlengo L, Ludvigsen R, Cottengim C, Anderson RN, Andrew T, et al. Classification system for the Sudden Unexpected Infant Death Case Registry and its application. Pediatrics. 2014;134:e210-9.

10. Corey TS, Hanzlick R, Howard J, Nelson C, Krous H. A functional approach to sudden unexplained infant deaths. Am J Forensic Med Pathol. 2007;28:271-277.

11. Bennett T, Martin LJ, Heathfield LJ. Global trends in the extent of death scene investigation performed for sudden and unexpected death of infant (SUDI) cases: A systematic review. Forensic Sci Int. 2019;301:435-444.

12. Centers for Disease Control and Prevention. Sudden Unexplained Infant Death Investigation Reporting Form 2007. www.cdc.gov/sids/pdf/suidiform2-1-2010.pdf. Accessed 1 Nov 2019.

13. Guideline for SIDS diagnosis, ver. 2. Ministry of Health, Labour and Welfare, Japan. (in Japanese), 2012. http://www.mhlw.go.jp/bunya/kodomo/sids_guideline.html of subordinate document. Accessed 2 Nov 2019.

14. Erck Lambert AB, Parks SE, Camperlengo L, Cottengim C, Anderson RL, Covington TM, et al. Death scene investigation and autopsy practices in sudden unexpected infant deaths. J Pediatr. 2016;174:84-90.

15. Osawa M, Nagao R, Kakimoto Y, Kakiuchi Y, Satoh F. Sudden infant death after vaccination: Survey of forensic autopsy files. Am J Forensic Med Pathol. 2019;40:232-237.

16. Takatsu A, Shigeta A, Sakai K, Abe S. Risk factors, diagnosis and prevention of sudden unexpected infant death. Leg Med. 2007;9:76-82.
17. Tokutake C, Haga A, Sakaguchi K, Samejima A, Yoneyama M, Yokokawa Y, et al. Infant suffocation incidents related to co-sleeping or breastfeeding in the side-lying position in Japan. Tohoku J Exp Med. 2018; 246:121-130.

18. Matthews T, McDonnell M, McGarvey C, Loftus G, O'Regan M. A multivariate “time based” analysis of SIDS risk factors. Arch Dis Child. 2004;89:267-271.

19. Howatson AG. The autopsy for sudden unexpected death in infancy. Curr Diagn Pathol. 2006;12:173-183.

20. Kakimoto Y, Seto Y, Ochiai E, Satoh F, Osawa M. Cytokine elevation in sudden death with respiratory syncytial virus: A Case Report of 2 Children. Pediatrics. 2016;138:e20161293.

21. Yamamoto T, Mishima H, Mizukami H, Fukahori Y, Umehara T, Murase T, et al. Metabolic autopsy with next generation sequencing in sudden unexpected death in infancy: Postmortem diagnosis of fatty acid oxidation disorders. Mol Genet Metab Rep. 2015;5:26-32.

22. Osawa M, Inaoka Y, Ochiai E, Hasegawa I, Satoh F. Variable single C repetitive tract in KCNQ1: Postmortem molecular testing in a sudden and unexpected death. Exp Clin Cardiol. 2014;20:927-930.

23. Moon RY, Hauck FR. Risk Factors and Theories In: Duncan JR, Byard RW, editors. SIDS Sudden Infant and Early Childhood Death: The Past, the Present and the Future. Adelaide (AU): University of Adelaide Press; 2018.

24. Garstang J, Ellis C, Sidebotham P. An evidence-based guide to the investigation of sudden unexpected death in infancy. Forensic Sci Med Pathol. 2015;11:345-357.

25. Colson ER, Willinger M, Rybin D, Heeren T, Smith LA, Lister G, et al. Trends and factors associated with infant bed sharing, 1993-2010: the National Infant Sleep
26. Blair PS, Sidebotham P, Berry PJ, Evans M, Fleming PJ. Major epidemiological changes in sudden infant death syndrome: a 20-year population-based study in the UK. *Lancet*. 2006;367:314-319.

27. Chang HP, Li CY, Chang YH, Hwang SL, Su YH, Chen CW. Sociodemographic and meteorological correlates of sudden infant death in Taiwan. *Pediatr Int*. 2013;55:11-16.

28. Hauck FR, Herman SM, Donovan M, Iyasu S, Merrick Moore C, Donoghue E, et al. Sleep environment and the risk of sudden infant death syndrome in an urban population: the Chicago Infant Mortality Study. *Pediatrics*. 2003;111:1207-1214.

29. Blair PS, Sidebotham P, Pease A, Fleming PJ. Bed-sharing in the absence of hazardous circumstances: is there a risk of sudden infant death syndrome? An analysis from two case-control studies conducted in the UK. *PLoS One*. 2014;9:e107799.

30. Li L, Fowler D, Liu L, Ripple MG, Lambros Z, Smialek JE. Investigation of sudden infant deaths in the State of Maryland (1990-2000). *Forensic Sci Int*. 2005;148:85-92.

31. Tanaka T, Kato N. Evaluation of child care practice factors that affect the occurrence of sudden infant death syndrome: Interview conducted by public health nurses. *Environ Health Prev Med*. 2001;6:117-120.

32. Anderson TM, Lavista Ferres JM, Ren SY, Moon RY, Goldstein RD, Ramirez JM, et al. Maternal smoking before and during pregnancy and the risk of sudden unexpected infant death. *Pediatrics*. 2019;143:e20183325.

33. James C, Klenka H, Manning D. Sudden infant death syndrome: bed sharing with
mothers who smoke. Arch Dis Child. 2003;88:112-113.

34. Pasquale-Styles MA, Tackitt PL, Schmidt CJ. Infant death scene investigation and the assessment of potential risk factors for asphyxia: a review of 209 sudden unexpected infant deaths. J Forensic Sci. 2007;52:924-929.
Reviewer #1:

The authors appreciate the detailed reviewing. According to the raised comments, the manuscript has been rewritten to a revised version. Alterations are indicated as track changes in the revised manuscript. The answers to the raised comments are as follows,

This paper describes the recent status of sudden unexpected death in infancy (SUDI) using the data obtained by a postmortem check in Japan. The study design was a retrospective case-control method. The authors analyzed 259 SUDI cases during 2013-2018 registered in 8 different universities. They found that SUDI most frequently occurred among infants at 1 month of age and significant associations with the infants born to mothers at their teenage, later born infants, and a smoking habit of a mother. They also mentioned possible associations with co-sleeping and prone positioning during sleep. Thus, the study is very important, however, the results from this study are weakened due to the lack of appropriate control subjects. Furthermore, the eligibility and selection criteria of sleep-related SUDI infants among all SUDI infants were not clear in the manuscript.

Answer;
The presented survey is not a typical case-control study. For forensic pathologists, most of the encountered infant deaths are SUDI, and we have only a small number of non-SUDI cases that were suitable for the control. Therefore, in this series of study, we used national population data as a substitute for a comparison with the SUDI cases. Concerning our limitation, a statement was added into the Methods and Discussion sections (lines 130 and 235 of the track changed text). Please also see lines 142-144 of page 6 and lines 244-245 of page 12 in the revised version.

Major comments.
1 Clarify the relationship between SUDI and sleep-related SUDI in Abstract and Manuscript.

Answer;
In this report, the authors used the term of ‘sleep-related SUDI’ as SUDI of which collapse was found during sleep. As the reviewer pointed out, the term of ‘sleep-related’ may mislead readers to sleep inducible sudden death. In the revised version, the term of ‘sleep-related’ has been replaced by ‘during sleep’ as possible. This statement was altered in
lines 33 and 50 of the Abstract in the track changed text. Moreover, we changed the title, and other five sites in lines 88, 149, 170, 193 and 242.

2 Method line 89. Explain why the study period of 2013-2018 was selected.

Answer;
In the initial attempt, we selected the five-year-period from 2013 to 2017. However, the number of gathered cases was around 200, which seemed insufficient for statistical analysis. Then, we extended the period one more year to 2018 because we thought that more than 250 cases should be desirable for statistically significant analysis. A phrase was added into the sentence of Methods.

3 Method lone 90-96 and 120-129. Explain the selection and classification methods of the study subjects precisely. Not clear even how many SUDI were registered totally. When and who decided? How to get a final agreement among investigators? Any audit by the third party? This is the most important point of this study.

Answer;
As the reviewer pointed out, the explanation was short in the manuscript. The principle investigator of the first author asked each head to extract SUDI cases during sleep. The number of 263 cases were originally registered to this project. The principle investigator selected them according to the criteria with the five researchers of the collaborating faculties in one room of the Tokai University School of Medicine. We excluded 4 cases of collapses during awakening (n = 3) and excepted death from heart anomaly at terminal stage (n = 1). The steps are described with new sentences in line 120 of the track changed text.

4 Method line 127. Is this stipulation feasible? Need more explanation.

Answer;
Pathological findings do not always reflect the real clinical stage of disease. This is the limitation in pathological diagnosis. For instance, bronchitis or bronchopneumonia was observed under microscopy. If it were severe, he or she might be in bed at hospital. But
the reality was that the baby laid in bed with their parent at home as usual. Pathologists tend to choose any apparent histological findings as the cause of death even though it might be fatal or not. We could not rule out retrospectively the possibility of overlay during sleep. No one have any means to show the evidence of overlay. Two sentences are added in line 127.

5 Method line 111 and 130-132. If this study covered only 14% of the total population in Japan, it would be hard to say “population based” (line 40). Rather say “regional investigation”.

Answer;
It was impossible for us to expand the research to the whole nation of which population is 125 million. This activity was supported by a national grant, but a small amount of budget such as 2,000 US$ was annually available. As the reviewer pointed out, our data of such limited area might not be applicable for the whole population data. But, as mentioned earlier, good control cases were not available for us. We could not find out another strategy except for using population data. Sentences are added to express our situations in more details in lines 130 and 235 of the track changed text.

6 Method line 130-132. It would be better to use the population background of the prefectures where 8 universities belong to.

Answer;
The area to which the eight joined faculties covered metropolitan cities like Fukuoka and Kyoto to rural side like small islands and isolated mountain side. The distribution was biased around the country, we thought that the data should represent the whole nation. Concerning the limitation of regional bias, a sentence is added into line 110 of the track changed text.

7 Results Table 2 line 162-163. Were these odds ratios adjusted against the background distributions of the control?

Answer;
No, the odds ratios were not adjusted. The reviewer should imply the Pearson’s $\chi^2$ test, which is calculated based on deviation of each fraction. The mean value and deviation are available for the whole national population data. But it was impossible to obtain the mean and deviation for grouped fractions separately such as $< 2500$ g and $> 2500$ g. Further, the $\chi^2$ value of exact method is usually compatible with that in the Pearson’s test.

8 Results the same as above. Explain why the early group consists of 0-2 months of age.

Answer;
As the reviewer pointed out, it should be unreasonable to separate the subjects into two groups of 0-2 month-old infants and others. The authors quitted the grouping. Tables 1 and 2 have been revised completely. Further, several sentences concerning this grouping were deleted from the test completely. Please see lines 155-157, 181, 183-184 and 189-191 of the original text.

9 Discussion. Summarize key results without repeating the data already mentioned in Results.

Answer;
The authors added major findings of this study into the first paragraph of the Discussion (line 235 of the track changed text). Please also see lines 246-251 in the revised version.

10 Discussion. Better to make a paragraph of limitations of the study with potential bias or imprecision.

Answer;
As the reviewer pointed out, a paragraph including the statement concerning the limitation is inserted into the beginning of the Discussion, which is the same way as indicated to the last comment.

11 Discussion line 250-252. Be careful about this interpretation because of the lack of control subjects.
Answer;
This sentence is not our interpretation. This is the results that Tokutake et al. investigated [17]. To circumvent the misleading, the sentence is changed a bit.

Minor comments
1 Discussion lines 279 and 286. The authors said the DSI was not reliable while the checklist was an official, very confusing description.

Answer;
The statement was inappropriate. The checklist form is widely utilized among health care stuffs of pediatricians and pathologists. The form is also distributed to police officers in some degree, but it is not mandatory for them to fill in. The authors discarded the word of ‘official’ at two sites. Please see lines 70 and 286 in the original version.

2 Better to show a flow diagram of subjects.

Answer;
The number of originally registered cases was 263. As mentioned earlier, only 4 cases were eliminated from the reasons of not found in sleep environment (n = 3) and fully explained clinical cause of heart disease (n = 1) among them. As mentioned earlier, the statement was inserted into the revised text. No flow diagram has been constructed because of the small number of selection.
Reviewer #2:

The detailed review of our article is appreciated. According to the raised comments, the manuscript has been rewritten to a revised version. Alterations are indicated as track changes in the revised manuscript. The answers to the raised comments are as follows,

Line 61. it might be easier to make a international comparison by giving rates instead of numbers per year, e.g. if rates of SIDS are given as 0.15 per 1000 livebirths

Answer;
As the reviewer advised, the number has changed to the annual rate per 1000 livebirths.

Line 73. Good that Japan has a SIDS investigation form - is it used for by the death scene investigation team or forensic pathologists? The authors might want to mention that it is similar to CDC SUDI investigation form since it is in Japanese.

Answer;
The checklist form is widely utilized among medical stuffs including pediatricians and pathologists. Items in the form is similar to the CDC one. The sentence is changed a bit.

Line 79. It would be interesting as an introduction to mention incidence of SUDI in Japan (0.4(?) per 1000 livebirths from Taylor et al's study) and any findings of sleep related SUDI from previous studies such as ref 17 or from using the DSI form, since that is the authors' major focus, rather than a mention of vaccination related SUDI

Answer;
As the reviewer found, the incidence of ‘SUDI’ in Japan is around 0.4 per 1000 livebirths, which is shown in the Tayler’s article [7]. But what the authors would like to say in this sentence was the number of ‘SIDS’, not ‘SUDI’. In the 1990s, the diagnosis of ‘SIDS’ was popular, but the diagnosis is considerably avoided among pathologists these days. Anyhow, the aim of our study was not clearly described in the last paragraph of Introduction. One sentence is added into the paragraph on line 82 of the track changed text). Further, the maternity passbook that was used in the last study was very useful for
the present study as well, particularly for the maternal smoking habit. The term of ‘maternity passbook’ is added into the last sentence as well (line 84).

Line 88. The authors' case definition included infants 0-365 days. According to most definitions, unexpected deaths in infants under 7 days of age are excluded from the SUDI category, and instead have been termed “sudden unexpected early neonatal death (SUEND)”. It would be interesting to know how many infants in the study were actually below 7 days of age to see if it would impact the findings related to early or late SUDI.

Answer;
In this revision, we provided the whole data set that was used in this series of studies. The earliest death was a 9-day-old infant. A phrase of ‘age less than 1 week’ is added into line 89 of the track changed text.

Line 134 - alignment of words (for editor)
Answer;
An equal line-width makes the prolonged arrangement. Sorry for no other expression.

Line 157, do the authors mean the later group is in where death occurred at or after 3 months of age .. . What about the infants of 2 months plus to 3 months of age if the later group is AFTER 3 months of age and Early group is within 2 months of age (<= 2 months old). Do the authors mean "below 3 months of age" ?
From the existing literature, the age groups are usually neonatal SUDI (i.e. below 28 days, approximately 1 month of age) and after the neonatal period. Is it an empirical decision or to take into account the preterm babies ?

Answer;
As the reviewer pointed out, it should be unreasonable to separate the subjects into two groups of 0-2 and 3-11-month-old infants. The authors agree with spoiling away the grouping. Tables 1 and 2 have been reconstructed completely. For Table 3, we demonstrated the data within 2-month-old infants because some of SUDI cases found in prone position prior to rolling over, which should be a good finding, we thought.
Line 159 Table 1. "SUDI" is used in the text but "SUID" is used in the Table, suggest to use one term only for consistency. Suggest to add 'livebirths' to become "Approx annual (incidence) rate per 1000 livebirths(LB)"

Answer;
We appreciate finding such careless spell miss. The term has been corrected at a total of three sites. Please see Table 1.

Line 179 - Is it the annual incidence rate of SUDI in low birth weight infants being significantly higher rather than the "percentage", the latter which is not shown in table 1

Answer;
The term of ‘percentage’ is corrected to ‘incidence’, as indicated by the reviewer.

Line 223 Table 3 - typo Supine

Answer;
The spell miss is corrected.

Statistical analysis:
Please excuse me if my understanding of the analysis is incorrect ...
Table 1 -
1. the annual rate per 1000 LB for male infants would be \[145*1000/\text{no. of LB (in the 6 years)}\] divided by 6 = 0.008 and so forth for the other variables. It may also not be necessary to have an annual incidence but just an overall incidence over the 6 years since the annual rate is very low

Answer;
The number was further divided by 0.14, of which number was from the rate of covered population in this study.
145 *1000 / no. of LB (in the 6 years) / 0.14 = 0.34
2. Line 190 and 191 - I am not sure if the number of early SUDI in one age group compared to early SUDI in the rest of the population can be used in chi squared calculation against total SUDI population- should it instead be compared with non event population in the same age group?

Answer;
The authors agreed with the comment by the reviewer. The distribution of occurrence is not even in the other generations, meaning that the comparison was very rough. As mentioned earlier, we quitted grouping of 0-2 and 3-11 month-old infants. We would like to delete this sentence.

Line 255. The effects of co-sleeping could not be evaluated but perhaps more details if available could be described under findings? Was there any related to wedging, inadvertent suffocation especially in co-sleeping cases? Or to mention Line 280..."not well trained in documentation".

Answer;
Situations of co-sleeping varied among cases such as with mother, with parents and with brothers and sisters, and in the same mattress and the separate mattresses, etc. Actually, two fathers confessed overlay during drunken sleeping. However, the detailed information was not obtained for all. It was difficult to evaluate the effects of co-sleeping further. In the next time, we would like to do another prospective study to evaluate effects of co-sleeping. The sentence has been changed a bit on line 256.

Discussion - Some comment re missing data would be helpful, 14 cases missing in gender, 25 cases in gestation and more than half cases had missing data on maternal smoking - how it may affect the reliability of the data esp with regards to smoking, although this is a known risk factor in sleep related SUDI. Sleeping position was missing in 35 cases. These are understandable given the retrospective nature of the study - so a comment may be useful to the reader

Answer;
Because this was a retrospective study, it was impossible to get all data without any lucks. A statement concerning this limitation was added into the revised text. The sentence was inserted into the first sentence of the first paragraph of Discussion (line 235 in the track changed text). Please also see lines 244-249 in the revised version.

Line 238 - Could the authors comment if the peak age of death at one month is related to the age group being studied to be 0-12 months of age as compared to other SUDI studies where the study group is from 2 to 12 months?

Answer;
Good point! Other SUDI studies [4,24] showed the peak age to 2 months. As far as we read the articles, no apparent differences were found. However, we thought that the difference in peak age might be caused by that a particularly higher risk was evident among teenage mothers, and that more first-born infants were dead during 0–2 months of age. This message is replaced on lines 239-241.

Prevention issues - of the risk groups are not discussed much. Any comments on how the babies of later birth order might be at risk?

Answer;
The authors are sorry for no idea about prevention issues to infants in later birth order, because we are not clinicians who care a number of alive patients. But according to the advice from the reviewer, we added a general sentence concerning prevention into line 278 of the track changed text.

Is there a concern about neglect if the duration of an infant seen alive is more than 5-6 hours for those found in the morning, and more than 2-3 hours for those found in the afternoon (since the parents or childminder would be awake then)? Is there a likely delay in reporting due to possible infanticide/ negligence in those reporting that last seen alive was 8 hours? Or is it a non carer who was reporting his duration? Lack of this data could be a discussion point in your study re improvement in investigation by the social workers or police.

Issues related to DSI itself could be a discussion point on quality improvement in
documentation and investigative process, were there any cases which could have been missed infanticide?

Answer;
The authors absolutely agree with this comment by the reviewer. A striking finding was the prolonged time of discovery. We thought no apparent infanticide was involved in because DSI was performed by police officers, and pathologists have experiences to find out enforced events. But neglect was highly suspected for a couple of cases, particularly for which more than 10 hours was spent to find the unresponsive infant. A new paragraph was created in the Discussion section (line 266 of the track changed text). Please also see lines 281-285 in the revised version. Moreover, a sentence concerning this finding is added into the last part of Abstract (lines 48-49 in the track changed text).