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To cite this article: Akiko Tokinobu, Takashi Yorifuji, Michiyo Yamakawa, Toshihide Tsuda & Hiroyuki Doi (2018): Association of early daycare attendance with allergic disorders in children: a longitudinal national survey in Japan, Archives of Environmental & Occupational Health, DOI: [10.1080/19338244.2018.1535481](https://doi.org/10.1080/19338244.2018.1535481)

To link to this article: <https://doi.org/10.1080/19338244.2018.1535481>

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Association of early daycare attendance with allergic disorders in children: a longitudinal national survey in Japan

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ABSTRACT

The association between early daycare attendance and risk of allergic diseases remains inconclusive. Therefore, we examined the association among Japanese children on a long-term basis using a nationwide longitudinal survey data. We estimated the association between daycare attendance at age 6 or 18 months and allergy development using information on outpatient visits for atopic dermatitis (AD), food allergy (FA), and asthma and admission for asthma up to 12 years of age as a proxy for developing these diseases, with multilevel logistic regression. Early daycare attendance was associated with increased odds of AD at ages 2.5–3.5 years: the adjusted odds ratio (OR) was 1.34 [95% CI: 1.21, 1.47]. The association with FA was equivocal. The odds of asthma was increased before age 3.5 years and afterwards decreased: the adjusted ORs were 1.60 [1.44, 1.77] for ages 1.5–2.5 years and 0.77 [0.69, 0.87] for ages 5.5–7 years. The effect of early daycare attendance depends on the type of allergies.

ARTICLE HISTORY

Received 1 May 2018

Accepted 13 September 2018

KEYWORDS

Allergies; asthma; children; epidemiology; exposure assessment; hygiene hypothesis

Introduction

Under the hygiene hypothesis, first proposed by Strachan in the late 1980s,¹ hygienic conditions with lack of exposure to infections in early childhood has been suggested to be a risk factor for allergic diseases in later life. This hypothesis has been investigated by numerous epidemiologic studies with different environmental factors that are considered to augment opportunities for infection, eg, older siblings,^{2,3} pet ownership,^{4,5} and farming environment.^{6,7} Among these factors, daycare attendance is an important factor that provides children the opportunity to be in contact with many other children, and is considered to be a substantial risk factor of infections.^{8,9} However, the number of previous studies that investigated the association of early daycare attendance with development of allergic diseases in subsequent life is less compared with studies examining other factors of the hygiene hypothesis.

Among the studies that have investigated the association of early daycare attendance with development of allergic diseases in subsequent life in various settings,^{10–15} findings have been mixed. For instance, a cohort study in the United States reported a preventive effect of daycare attendance during the first 6 months of age on asthma incidence when the child was 6–13 years old,² while a cross-sectional study in Rome found a positive association between daycare attendance and asthma prevalence among children ages 3–5 years.¹⁶ This inconsistency may be due to previous studies' differences in target age groups, study design, study population and daycare system, among other factors.^{10–15}

In the present study, we examined individuals ages between 1.5 and 12 years using data from a large, nationwide, population-based, longitudinal survey in Japan. In this population, we investigated the association between early daycare attendance and development of allergies, ie, atopic dermatitis (AD), food allergy (FA) and asthma.

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 Supplemental data for this article can be accessed on the [publisher's website](#).

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Methods

Study participants

The Longitudinal Survey of Babies in the 21st Century (LSB21) is a national survey that has been conducted by the Ministry of Health, Labor and Welfare (MHLW) of Japan since 2001. A detail description of this survey can be found elsewhere.^{17,18} In the current study, we extracted data from the LSB21. The eligible participants of this survey were all children in Japan who were born during 10–17 January or 10–17 July in 2001. The MHLW mailed baseline questionnaires to all eligible families to collect information on infants and their families when children were 6 months of age. Among the 53,575 questionnaires sent, 47,015 were answered and returned (response rate: 87.8%). Subsequent follow-up questionnaires were sent annually to the families who responded to the baseline survey (Supplemental Table 1). Birth records from vital statistics of Japan were also linked to the data individually, which included length and weight at birth, gestational age, singleton or twin or other multiple birth, sex, parity and parental age.

In the present study, we used data from the baseline survey (age 6 months) to 12th survey (age 12 years).

Daycare attendance

Daycare centers in Japan are institutes for children whose parents or guardians cannot look after children because of work, illness, etc. The age range is from birth to compulsory school age. The standard time of the daycare service is 8 h a day.¹⁹ Information on daycare attendance was extracted from the baseline survey (age 6 months) and second survey (age 18 months). The baseline and second surveys queried who was taking care of the child during the daytime on weekdays. If the answer was ‘nursery school teacher’, this was determined as daycare attendance. When daycare attendance status was positive at least either at age 6 or 18 months, we counted early daycare attendance status as positive and used this information as measurement of exposure. Because some participants were lost to follow-up at age 18 months, we could not obtain information on daycare attendance either at age 6 or 18 months from 3,232 participants. Thus, the number of eligible children at baseline was 43,783.

Incidence of allergic diseases

We used information on outpatient visits as an outcome variable indicating the incidence of the diseases

of interest, namely, AD, FA, and asthma. The history of outpatient visit for these three allergic diseases during the previous 1 year was asked annually from the second survey (at age 18 months) onwards to the 12th survey (at age 12 years). The guardians answered this query. Because daycare attendance status either at age 6 or 18 months was used as a measurement of exposure, we used the data of the third survey (at age 2.5 years) onwards in the analyses, which enabled us to evaluate the outcome data between ages 18 months and 12 years. Regarding asthma, we additionally observed hospital admission because incidence of hospital admission for asthma was not negligible in number in this LSB21 survey. Thus, we used the data on outpatient visit for the aforementioned three diseases and hospital admission for asthma.

Covariates

We selected the following variables, which were available from data, as potential confounding factors based on previous studies^{10–14} and prior knowledge. Child factors included sex (dichotomous), singleton or multiple birth (dichotomous), term or preterm birth (gestational age of <37 weeks or not; dichotomous), and parity (number of previous pregnancies including stillbirth; eg, parity 0 denotes no previous pregnancies; 0, 1, ≥ 2 ; categorical), which is an indicator of the presence of older siblings and is considered to be an important factor in hygiene hypothesis.^{1–3} We treated the information of parity as a child factor. Maternal factors included maternal age at delivery (in years; continuous), smoking status (nonsmoker, smoker with ≤ 10 cigarettes per day, or smoker with > 10 cigarettes per day; categorical), and educational attainment (university or higher, junior college or vocational school, high school, junior high school or others; categorical). Residential information included the residential area where the child was born (wards, cities, town, or villages; categorical). Information on all child factors, maternal age at delivery and residential area were extracted from birth records. Maternal smoking status information was available from the baseline survey and was addressed by two queries on maternal smoking status. The first query related to whether or not the mother was smoking. The second query addressed the number of cigarettes per day the mother smoked, and was asked only when the answer regarding maternal smoking was positive. We used these two queries to create the maternal smoking status category. Maternal educational attainment information was obtained from the second survey. We categorized

Table 1. Demographic characteristics of eligible children ($N = 43,783$).

Attending daycare	No ($N = 36,514$)	Yes ($N = 7,269$)
Characteristics of children		
Sex, n (%) [*]		
Boys	18,870 (51.7)	3,872 (53.3)
Girls	17,644 (48.3)	3,397 (46.7)
Singleton birth, n (%) [*]	35,775 (98.0)	7,116 (97.9)
Multiple birth, n (%) [*]	739 (2.0)	153 (2.1)
Mean gestational age, weeks (SD) [*]	38.9 (1.6)	38.9 (1.6)
Term birth, n (%) [*]	34,660 (95.0)	6,924 (95.3)
Preterm birth, n (%) [*]	1,825 (5.0)	343 (4.7)
Parental characteristics		
Mean maternal age at delivery, years (SD) [*]	30.1 (4.4)	30.1 (4.6)
Parity, n (%)		
0	18,108 (49.6)	3,278 (45.1)
1	13,216 (36.2)	2,774 (38.2)
≥2	5,190 (14.2)	1,217 (16.7)
Maternal smoking status, n (%) [†]		
Nonsmoker	30,698 (84.6)	5,769 (79.9)
Smoker (Less than or equal to 10 cigarettes per day)	3,714 (10.2)	915 (12.7)
Smoker (More than 10 cigarettes per day)	1,881 (5.2)	536 (7.4)
Maternal educational attainment, n (%) [‡]		
University or higher	4,789 (13.2)	1,233 (17.1)
Junior college or vocational school	15,466 (42.6)	3,103 (43.0)
High school	14,524 (40.0)	2,569 (35.6)
Junior high school and others	1,545 (4.3)	312 (4.3)
Residential area, n (%)		
Wards	8,101 (22.2)	1,522 (20.9)
Cities	21,476 (58.8)	4,336 (59.7)
Towns or villages	6,937 (19.0)	1,411 (19.4)

SD, standard deviation.

^{*}Obtained from birth records.[†]Obtained from the first survey (at the age of 6 months).[‡]Obtained from the second survey (at the age of 18 months).

originally eight categories into four; university (4 years) and higher; junior college (2 years) or vocational school; high school; and junior high school or others.

Statistical analysis

We performed multilevel logistic regression analyses to evaluate the relationships between daycare attendance at an early age and incidence of allergic diseases from age 1.5 to 12 years, clustering the participants within each of the 47 prefectures in Japan. We did not apply analyses with repeated measures for this study because each allergic disease has heterogeneous pathologic conditions depending on age, and we intended to evaluate the impact of daycare attendance on disease risk in each age period. We estimated the odds ratio (OR) for the risk of developing each allergic disease of early daycare attendance. Throughout the analyses, we used the no daycare attendance category as our reference group. For each outcome, we

first estimated the crude OR and 95% confidence interval (CI), and then estimated the adjusted OR and 95% CI after controlling for all the covariates mentioned below. We excluded cases with missing data and conducted our analyses with complete cases.

We performed the sensitivity analyses by adding the following information into the adjusted model. We added information regarding pet ownership and rural living environment individually from the 4th survey, ie, at 3.5 years of age, and observed the association after age 3.5 years onwards annually. We defined pet ownership as owning and caring for any of the following animals: dogs, cats, rabbits, small animals such as hamsters, and birds. Information on living environment was obtained from the query that addressed whether or not the family was living in a residential area, shopping area, industrial area or rural districts/mountainous regions. We defined rural living environment as living in rural districts or mountainous regions. Furthermore, we performed the additional sensitivity analyses to evaluate whether the results would change with different exposure levels. We combined the daycare attendance either at age 6 or 18 months and categorized the exposure level of daycare attendance as follows: (1) no attendance either at 6 or 18 months, (2) attendance only at 6 months, (3) attendance only at 18 months, (4) attendance at both 6 and 18 months. We then repeated the analyses.

All CIs were calculated at the 95% level. All analyses were performed using Stata statistical software (Stata SE version 12.1, Stata Corp LP, TX, USA). Approval for this study was obtained from the institutional ethics committee of Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Okayama University Hospital (No. 1506-073).

Results

Some loss to follow-up for each subsequent follow-up survey was experienced, and we conducted analyses using complete data from each follow-up survey. For example, we included 41,536 children at the third survey and 31,630 at the 12th survey for analyses (Supplemental Table 1). The proportion of loss to follow-up for each survey was larger in the daycare attendance group than the nonattendance group.

Table 1 shows the baseline demographic characteristics of eligible children ($N = 43,783$). Up to 16.6% of children attended daycare at age 6 months or 18 months. Children attending daycare were more likely to have older siblings compared with children

Table 2. Crude and adjusted* ORs for associations between daycare attendance and atopic dermatitis from 1.5 to 12 years of age.

Daycare attendance at age 6 or 18 months	N case/N	% of cases	Crude ORs (95% CI)	Adjusted* ORs (95% CI)
Between 1.5 and 2.5 years				
No	5,436/34,740	15.6	1 (ref.)	1 (ref.)
Yes	1,176/6,796	17.3	1.14 (1.07–1.23)	1.13 (1.06–1.22)
Between 2.5 and 3.5 years				
No	2,351/34,010	6.9	1 (ref.)	1 (ref.)
Yes	601/6,642	9.0	1.35 (1.23–1.48)	1.34 (1.21–1.47)
Between 3.5 and 4.5 years				
No	2,267/32,641	6.9	1 (ref.)	1 (ref.)
Yes	533/6,356	8.4	1.23 (1.12–1.36)	1.22 (1.10–1.34)
Between 4.5 and 5.5 years				
No	2,437/31,694	7.7	1 (ref.)	1 (ref.)
Yes	537/6,133	8.8	1.16 (1.05–1.28)	1.15 (1.04–1.27)
Between 5.5 and 7 years				
No	2,097/30,333	6.9	1 (ref.)	1 (ref.)
Yes	453/5,839	7.8	1.14 (1.03–1.27)	1.14 (1.02–1.27)
Between 7 and 8 years				
No	1,969/29,818	6.6	1 (ref.)	1 (ref.)
Yes	387/5,747	6.7	1.04 (0.93–1.17)	1.04 (0.93–1.17)
Between 8 and 9 years				
No	1,789/29,124	6.1	1 (ref.)	1 (ref.)
Yes	356/5,597	6.4	1.06 (0.94–1.19)	1.04 (0.93–1.18)
Between 9 and 10 years				
No	1,569/28,178	5.6	1 (ref.)	1 (ref.)
Yes	341/5,440	6.3	1.15 (1.01–1.30)	1.14 (1.01–1.29)
Between 10 and 11 years				
No	1,618/27,243	5.9	1 (ref.)	1 (ref.)
Yes	308/5,197	5.9	1.01 (0.89–1.15)	1.01 (0.89–1.15)
Between 11 and 12 years				
No	1,394/26,572	5.2	1 (ref.)	1 (ref.)
Yes	276/5,058	5.5	1.05 (0.92–1.20)	1.05 (0.92–1.20)

CI, confidence interval; OR, odds ratio.

*Adjusted for child factors (sex, singleton or not, and preterm birth), maternal factors (maternal age at delivery, parity, maternal smoking status, and maternal educational attainment), and residential area.

who were not attending. The percentage of maternal smoking was greater in the daycare attending group. Maternal educational attainment tended to be higher in the daycare attending group.

Tables 2–5 show the results for associations between daycare attendance and incidence of each allergic disease in each follow-up survey. Table 2 shows that attending daycare was associated with increased odds of developing AD between ages 1.5 and 7 years in both crude and adjusted analyses. The highest adjusted OR for developing AD by daycare attendance was observed between ages 2.5 and 3.5 years: 1.34 [95% CI: 1.21, 1.47]. After age 7 years, the higher odds of daycare attendance was not statistically significant except between ages 9 and 10 years.

In association with FA (Table 3), children attending daycare were observed to have a J-curve association based on point estimates. The lowest odds were observed between ages 5.5 and 7 years; the adjusted OR for developing FA by daycare attendance was 0.72 [95% CI: 0.52, 0.98]. However, the overall association was equivocal because the result was unstable with broad confidence intervals.

Table 4 shows the association with asthma (outpatient visit). Between ages 1.5 and 3.5 years,

children attending daycare were at an elevated odds for asthma; the adjusted OR for developing asthma (outpatient visit) by daycare attendance was 1.60 [95% CI: 1.44, 1.77] and 1.12 [95% CI: 1.00, 1.24] between ages 1.5 and 2.5 years, and 2.5 and 3.5 years, respectively. From age 3.5 years onwards, in contrast, daycare attendance was observed to lower the odds for asthma. Between ages 3.5 and 9 years, the preventive association was observed. The lowest OR was observed between ages 5.5 and 7 years, ie, 0.77 [95% CI: 0.69, 0.87] in adjusted analysis.

Table 5 shows the association with asthma (hospitalization). Although the result became unstable due to the small number of cases, the overall trend was similar to that of outpatient visit for asthma.

In sensitivity analyses, adjusted individually with pet ownership and rural living environment, the results were almost unchanged (data not shown). In analyses with the different exposure level, although the point estimates slightly differed among the category of daycare attendance only at 18 months, either at 6 or 18 months, and both at 6 and 18 months, the overall trends remained the same (data not shown).

Table 3. Crude and adjusted* ORs for associations between daycare attendance and food allergy from 1.5 to 12 years of age.

Daycare attendance at age 6 or 18 months	N case/N	% of cases	Crude ORs (95% CI)	Adjusted* ORs (95% CI)
Between 1.5 and 2.5 years				
No	831/34,740	2.4	1 (ref.)	1 (ref.)
Yes	179/6,796	2.6	1.11 (0.94–1.31)	1.13 (0.95–1.33)
Between 2.5 and 3.5 years				
No	534/34,010	1.6	1 (ref.)	1 (ref.)
Yes	113/6,642	1.7	1.09 (0.89–1.34)	1.10 (0.89–1.35)
Between 3.5 and 4.5 years				
No	453/32,641	1.4	1 (ref.)	1 (ref.)
Yes	83/6,356	1.3	0.95 (0.75–1.20)	0.94 (0.74–1.20)
Between 4.5 and 5.5 years				
No	458/31,694	1.4	1 (ref.)	1 (ref.)
Yes	73/6,133	1.2	0.83 (0.64–1.06)	0.82 (0.64–1.05)
Between 5.5 and 7 years				
No	341/30,333	1.1	1 (ref.)	1 (ref.)
Yes	46/5,839	0.8	0.70 (0.51–0.95)	0.72 (0.52–0.98)
Between 7 and 8 years				
No	259/29,818	0.9	1 (ref.)	1 (ref.)
Yes	42/5,747	0.7	0.84 (0.61–1.17)	0.84 (0.61–1.17)
Between 8 and 9 years				
No	246/29,124	0.8	1 (ref.)	1 (ref.)
Yes	45/5,597	0.8	0.95 (0.69–1.31)	0.91 (0.66–1.27)
Between 9 and 10 years				
No	211/28,178	0.7	1 (ref.)	1 (ref.)
Yes	39/5,440	0.7	0.97 (0.68–1.36)	0.97 (0.69–1.37)
Between 10 and 11 years				
No	266/27,243	1.0	1 (ref.)	1 (ref.)
Yes	40/5,197	0.8	0.79 (0.56–1.10)	0.80 (0.57–1.12)
Between 11 and 12 years				
No	203/26,572	0.8	1 (ref.)	1 (ref.)
Yes	42/5,058	0.8	1.11 (0.80–1.56)	1.12 (0.80–1.56)

Table 4. Crude and adjusted* ORs for associations between daycare attendance and asthma from 1.5 to 12 years of age.

Daycare attendance at age 6 or 18 months	N case/N	% of cases	Crude ORs (95% CI)	Adjusted* ORs (95% CI)
Between 1.5 and 2.5 years				
No	1,668/34,740	4.8	1 (ref.)	1 (ref.)
Yes	530/6,796	7.8	1.66 (1.49–1.85)	1.60 (1.44–1.77)
Between 2.5 and 3.5 years				
No	2,038/34,010	6.0	1 (ref.)	1 (ref.)
Yes	459/6,642	6.9	1.14 (1.03–1.27)	1.12 (1.00–1.24)
Between 3.5 and 4.5 years				
No	2,334/32,641	7.2	1 (ref.)	1 (ref.)
Yes	411/6,356	6.5	0.89 (0.80–0.99)	0.87 (0.78–0.98)
Between 4.5 and 5.5 years				
No	2,787/31,694	8.8	1 (ref.)	1 (ref.)
Yes	446/6,133	7.3	0.80 (0.72–0.89)	0.79 (0.71–0.88)
Between 5.5 and 7 years				
No	2,233/30,333	7.4	1 (ref.)	1 (ref.)
Yes	345/5,839	5.9	0.76 (0.66–0.88)	0.77 (0.69–0.87)
Between 7 and 8 years				
No	1,924/29,818	6.5	1 (ref.)	1 (ref.)
Yes	302/5,747	5.3	0.80 (0.70–0.90)	0.79 (0.70–0.90)
Between 8 and 9 years				
No	1,798/29,124	6.2	1 (ref.)	1 (ref.)
Yes	305/5,597	5.4	0.85 (0.73–1.00)	0.86 (0.76–0.98)
Between 9 and 10 years				
No	1,616/28,178	5.7	1 (ref.)	1 (ref.)
Yes	289/5,440	5.3	0.90 (0.76–1.06)	0.91 (0.80–1.04)
Between 10 and 11 years				
No	1,488/27,243	5.5	1 (ref.)	1 (ref.)
Yes	276/5,197	5.3	0.95 (0.81–1.12)	0.96 (0.84–1.10)
Between 11 and 12 years				
No	1,166/26,572	4.4	1 (ref.)	1 (ref.)
Yes	220/5,058	4.3	0.97 (0.80–1.17)	0.98 (0.84–1.13)

Table 5. Crude and adjusted* ORs for associations between daycare attendance and asthma hospitalization from 1.5 to 12 years of age.

Daycare attendance at age 6 or 18 months	N case/N	% of cases	Crude ORs (95% CI)	Adjusted* ORs (95% CI)
Between 1.5 and 2.5 years				
No	370/34,740	1.1	1 (ref.)	1 (ref.)
Yes	119/6,796	1.8	1.65 (1.34–2.04)	1.60 (1.30–1.98)
Between 2.5 and 3.5 years				
No	347/34,010	1.0	1 (ref.)	1 (ref.)
Yes	66/6,642	1.0	0.96 (0.74–1.25)	0.93 (0.71–1.22)
Between 3.5 and 4.5 years				
No	251/32,641	0.8	1 (ref.)	1 (ref.)
Yes	33/6,356	0.5	0.66 (0.46–0.95)	0.65 (0.45–0.94)
Between 4.5 and 5.5 years				
No	203/31,694	0.6	1 (ref.)	1 (ref.)
Yes	34/6,133	0.6	0.86 (0.60–1.24)	0.84 (0.58–1.21)
Between 5.5 and 7 years				
No	116/30,333	0.4	1 (ref.)	1 (ref.)
Yes	18/5,839	0.3	0.61 (0.25–1.49)	0.74 (0.45–1.22)
Between 7 and 8 years				
No	83/29,818	0.3	1 (ref.)	1 (ref.)
Yes	12/5,747	0.2	0.75 (0.41–1.37)	0.69 (0.37–1.27)
Between 8 and 9 years				
No	79/29,124	0.3	1 (ref.)	1 (ref.)
Yes	15/5,597	0.3	0.99 (0.57–1.72)	1.02 (0.58–1.77)
Between 9 and 10 years				
No	45/28,178	0.2	1 (ref.)	1 (ref.)
Yes	14/5,440	0.3	1.61 (0.88–2.94)	1.61 (0.88–2.96)
Between 10 and 11 years				
No	32/27,243	0.1	1 (ref.)	1 (ref.)
Yes	5/5,197	0.1	0.82 (0.32–2.10)	0.85 (0.33–2.18)
Between 11 and 12 years				
No	19/26,572	0.1	1 (ref.)	1 (ref.)
Yes	4/5,058	0.1	1.07 (0.36–3.16)	0.90 (0.30–2.70)

Discussion

In the present study, we examined the association between early daycare attendance and development of allergies, ie, AD, FA and asthma, at subsequent ages until age 12 years annually, using data from a large, nationwide, population-based, longitudinal survey in Japan. We observed the elevated odds of developing AD according to early daycare attendance between ages 1.5 and 7 years. The association with FD was J-curved but obscure. Regarding asthma (outpatient visit), daycare attendance elevated the odds of developing AD before age 3.5 years and afterwards lowered the odds. This is the largest published study to date examining the association between early daycare attendance and development of allergies at subsequent ages annually on a long-term basis in a nationwide population.

The mechanism of allergy as well as the hygiene hypothesis is still under discussion. For a long time, the theory of the hygiene hypothesis has been understood that reduced opportunities to catch infections due to the Western lifestyle environment induces imbalance among type 1 T helper, type 2 T helper, T helper 17 and regulatory T cells, which ultimately cause allergic diseases.²⁰ In recent years, a new mechanism related to the hygiene hypothesis has emerged

and been addressed. When the airways are exposed to endotoxin, the lung epithelium starts to induce the ubiquitin-modifying enzyme A20, which suppresses the activation of barrier epithelial cells and dendritic cells, thus protecting against allergies.²¹ Meanwhile, attending daycare involves more intricate interplay of various factors than home that contribute to childhood diseases, such as infections, an unhygienic environment and mismanagement of medication. All these factors may work together to have an effect on the association between early daycare attendance and the development of allergic diseases.

Atopic dermatitis

In our study, early daycare attendance was associated with increased odds of occurrence of AD up to age 7 years. Even beyond this age, the tendency of daycare attendance to increase the odds of AD was observed. This result was in accordance with the findings of some previous studies. For instance, Zutavern et al. reported that daycare attendance was associated with an increased odds of AD symptoms at ages 5–7 and 9–11 years.²² However, they did not specify the age at which the children were attending daycare centers, and whether the association was due to an early age effect of daycare attendance remains unclear. In

contrast, other studies have observed the protective effects of daycare attendance on AD. Benn et al. observed that early daycare attendance before age 6 months was inversely associated with development of AD during the first 18 months of life.²³

Our results showed a contradiction to the hygiene hypothesis with regard to AD. Skincare with emollient has been demonstrated to be a primary preventive measure for the development of AD.²⁴ In daycare centers, the development of rough skin is more likely to occur than in the home environment because keeping skin moisturized by applying emollient in a clean environment is more difficult due to social norms and lack of time of childcare workers.²⁵ This difficulty of proper skincare management at daycare centers might contribute to the increased risk of developing AD.

Food allergy

In our study, the association between early daycare attendance and development of FA was J-curved, with an inverse association between ages 5.5 and 7 years. However, the result was unstable with broad confidence intervals. Conversely, some studies have indicated an association between daycare attendance and risk of FA. For instance, Hagerhed-Engman et al. reported that daycare attendance increased the odds of allergic reactions to food at ages 1–4 and 4–6 years.¹⁴ This result is inconsistent with our result. A possible reason may lie in different definitions of daycare attendance. Specifically, in their analysis, either daycare center or family daycare (with 3–6 children) was considered to comprise daycare attendance, and the time spent in a daycare center was unrestricted whether less than 20 or 20 h/week or more. In addition, reporting for FA incidence differed from the method applied in our study. Hagerhed-Engman et al. used the outcome data of FA that were reported by parents, not based on diagnosis by a medical doctor. This might have increased the number of cases of FA.

Asthma

Our results showed that early daycare attendance was associated with increased odds of developing asthma before age 3.5 years and thereafter protectively associated. The positive association between daycare attendance and development of asthma is consistent with the findings of previous studies. Indinnimeo et al. used a cohort study design and reported that daycare attendance was associated with increased odds of asthma at ages 3–5 years in Rome.¹⁶ By contrast, the

protective association observed after age 3.5 years is also consistent with the results of many previous studies^{2,10,11,13,26,27} and supports the hygiene hypothesis. Additionally, the recently addressed mechanism related to the aforementioned enzyme A20 can be applied here.

A possible explanation as to why the risk of developing asthma increased in early childhood and decreased in later childhood among daycare attendance children is as follows. Asthma is often diagnosed based on clinical symptoms, such as recurrent wheeze and cough. Most asthma cases during early childhood are reported to be transient wheeze from respiratory infections,²⁸ and after age 6 years IgE-associated atopic asthma becomes more common.²⁹ Children attending daycare centers catch more infections than children cared for in their homes,³⁰ which could explain the higher odds of developing asthma among daycare-attending children in early childhood, as observed in this study. Further, the balance of Th1, Th2, Th17 and regulatory T cells to suppress allergic reactions was established by encountering sufficient pathogens during infancy.²⁰ Catching more infections in daycare centers during early childhood could reduce the incidence of asthma, such as IgE-associated atopic asthma, in later childhood, as observed in this study.

One of the strengths of the current paper is that a large, nationally representative sample of Japanese children born in 2001 was examined. Because the number of participants was large, we could investigate a relatively large number of cases of the target diseases. Another advantage is that we estimated the association between early daycare attendance and the development of allergic diseases annually in each survey, and could therefore observe the long-term trend of the association corresponding to the growth of children.

Our study has some limitations as well. First, information on family history of allergy was unavailable. Family history was demonstrated to be an important factor for development of AD,³¹ FA³² and asthma³¹ in children.³³ We tried the sensitivity analysis by adding the variable of paternal educational attainment which was an indicator of socioeconomic status and was available in LSB21 as a proxy of family history of allergies. However, we did not find the convincing evidence that paternal education attainment is associated with allergies.³³ Second, we could not take into account other important factors of the hygiene hypothesis, such as pet ownership and farm environment, during early childhood. Nevertheless, possible confounding caused by pet ownership or rural living

environment at age 3.5 years was unlikely because our findings were robust in the sensitivity analyses.

Third, loss to follow-up may be a concern because the proportion of loss to follow-up was higher in the daycare attendance group throughout the survey (Supplementary Table 1). The proportion of maternal smoking was higher in the daycare attendance group (Table 1). An association between maternal smoking and the risk of child allergies has been suggested in numerous studies.³⁴ Thus, children lost to follow-up were more likely to have allergies. Such a differential loss might overestimate the protective effects of daycare attendance on development of allergic diseases. However, the influence of this possible overestimation on the result would not be substantial because the difference of the loss to follow-up proportion between groups is not large and the ORs for developing allergic diseases did not linearly decline.

We classified the status of daycare attendance either age at 6 or 18 months using the information from answers to the query about who was taking care of the child during the daytime on weekdays. Although misclassification in this exposure measurement could be unlikely to occur, the misclassification, even if it occurred, would be nondifferential because outcome information was obtained after the third survey (at age 2.5 years).

We used information on guardian-reported outpatient visit for each target disease and on admission for asthma as the outcome variable. Some cases may have occurred in which guardians did not take their child to see a doctor even though the child presented some symptoms. Thus, a discrepancy likely exists between the number of guardian-reported outpatient visits or admission and the actual cases of that disease. Children attending daycare centers likely have less opportunity to see a doctor because their parents are working. Thus, this differential information misclassification would overestimate the protective effects of daycare attendance on development of allergic diseases. However, children who were advised inpatient treatment for asthma by their doctors would be hospitalized regardless of daycare attendance status. Therefore, the misclassification of hospital admission for asthma is less likely. Even so, there might be a chance of misclassification as this information was obtained from self-reported data. However, this misclassification would be nondifferential and move the effect estimate towards the null. The overall tendency of the odds for asthma at outpatient visit and hospital admission was observed to be similar. Thus, the effect

due to the above differential information misclassification may be negligible.

Conclusions

We observed that early daycare attendance was associated with an elevated odds for developing AD and a J-curve association with FA. The odds of developing asthma was increased at early ages before 3.5 years and then lowered thereafter. Accordingly, our findings were partly consistent with the hygiene hypothesis with regard to asthma, and add evidence that the effect of early daycare attendance depends on the type of allergic diseases.

Acknowledgments

The sponsor had no involvement in the study design; the collection, analysis, or interpretation of the data; the writing of the report; or the decision to submit the paper for publication. We thank Saori Irie for the variable support in collecting the data. We thank Edanz Group (www.edanzediting.com/ac) for editing a draft of this manuscript.

Funding

This study was partly supported by a grant from Okayama University, which was distributed by the Ministry of Education, Culture, Sports, Science and Technology, Japan [grant number 5001700014].

References

1. Strachan DP. Hay fever, hygiene, and household size. *Br Med J*. 1989;299(6710):1259–1260.
2. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day-care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med*. 2000;343(8):538–543.
3. Schmitz R, Atzpodien K, Schlaud M. Prevalence and risk factors of atopic diseases in German children and adolescents. *Pediatr Allergy Immunol*. 2012;23(8):716–723.
4. Anyo G, Brunekreef B, de Meer G, Aarts F, Janssen NA, van Vliet P. Early, current and past pet ownership: associations with sensitization, bronchial responsiveness and allergic symptoms in school children. *Clin Exp Allergy*. 2002;32(3):361–366.
5. Lodrup Carlsen KC, Roll S, Carlsen KH, et al. Does pet ownership in infancy lead to asthma or allergy at school age? Pooled analysis of individual participant data from 11 European birth cohorts. *PLoS One*. 2012;7(8):e43214.
6. Illi S, Depner M, Genuneit J, et al. Protection from childhood asthma and allergy in Alpine farm environments—the GABRIEL Advanced Studies. *J Allergy Clin Immunol*. 2012;129(6):1470–1477. e1476.

7. Parsons MA, Beach J, Senthilselvan A. Association of living in a farming environment with asthma incidence in Canadian children. *J Asthma*. 2017;54(3): 239–249.
8. Lu N, Samuels ME, Shi L, Baker SL, Glover SH, Sanders JM. Child day care risks of common infectious diseases revisited. *Child Care Health Dev*. 2004; 30(4):361–368.
9. Schuez-Havupalo L, Toivonen L, Karppinen S, Kaljonen A, Peltola V. Daycare attendance and respiratory tract infections: a prospective birth cohort study. *BMJ Open*. 2017;7(9):e014635.
10. Caudri D, Wijga A, Scholtens S, et al. Early daycare is associated with an increase in airway symptoms in early childhood but is no protection against asthma or atopy at 8 years. *Am J Respir Crit Care Med*. 2009; 180(6):491–498.
11. Cheng G, Smith AM, Levin L, et al. Duration of day care attendance during infancy predicts asthma at the age of seven: the Cincinnati Childhood Allergy and Air Pollution Study. *Clin Exp Allergy*. 2014;44(10): 1274–1281.
12. Cramer C, Link E, Bauer CP, et al. Association between attendance of day care centres and increased prevalence of eczema in the German birth cohort study LISAPlus. *Allergy* 2011;66(1):68–75.
13. Gaffin JM, Spergel JM, Boguniewicz M, et al. Effect of cat and daycare exposures on the risk of asthma in children with atopic dermatitis. *Allergy Asthma Proc*. 2012;33(3):282–288.
14. Hagerhed-Engman L, Bornehag CG, Sundell J, Aberg N. Day-care attendance and increased risk for respiratory and allergic symptoms in preschool age. *Allergy* 2006;61(4):447–453.
15. Svanes C, Jarvis D, Chinn S, et al. Early exposure to children in family and day care as related to adult asthma and hay fever: results from the European Community Respiratory Health Survey. *Thorax*. 2002; 57(11):945–950.
16. Indinnimeo L, Porta D, Forastiere F, et al. Prevalence and risk factors for atopic disease in a population of preschool children in Rome: challenges to early intervention. *Int J Immunopathol Pharmacol*. 2016;29(2): 308–319.
17. Kato T, Yorifuji T, Inoue S, Doi H, Kawachi I. Association of birth length and risk of hospitalisation among full-term babies in Japan. *Paediatr Perinat Epidemiol*. 2013;27(4):361–370.
18. Yorifuji T, Tsukahara H. Breastfeeding and risk of Kawasaki disease: A Nationwide Longitudinal Survey in Japan. *Pediatrics*. 2016;137(6):e20153919.
19. Ichimi M. Preschool education and care in Japan. National Institute for Education Policy Research Web site. <http://www.nier.go.jp/English/educationjapan/pdf/201109ECEC.pdf>. Accessed April 13, 2018.
20. Mak TW, Saunders ME, Jett BD. Immune hypersensitivity. In: *Primer to the Immune Response*. Burlington, VT: Elsevier Science; 2013:487–516.
21. Schuijs MJ, Willart MA, Vergote K, et al. Farm dust and endotoxin protect against allergy through A20 induction in lung epithelial cells. *Science* 2015; 349(6252):1106–1110.
22. Zutavern A, Hirsch T, Leupold W, Weiland S, Keil U, von Mutius E. Atopic dermatitis, extrinsic atopic dermatitis and the hygiene hypothesis: results from a cross-sectional study. *Clin Exp Allergy*. 2005;35(10): 1301–1308.
23. Benn CS, Melbye M, Wohlfahrt J, Bjorksten B, Aaby P. Cohort study of sibling effect, infectious diseases, and risk of atopic dermatitis during first 18 months of life. *Br Med J*. 2004;328(7450):1223.
24. Simpson EL, Chalmers JR, Hanifin JM, et al. Emollient enhancement of the skin barrier from birth offers effective atopic dermatitis prevention. *J Allergy Clin Immunol*. 2014;134(4):818–823.
25. Soejima S. A fact-finding survey on medication to children in certified centers for early childhood education. 2018; https://www.maruho.co.jp/medical/academic/square/rvcck400000006lh-att/vol28_03.pdf. (in Japanese) Accessed 7 August.
26. Barry RJ, Pickett W, Rennie DC, Senthilselvan A, Cockcroft DW, Lawson JA. Factors contributing to risks for pediatric asthma in rural Saskatchewan. *Ann Allergy Asthma Immunol*. 2012;109(4):255–259.
27. Midodzi WK, Rowe BH, Majaesic CM, Saunders LD, Senthilselvan A. Early life factors associated with incidence of physician-diagnosed asthma in preschool children: results from the Canadian Early Childhood Development cohort study. *J Asthma*. 2010;47(1): 7–13.
28. Jackson DJ, Gangnon RE, Evans MD, et al. Wheezing rhinovirus illnesses in early life predict asthma development in high-risk children. *Am J Respir Crit Care Med*. 2008;178(7):667–672.
29. Silverman M, Wilson N. Wheezing phenotypes in childhood. *Thorax* 1997;52(11):936–937.
30. Canadian Paediatric Society. Infections in child care. *Paediatr Child Health*. 2000;5(8):495–498.
31. Dold S, Wjst M, von Mutius E, Reitmeir P, Stiepel E. Genetic risk for asthma, allergic rhinitis, and atopic dermatitis. *Arch Dis Child*. 1992;67(8):1018–1022.
32. Koplin JJ, Allen KJ, Gurrin LC, et al. The impact of family history of allergy on risk of food allergy: a population-based study of infants. *Int J Environ Res Public Health*. 2013;10(11):5364–5377.
33. Miyake Y, Tanaka K, Sasaki S, Hirota Y. Parental employment, income, education and allergic disorders in children: a prebirth cohort study in Japan. *Int J Tuberc Lung Dis*. 2012;16(6):756–761.
34. Keil T, Lau S, Roll S, et al. Maternal smoking increases risk of allergic sensitization and wheezing only in children with allergic predisposition: longitudinal analysis from birth to 10 years. *Allergy*. 2009; 64(3):445–451.

Supplemental Table 1. Proportion of loss to follow-up, separated by early daycare attendance status in each follow-up period (N = 43,783)

Daycare attendance at age 6 or 18 months	Included in the analysis, n (%)	Loss to follow-up, n (%)
Third survey (at 2.5 y)		
No	34,740 (95.14)	1,774 (4.86)
Yes	6,796 (93.49)	473 (6.51)
Fourth survey (at 3.5 y)		
No	34,010 (93.14)	2,504 (6.86)
Yes	6,642 (91.37)	627 (8.63)
Fifth survey (at 4.5 y)		
No	32,641 (89.39)	3,873 (10.61)
Yes	6,356 (87.44)	913 (12.56)
Sixth survey (at 5.5 y)		
No	31,694 (86.80)	4,820 (13.20)
Yes	6,133 (84.37)	1,136 (15.63)
Seventh survey (at 7 y)		
No	30,333 (83.07)	6,181 (16.93)

Yes	5,839 (80.33)	1,430 (19.67)
Eighth survey (at 8 y)		
No	29,818 (81.66)	6,696 (18.34)
Yes	5,747 (79.06)	1,522 (20.94)
Ninth survey (at 9 y)		
No	29,124 (79.76)	7,390 (20.24)
Yes	5,597 (77.00)	1,672 (23.00)
Tenth survey (at 9 y)		
No	28,178 (77.17)	8,336 (22.83)
Yes	5,440 (74.84)	1,829 (25.16)
Eleventh survey (at 10 y)		
No	27,243 (74.61)	9,271 (25.39)
Yes	5,197 (71.50)	2,072 (28.50)
Twelfth survey (at 11 y)		
No	26,572 (72.77)	9,942 (27.23)
Yes	5,058 (69.58)	2,211 (30.42)
