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Birth month, climate conditions, and atopic dermatitis

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Original research

Birth month, climate conditions, and atopic dermatitis

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Abstract

Objective This study aimed to compare the incidence of atopic dermatitis in children aged from 6 months to 3 years across birth seasons and climate conditions.

Design Cohort study.

Setting Fifteen Regional Centres across Japan.

Participants A total of 100,304 children born from 2011 to 2014.

Exposure Birth month, sunshine duration, and humidity.

Primary outcome measure Incidence of atopic dermatitis.

Results The highest incidence of atopic dermatitis was in the months of October to December and in periods with a long duration of sunshine and high humidity. The lowest incidence of atopic dermatitis was in the months of April to June and in periods with a short duration of sunshine and high humidity. The differences in the incidence for sunshine duration and humidity were statistically significant and consistent across analyses stratified by birth season and parental history of allergic disease.

Conclusions In Japan, being born in the late autumn to early winter months is associated with a risk of developing atopic dermatitis. A long duration of sunshine may be positively correlated with the incidence of atopic dermatitis, potentially because the duration of sunshine could be related to dry skin and itchiness.

(191 words)

Strengths and limitations of this study

- Six monthly meteorological data were used, corresponding to individual children.
- History of infection was not considered theoretically as a confounder.
- Metrological data of children's residence were averaged.
- The type of atopic dermatitis was not analysed.

Introduction

Approximately 10% to 20% of children suffer from atopic dermatitis (AD).[1 2] Many genetic and environmental factors may be associated with the incidence and aggravation of AD,[3] and evidence identifying causal factors is needed. Possible environmental factors of AD include seasonal climate conditions, chemical irritants, bacterial colonisation, psychological stress,[4] and birth month.[4] In this study, we collected data from a large Japanese population to examine potential associations between the incidence of AD and birth month, sunshine duration, and humidity.[5 6]

Methods

Measures

Details on the Japan Environment and Children's Study (JECS) project are published elsewhere.[5] Briefly, the JECS comprises a cohort of 104,062 children born from 2011 to 2014 in 15 regional centres covering 18 prefectures across Japan.[7] We used the JECS data "jecs-ta-20190930-qsn" for generating questionnaires, which were sent to caregivers by post when their children were aged 6 months, 1 year, 2 years, and 3 years. We asked if physicians had diagnosed the children with AD.

We collected climate condition data per prefecture and month from the Japan Meteorological Agency website.[8] The sunshine duration was defined as hours with ≥120 Watt/m^2 of direct sunshine, as measured by a solarimeter. The mean sunshine duration and humidity of the 18 prefectures from April 2011 to March 2015 were 166.1 hours/month and 68.4%, respectively. These values were used as cut-off values

for categorising children as being exposed to a long/short sunshine duration and high/low humidity while taking into account their resident area and birth month. For this categorisation, the mean sunshine duration and humidity in the child's resident area over 6 months beginning with the child's birth month were compared with the cut-off values. An example of this categorisation is that a child who was born in April 2011 would be categorised on the basis of meteorological data from April to September 2011. For considering a child's genetic predisposition to AD, we used a parental history of asthma, allergic rhinitis, pollen allergy, AD, allergic conjunctivitis, food allergy, medication allergy, urticaria, and/or contact dermatitis.

Analyses

The 12 months of the year were categorized into four seasons in three different ways (i.e., starting with January–March, February–April, or March–May). We compared Kaplan–Meier curves of the incidence of AD among seasons by performing log-rank tests. Data from participants who were lost to follow-up or developed AD after 3 years of age were considered as being censored. We conducted all statistical analyses using SAS statistical software version 9.4. Kaplan–Meier curves were drawn using RStudio version 1.2.1335. Two-sided p-values of <0.05 were considered to indicate a significant difference.

Patient and public involvement

Written informed consent was obtained from all participants. Patient consent for publication was not required. Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our research.

Results

We analysed data from 100,304 births. By the ages of 6 months, 1 year, 2 years, and 3 years, 1,715, 4,505, 7,299, and 9,704 children, respectively, had developed AD. Figures 1 and 2 and supplementary figures 1 and 2 show the incidence of AD curves for birth months and seasons. The highest and lowest incidence of AD was observed in the October to December group and the April to June group, respectively.

We also assessed the incidence of AD among four climate categories, including combinations of a long/short sunshine duration and high/low humidity. The highest and lowest incidence of AD was observed in the long sunshine duration/high humidity group and the short sunshine duration/high humidity group, respectively (Figure 3). To confirm this result, we examined the incidence of AD by climate combinations for all birth seasons. Figure 4 and supplementary figures 3 to 5 show the incidence of AD curves for the four climate categories of neonates born in October to December, January to March, April to June, and July to September, respectively. The observed highest and lowest incidence of AD in figure 4 and supplementary figures 3 to 5 was consistent with that shown in Figure 3.

Finally, we analysed the incidence of AD on the basis of parental history of any allergic disease. Figure 5 and supplementary figures 6 to 8 show the incidence of AD by birth season and climate combinations, respectively, as stratified by parental history of allergic disease. The observed highest and the lowest incidence of AD in figure 5 and supplementary figures 6 to 8 was consistent with that shown in figures 1 and 2. The order of accumulated incidence of AD among the seasons and climate conditions did not change from 6 months to 3 years of age.

Discussion

Birth in autumn or winter is a risk factor for developing AD. Potential aetiologies of this association are viral infection, dry air, high solar radiation/sunshine hours, and atmospheric pressure. Dry skin and itchiness are common in low humidity. In the USA, a higher incidence of AD is associated with indoor heating use and low humidity, UV exposure, and outdoor temperature.[9] In Japan, a negative correlation between humidity and dermatological visits concerning AD was observed.[10] In our study, we did not observe a clear correlation between high or low humidity and the risk of AD, which suggested that humidity may not be critical for inducing AD.

In Japan, AD shows remittance in 50% of 4-month-old patients before the age of 18 months. However, a previous study reported a high cumulative incidence rate of AD of 30% in children who were younger than 3 years.[11] In mice, low humidity caused higher cutaneous immune reaction by an increase in Langerhans cells and penetration of allergen.[12] The mean humidity in Japan was 70% in 2016, which is not high compared with other countries.[13] High humidity is clearly associated with a higher incidence of hand, foot and mouth disease of fever, ulcers, and vesicles.[14] Dry and itchy skin are caused by low humidity and low temperature.[15] However, in this study, there was no effect of high or low humidity on the risk of AD risk (Figures 3 and 4). Therefore, in the present children, humidity did not appear to be important for inducing AD. Our study suggested that a long sunshine duration could induce AD because we found that a long sunshine duration was a risk factor for AD (figures 3 to 5 and supplementary figures 3 to 5 and 8). The reason why the duration of sunshine is related to the incidence of AD is unknown

In Mongolia, where the sunshine duration is long and humidity is low throughout the year, AD is rare. Additionally, ultraviolet lighting is sometimes used clinically for reducing itchiness from severe AD. However, a long sunshine duration can also cause dry skin, which is a known risk factor of AD. Furthermore, heat from a long sunshine duration can cause sweating, leading to itchiness and psychological stress from discomfort, both of which can exacerbate AD. In Japan, humidity is fairly constant. Therefore, in Japan, itchiness and psychological stress from the duration of sunshine may be a major cause of AD in children. Alternatively, rather than sunshine duration or humidity alone, the combination with climate may be an important factor for the incidence of AD.

Notably, the association between the incidence rate of AD across birth seasons, sunshine duration, and humidity levels did not change from 6 months old to 3 years old. This finding indicates that environmental factors with an adverse or preventive effect persist through early childhood. Allergic predisposition may not be determined until 6 months of age. Before that age, most infants only drink milk and do not eat allergenic solid products. A recent meta-analysis did not show clear evidence for a protective effect of breast feeding on the incidence of AD.[16] Our analysis did not examine the feeding behaviour of the children; however, the combination of climate conditions appeared to be a strong determinant of the incidence of AD.

Even when considering genetic predisposition, a high incidence of AD was found among children who were born in October to December and residing in high humidity regions. However, a low incidence of AD was observed for residents in regions with short sunshine duration/high humidity. Genetic predisposition and other non-climate environmental factors could not theoretically confound the observed associations.

Limitations

Our results are limited by infection not being examined as a potential confounder. Additionally, we used 6 monthly means of sunshine duration and humidity. Individual experience was not considered. Furthermore, we were unable to consider types of AD. Notably, AD can be caused by several mechanisms, and analysis of disease severity may lead a further understanding of its aetiology.

Conclusions

Births in October to December have the highest incidence of AD. Additionally, the highest and lowest incidence of AD is found in residents in regions with a long sunshine duration/high humidity and short sunshine duration/high humidity, respectively. These results are consistent when parental history of allergic disease is considered. The incidence of AD persists from 6 months through to 3 years in childhood.

(1,485 words)

Footnotes

Contributors: All of the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY and MM conceived the study. HY and MM contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, MM, AT, RK, SH, TO, YA, and KM wrote the first draft of the manuscript. All authors contributed to revision of the manuscript. ZY was responsible for data integrity. ZY obtained funding.

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Competing interests: None.

Ethics approval: The protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the Ethics Committees of all participating institutions, in accordance with the ethical guidelines and regulations of the Declaration of Helsinki.

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

Acknowledgment: We thank Doctor Ellen Knapp for editing a draft of this manuscript. †Members of the JECS Group as of 2020: Michihiro Kamijima (principal investigator, Nagoya City University, Nagoya, Japan), Shin Yamazaki (National Institute for Environmental Studies, Tsukuba, Japan), Yukihiro Ohya (National Center for Child Health and Development, Tokyo, Japan), Reiko Kishi (Hokkaido University,

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Figure legends

Figure 1. Incidence of atopic dermatitis in relation to birth month.

Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort.

Figure 3. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity.

Figure 4. Incidence of atopic dermatitis in neonates who were born in October to December in regions with a long/short mean sunshine duration and high/low mean humidity.

Figure 5. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity in children whose parents had a history of allergic disease.

Supplementary Figure 1. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from December.

Supplementary Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from February.

Supplementary Figure 3. Incidence of atopic dermatitis in neonates who were born in January to March in regions with a long/short mean sunshine duration and high/low mean humidity.

Supplementary Figure 4. Incidence of atopic dermatitis in neonates who were born in April to June in regions with a long/short mean sunshine duration and high/low mean humidity.

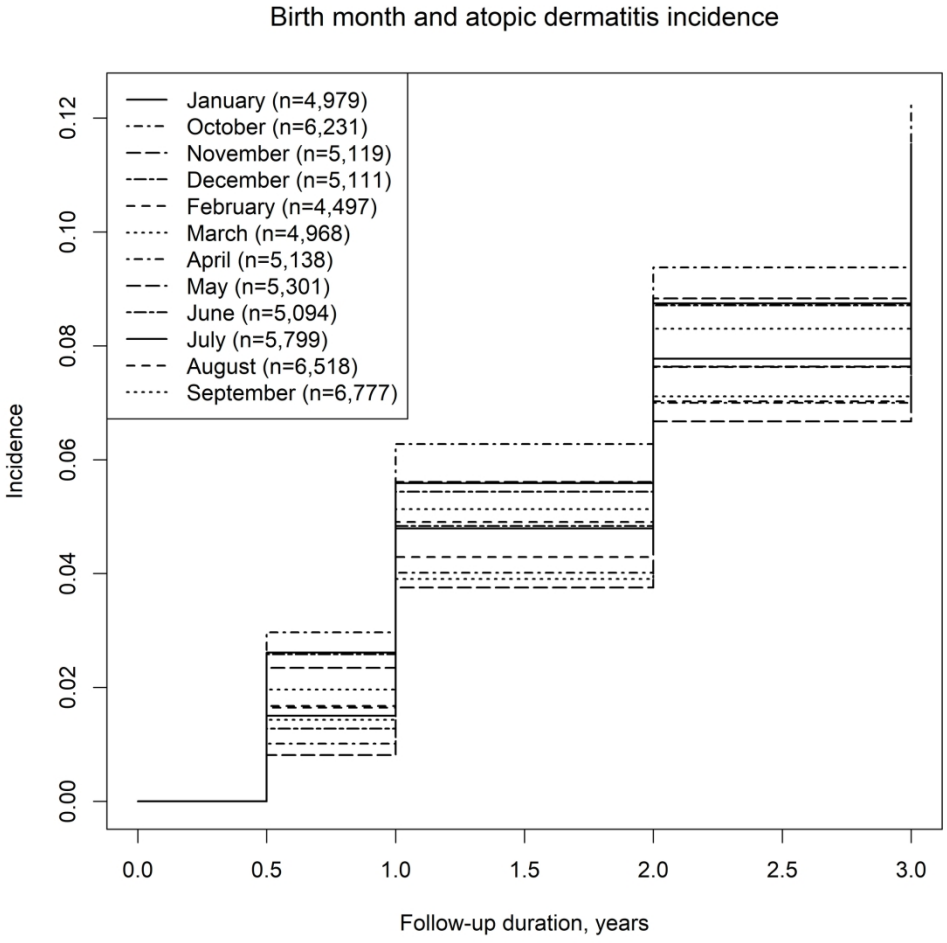
Supplementary Figure 5. Incidence of atopic dermatitis in neonates who were born in July to September in

regions with a long/short mean sunshine duration and high/low mean humidity.

Supplementary Figure 6. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.

Supplementary Figure 7. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.

Supplementary Figure 8. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity in children whose parents had no history of allergic disease.



Incidence of atopic dermatitis among birth months.

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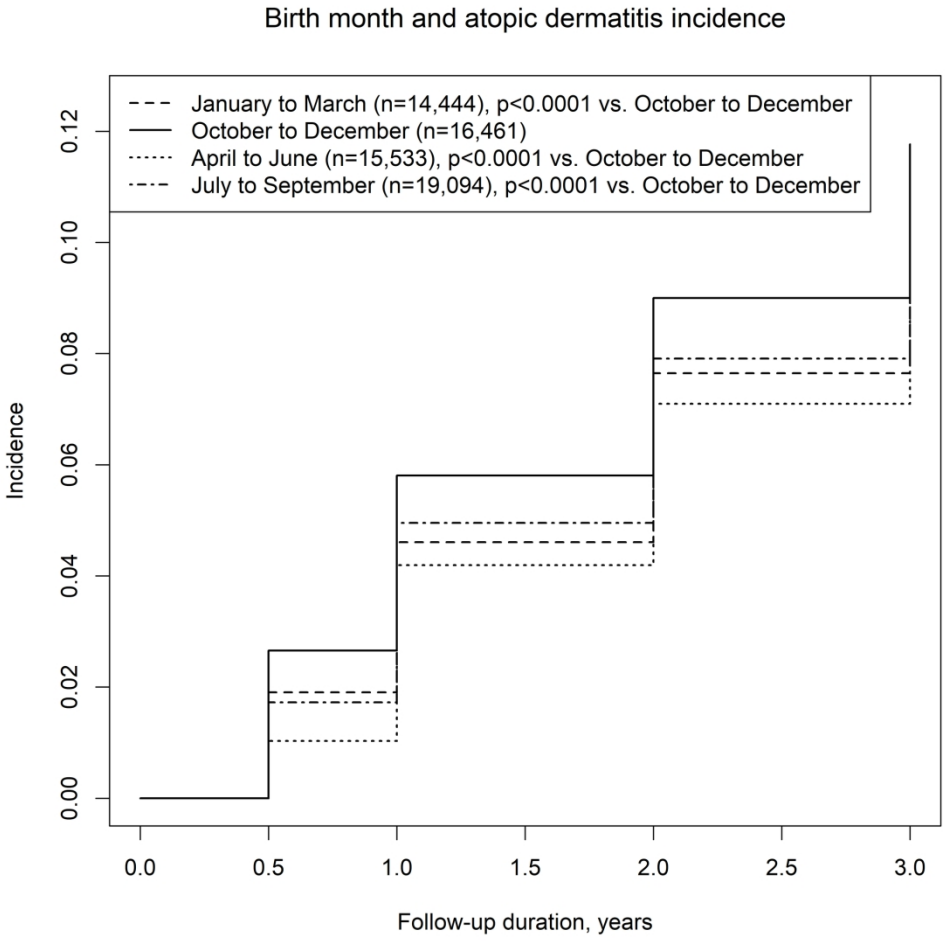

Birth season and incidence of atopic dermatitis in a Japanese birth cohort.

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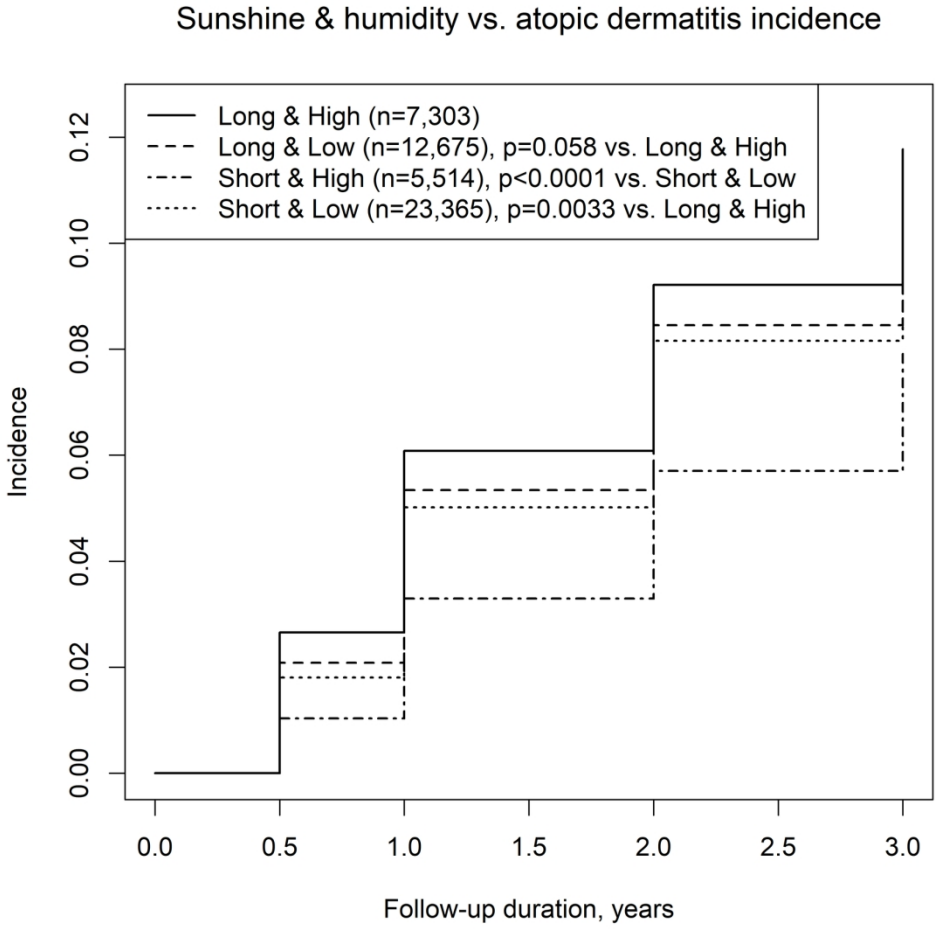

Incidence of atopic dermatitis in regions with long/short mean sunshine duration and high/low mean humidity.

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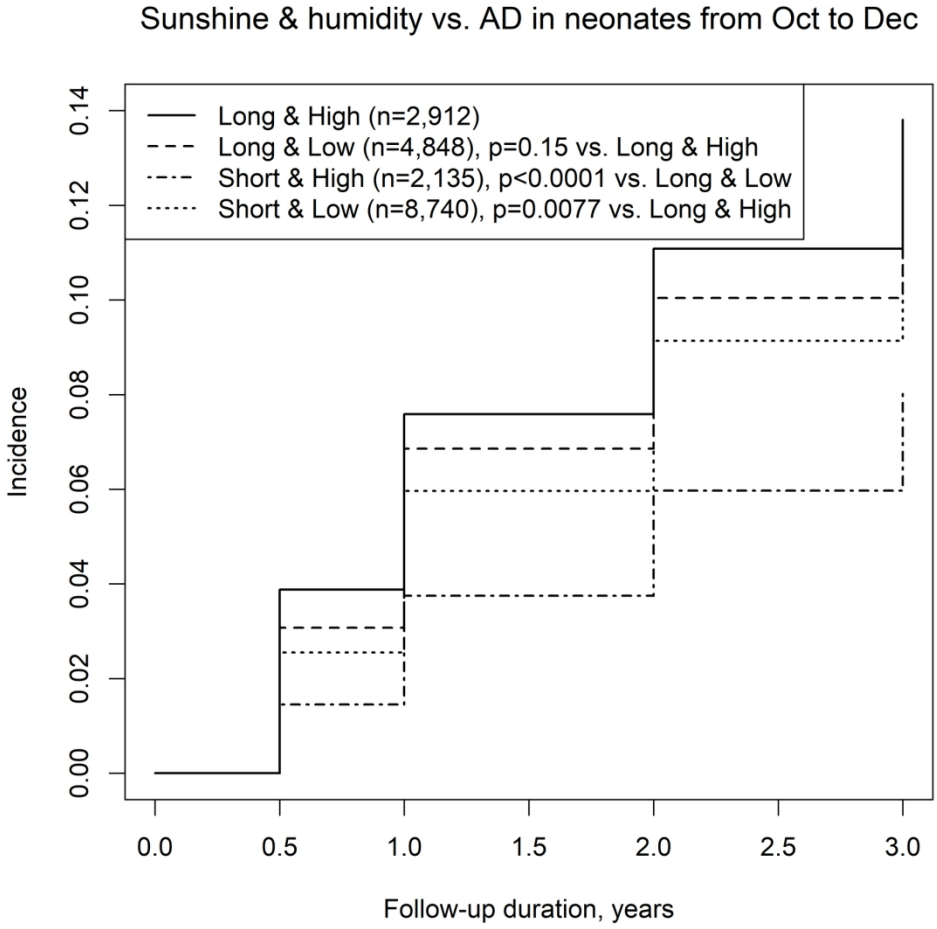

Incidence of atopic dermatitis among neonates who were born in October–December in regions with long/short mean sunshine durations and high/low mean humidity.

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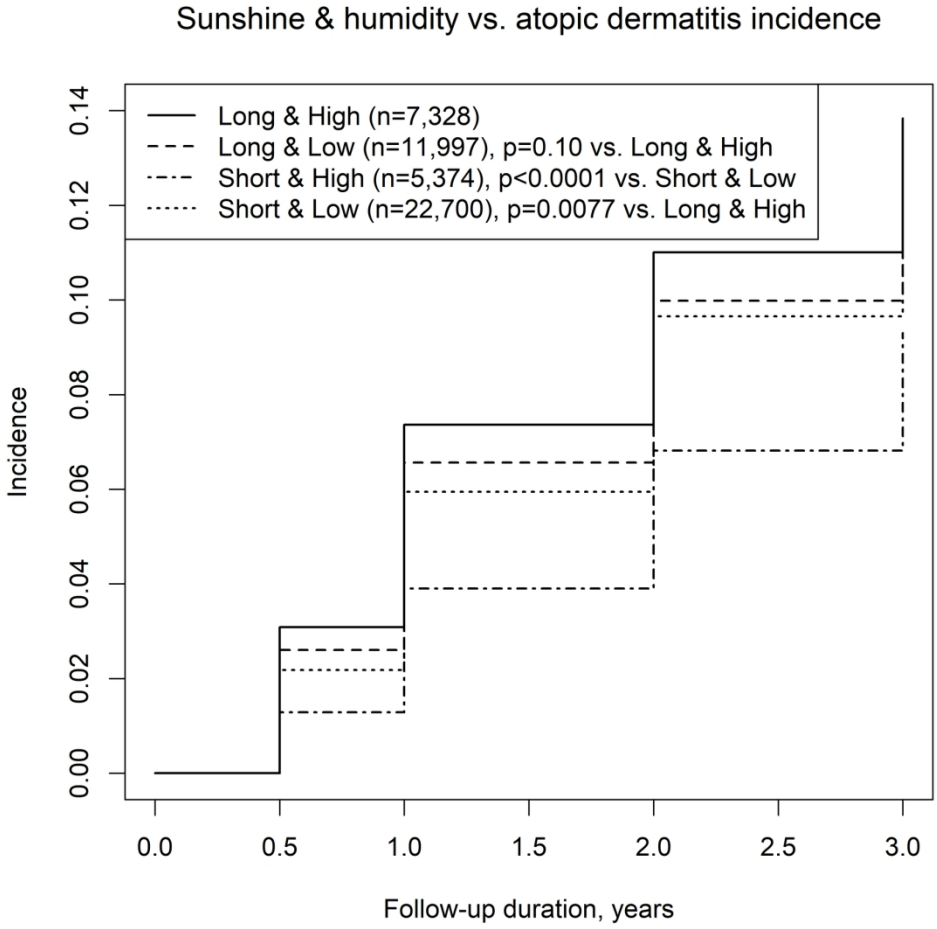

Incidence of atopic dermatitis in regions with long/short mean sunshine durations and high/low mean humidity, in children whose parents had a history of allergic disease.

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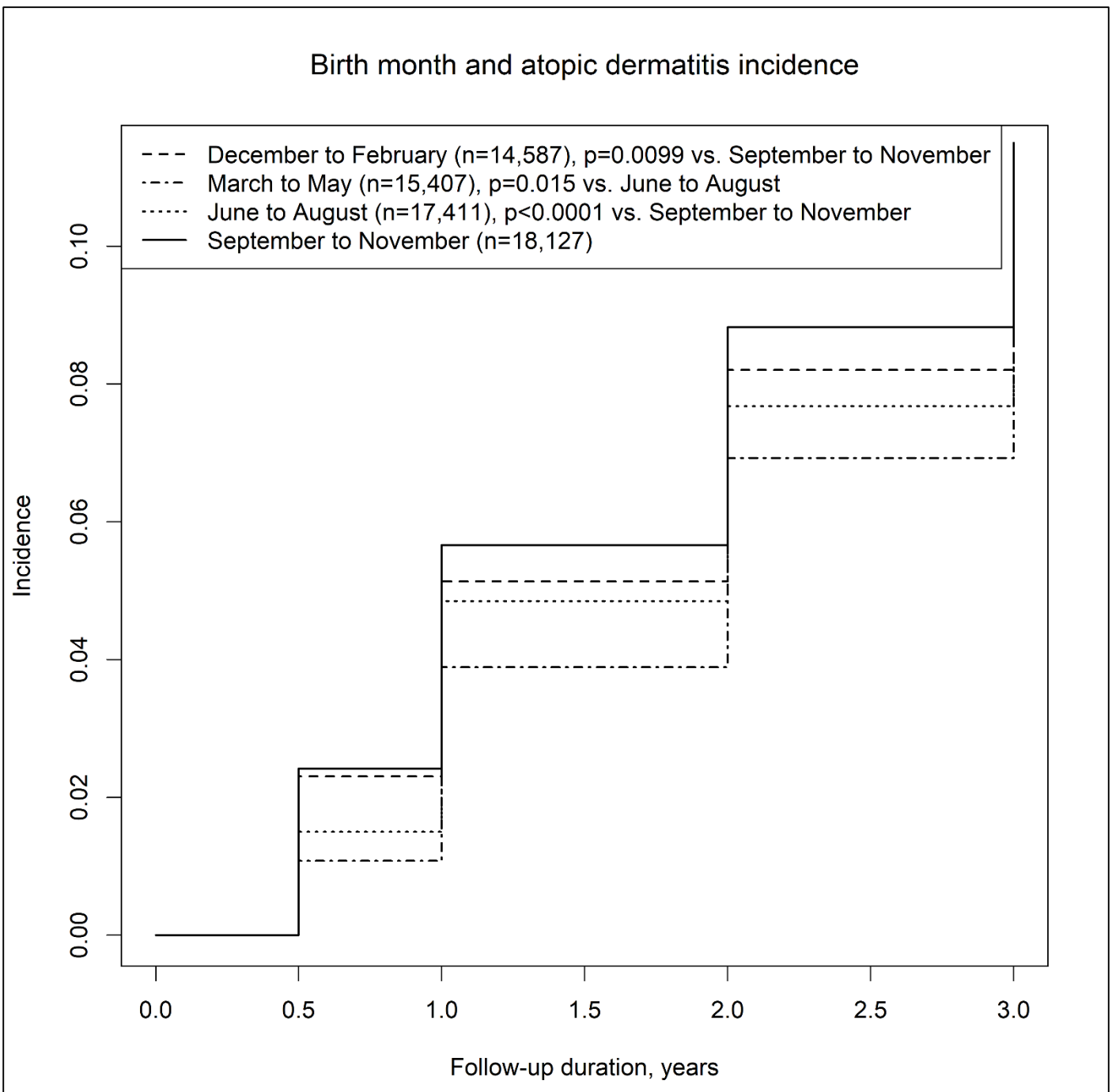
Supplementary materials

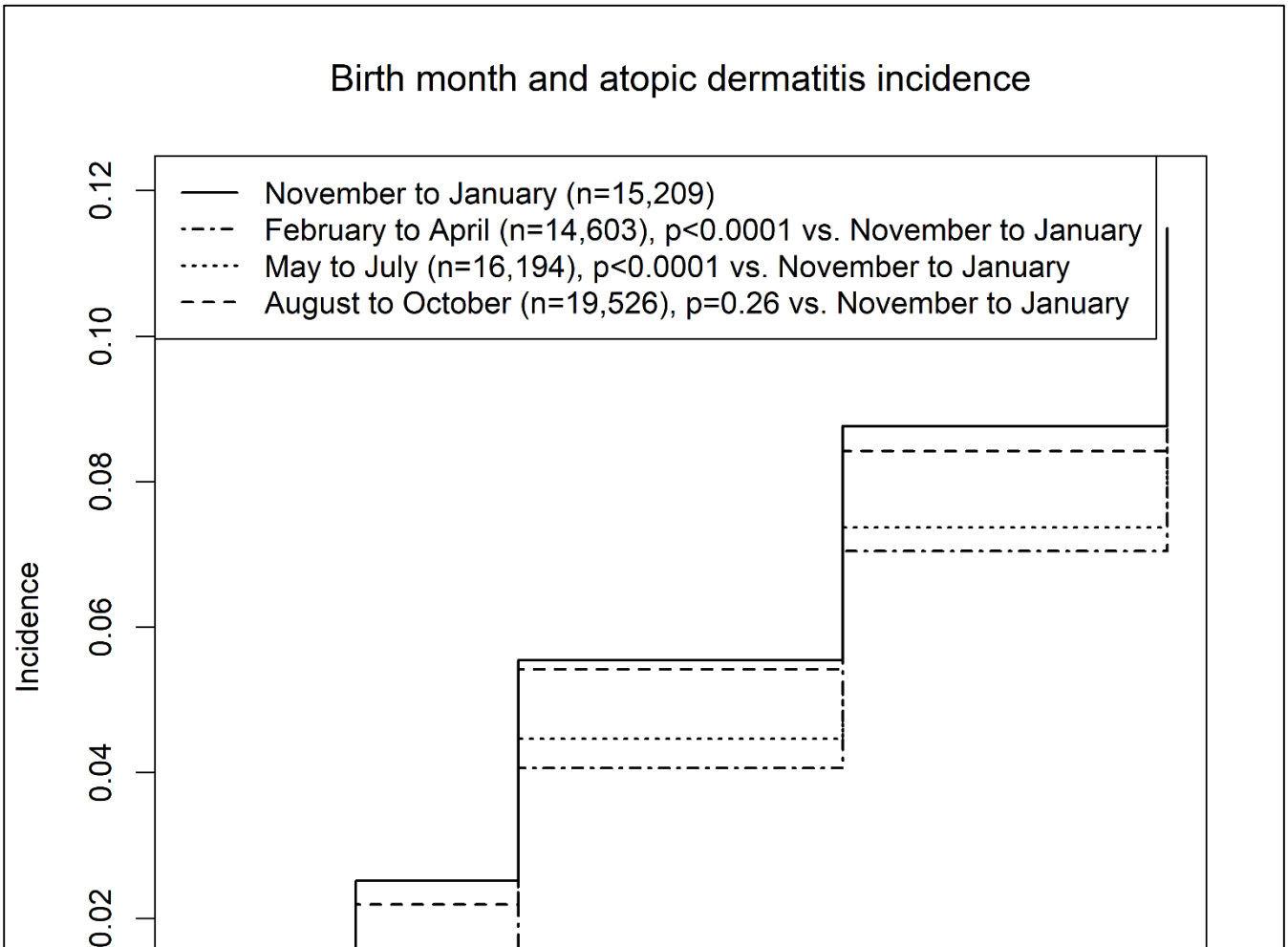
Supplementary figure 1. Birth season and incidence of atopic dermatitis in a Japanese birth cohort.

Seasons were started from December.

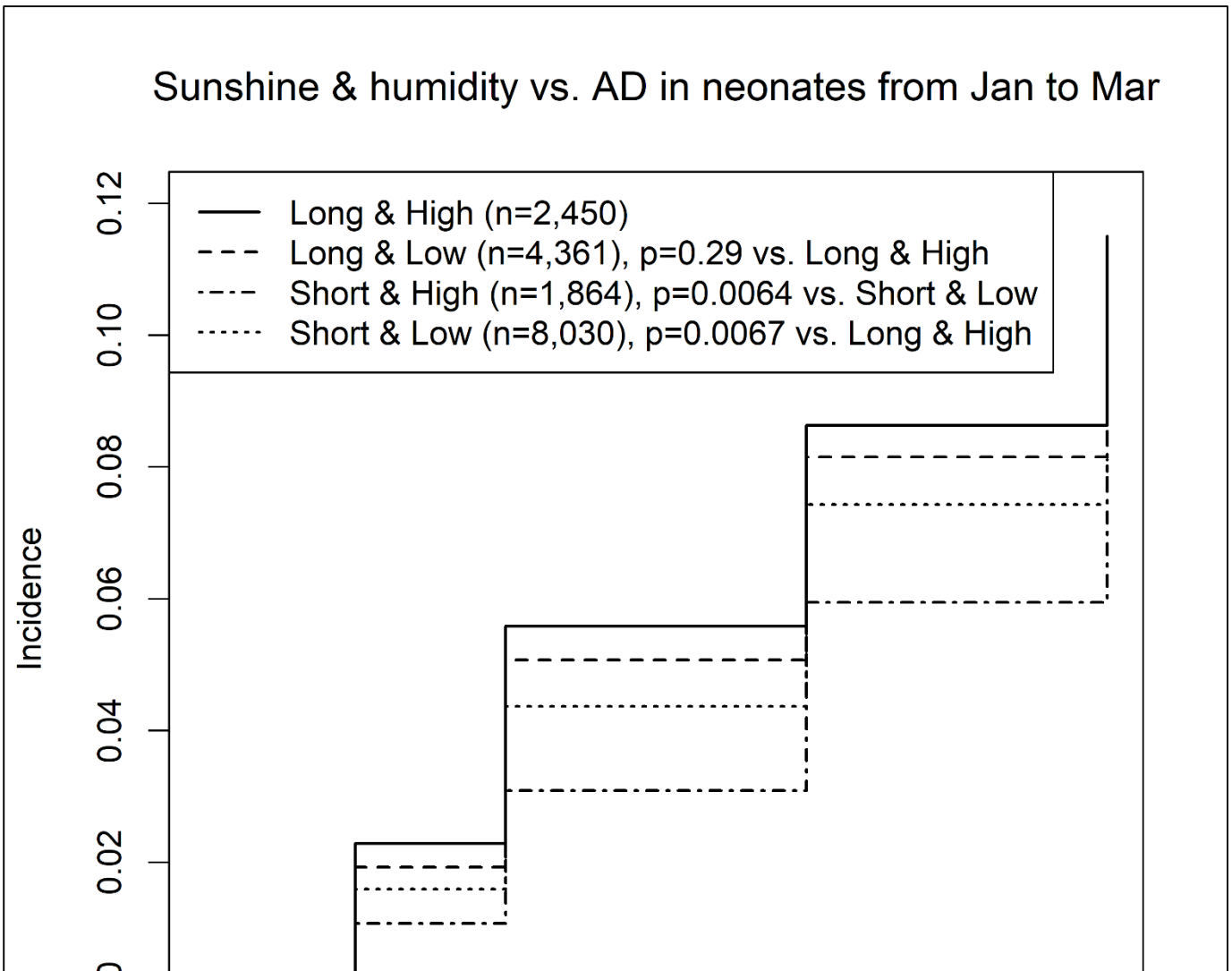


Supplementary figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort.

Seasons were started from February.

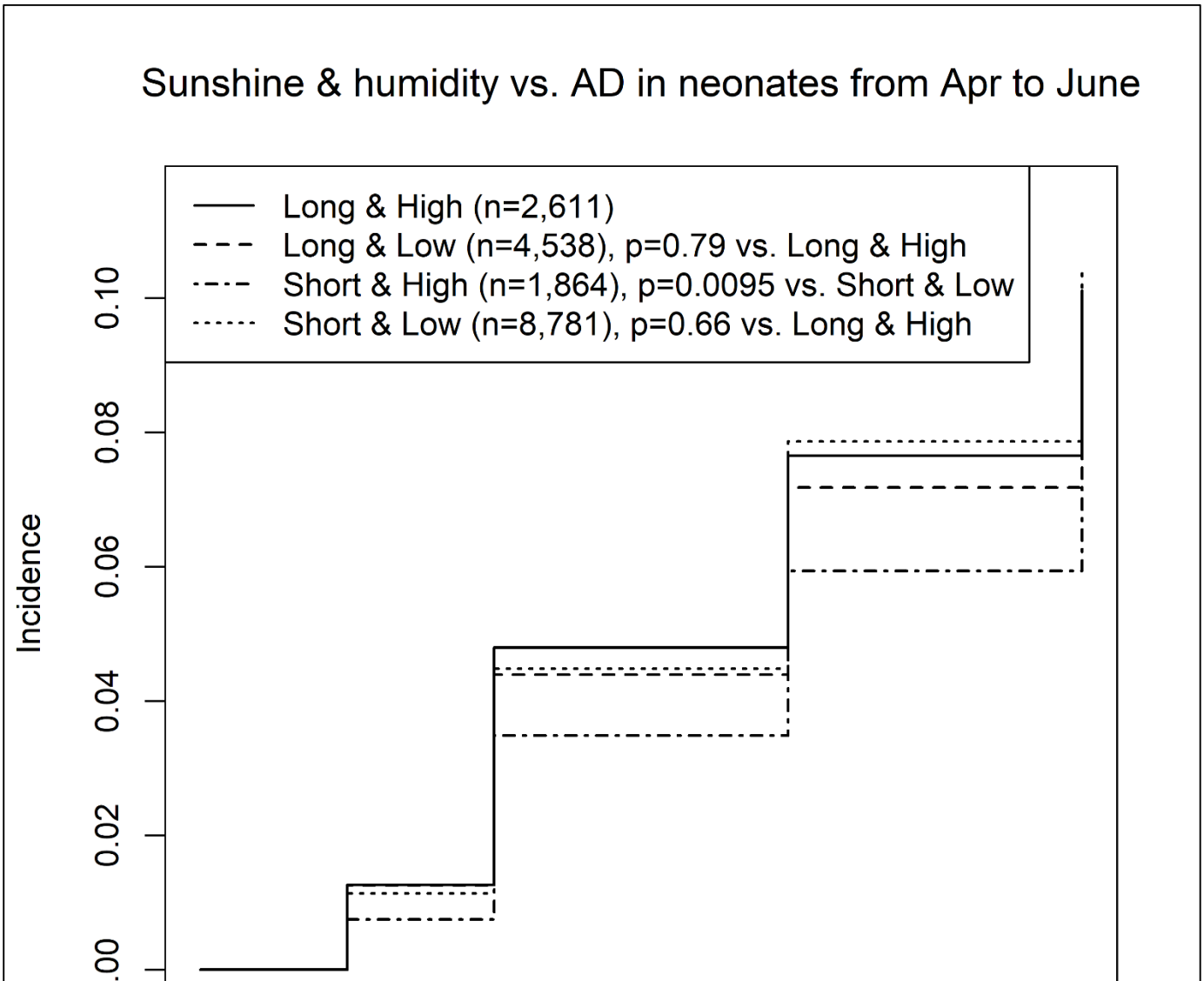


Supplementary figure 3. Incidence of atopic dermatitis among neonates who were born in January–March in regions with long/short mean sunshine durations and high/low mean humidity.



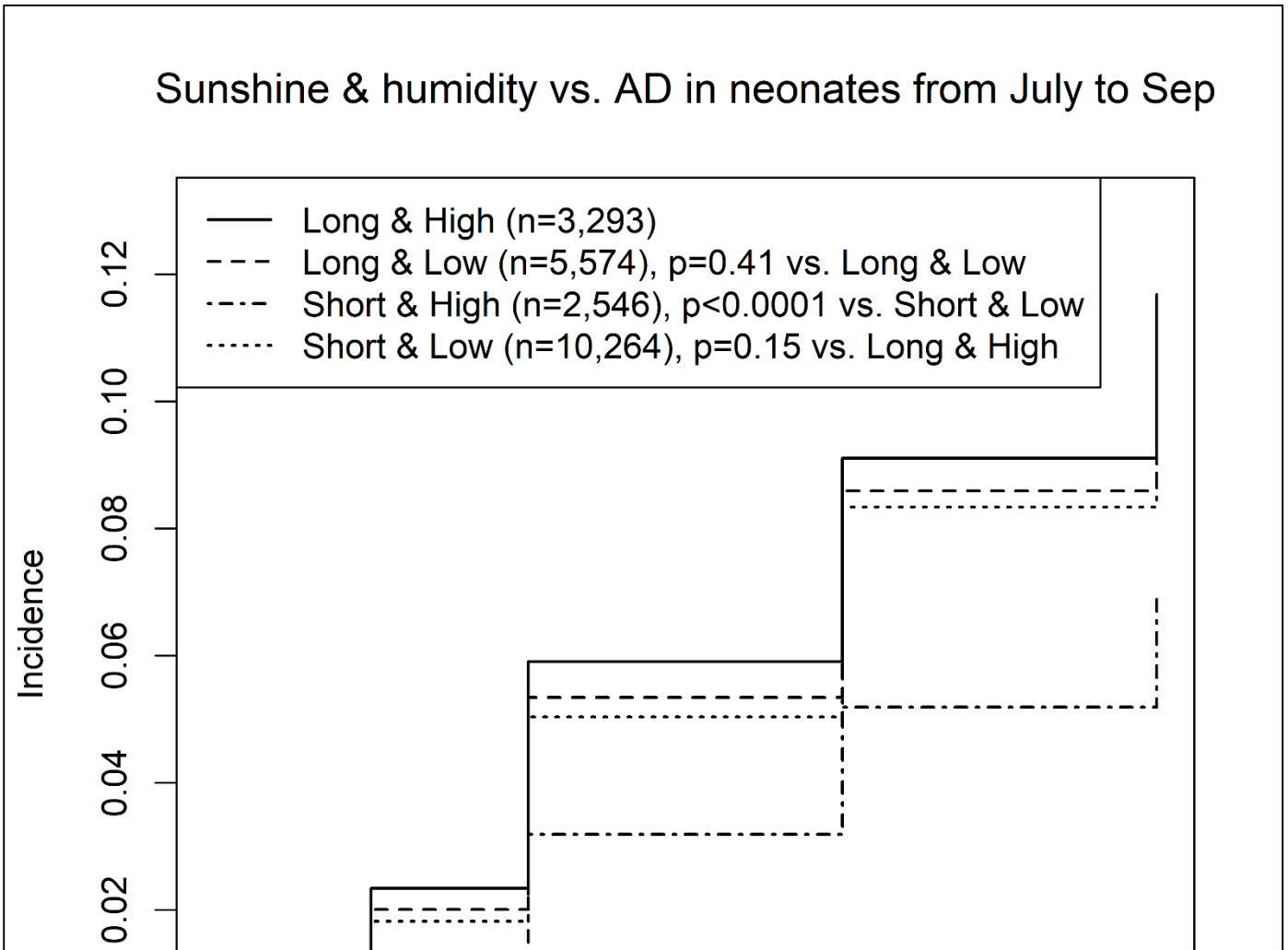
AD, atopic dermatitis.

Supplementary figure 4. Incidence of atopic dermatitis among neonates who were born in April–June in regions with long/short mean sunshine durations and high/low mean humidity.



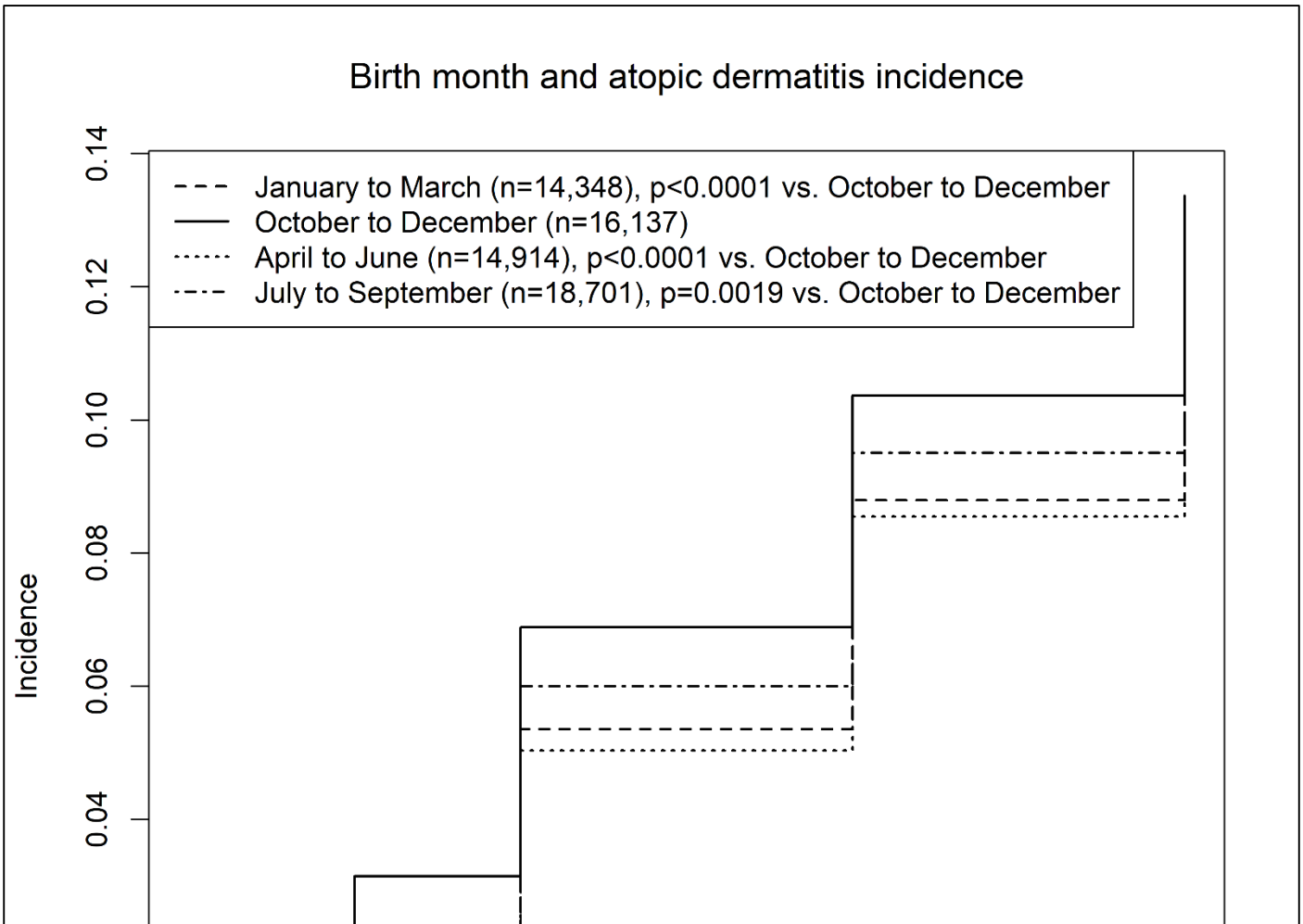
AD, atopic dermatitis.

Supplementary figure 5. Incidence of atopic dermatitis among neonates who were born in July–September in regions with long/short mean sunshine durations and high/low mean humidity.

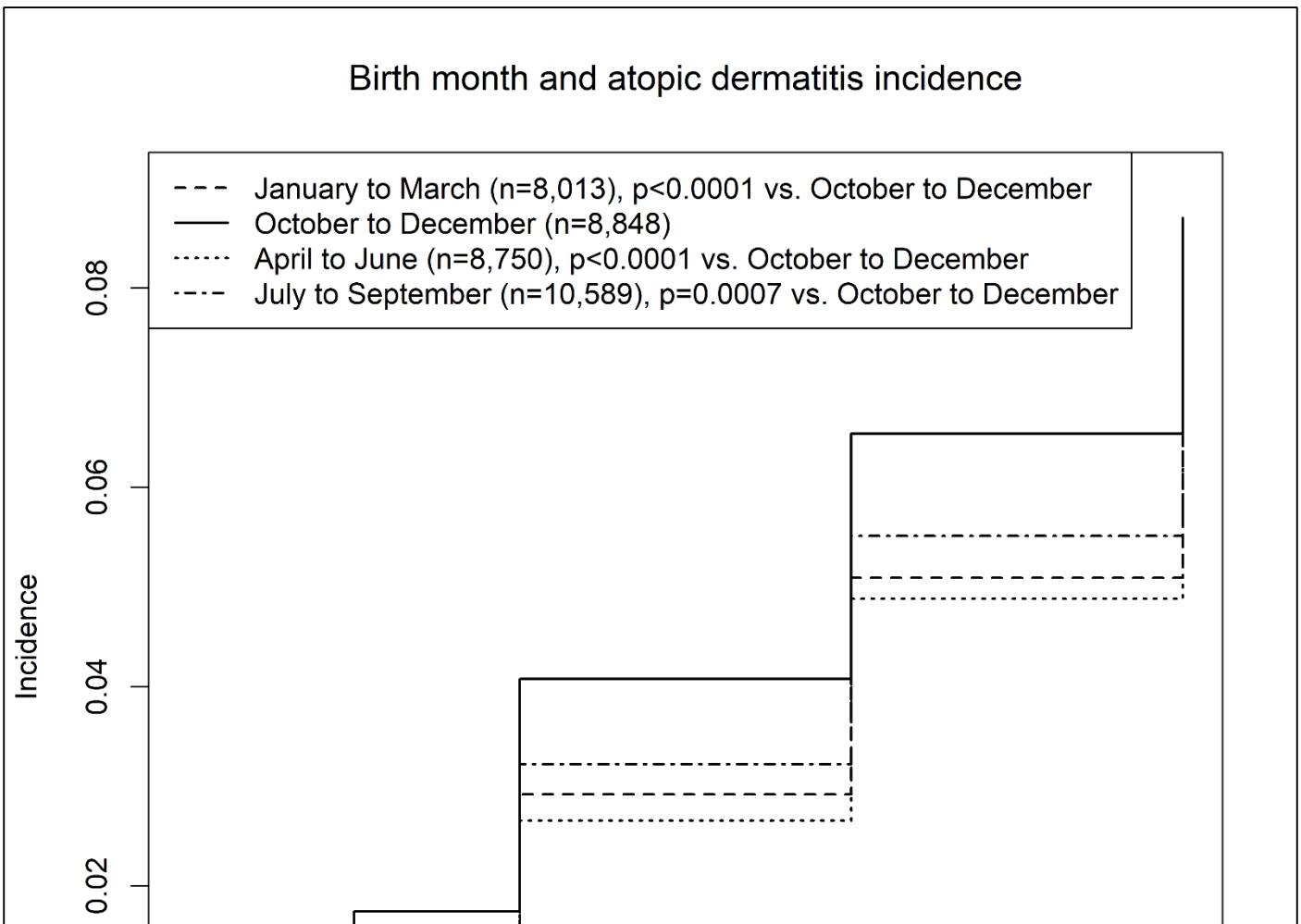


AD, atopic dermatitis.

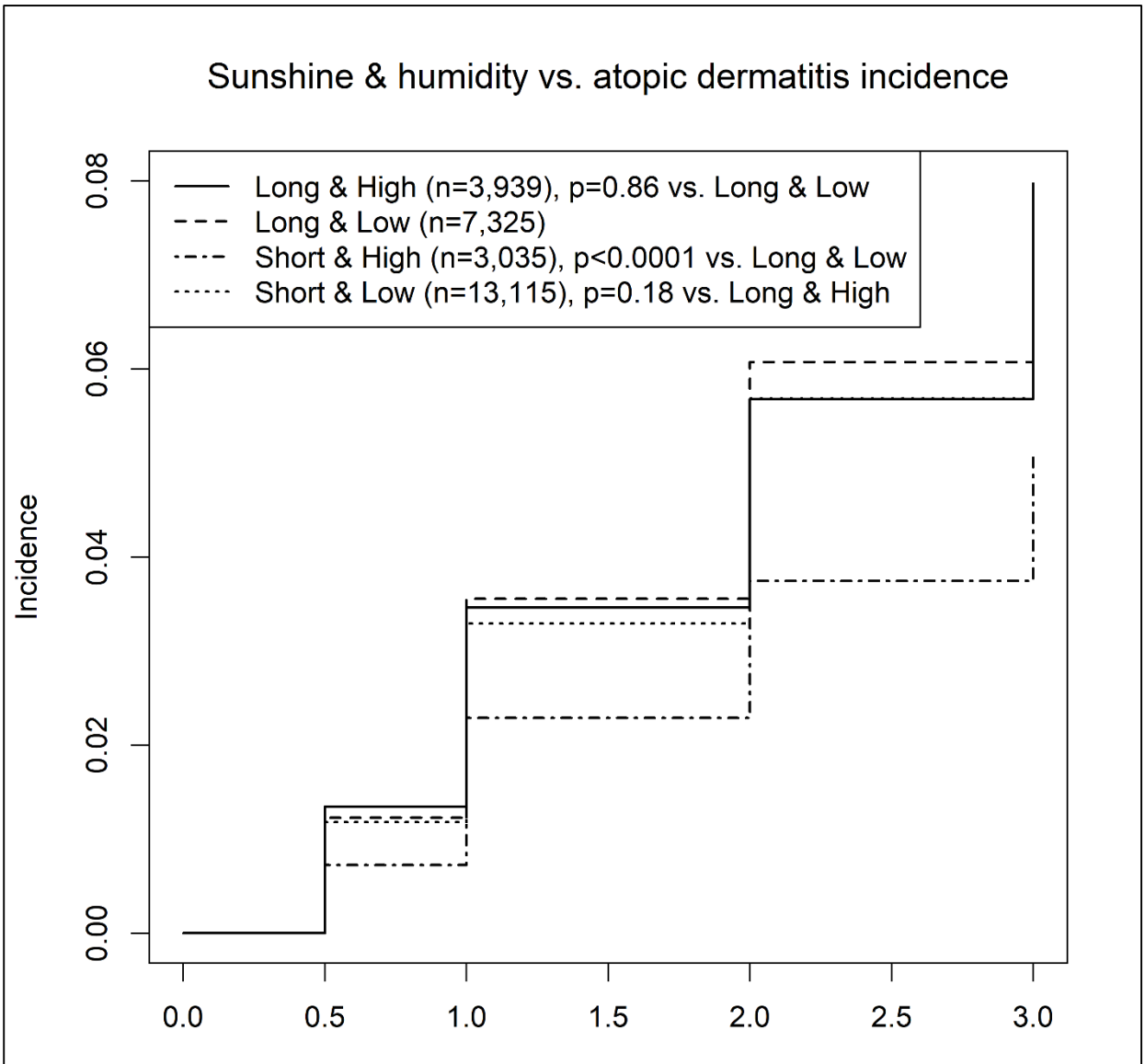
Supplementary figure 6. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.



Supplementary figure 7. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.



Supplementary figure 8. Incidence of atopic dermatitis in regions with long/short mean sunshine durations and high/low mean humidity, in children whose parents had no history of allergic disease.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	5
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	5
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	5
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	5-6
Bias	9	Describe any efforts to address potential sources of bias	6
Study size	10	Explain how the study size was arrived at	5
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	6
		(*b*) Describe any methods used to examine subgroups and interactions	6
		(*c*) Explain how missing data were addressed	Not Applicable
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	6
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	7
		(b) Give reasons for non-participation at each stage	Not Applicable
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	7
		(b) Indicate number of participants with missing data for each variable of interest	Not Applicable
Outcome data	15*	Report numbers of outcome events or summary measures	7
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Page 7 and figures 2 and 3
		(*b*) Report category boundaries when continuous variables were categorized	Figure 2 and supplementary figures 1 and 2
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Figures 4 and 5 and supplementary figures 3 to 8
Discussion			
Key results	18	Summarise key results with reference to study objectives	8
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	10
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	8–9
Generalisability	21	Discuss the generalisability (external validity) of the study results	9
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	11

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Association of the incidence of atopic dermatitis until 3 years old with birth month, sunshine duration, and humidity: Japan Environment and Children's Study

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Original research

Association of the incidence of atopic dermatitis until 3 years old with birth month, sunshine duration, and humidity: Japan Environment and Children's Study

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ABSTRACT

Objective To compare the incidence of atopic dermatitis in children aged from 6 months to 3 years across birth seasons and climate conditions.

Design Cohort study.

Setting Fifteen regional centres across Japan.

Participants A total of 100,304 children born from 2011 to 2014.

Exposure Birth month, sunshine duration, and humidity.

Primary outcome measure Incidence of atopic dermatitis.

Results The highest incidence of atopic dermatitis was in the months of October to December. The lowest incidence of atopic dermatitis was in the months of April to June and in periods with a long duration of sunshine and high humidity. Low humidity was significantly associated with a higher incidence of atopic dermatitis. However, this significant difference disappeared when the birth season and parental history of allergic disease were considered in multivariate analysis.

Conclusions In Japan, being born in the late autumn to early winter months is associated with a risk of developing atopic dermatitis. Sunshine duration and humidity from birth to 6 months of age, which may be associated with dry skin and itchiness, are not associated with the incidence of atopic dermatitis.

Strengths and limitations of this study

- Six monthly meteorological data were used, corresponding to individual children.
- The parental history of allergic disease was considered.
- A history of bacterial infection was not considered theoretically as a confounder.
- Metrological data of children's residence were not individual but averaged.
- The severity of atopic dermatitis was not analysed.

INTRODUCTION

Approximately 10%–20% of children have atopic dermatitis (AD).[1 2] Many genetic and environmental factors may be associated with the incidence and aggravation of AD.[3] An epidemiological investigation identifying the causal factors would be helpful for reducing the number of child patients who suffer from this disease from infancy.

Possible environmental factors of AD include seasonal climate conditions, chemical irritants, bacterial colonisation, psychological stress,[4] and birth month.[4] Among environmental factors, being born from autumn to winter in the northern hemisphere increases the risk of developing AD, while birth from spring to summer may decrease the incidence of AD.[5] The mechanism of this association could be confounded by prevailing seasonal viruses, flying natural antigens, or sunshine duration and humidity, which could be related to psychological stress, dry skin, and itchiness. Exposure to ultraviolet may improve skin barrier performance,[6] and may reduce the risk of developing AD.[7] Low humidity may be related to a high incidence of AD.[8] Relating birth cohort data[9 10] and metrological data[11] may help answer the question of how birth month is associated with the incidence of AD. Therefore, this study aimed to investigate how birth month is associated with the incidence of AD.

METHODS

Measures

Details on the Japan Environment and Children's Study (JECS) project are published elsewhere.[9] Briefly, the JECS comprises a cohort of 104,062 children born from 2011 to 2014 in 15 regional centres covering 18 prefectures across Japan.[12] We used the JECS data "jecs-ta-20190930-qsn" for generating questionnaires, which were sent to caregivers by post when their children were aged 6 months, 1 year, 2 years, and 3 years. We asked if physicians had diagnosed the children with AD.

In Japan, sunshine duration almost peaks on 21 June (the summer solstice) and is at its shortest on 21 December (the winter solstice). Humidity, which is lowest in winter, rises proportionally with a rise in sunshine duration to summer. Sunshine duration varies depending on regions from approximately 125 to 180 hours/month. Humidity also varies depending on region and month from approximately 50% to 80% in Japan. Therefore, sunshine duration and humidity of the 18 studied prefectures from the northern to southern regions of Japan varied. Overall in Japan, among seasons, summer has the longest sunshine duration and highest humidity, and winter has the shortest sunshine duration and lowest humidity.

We collected climate condition data per prefecture and month from the Japan Meteorological Agency website.[11] The sunshine duration was defined as hours with ≥120 Watt/m^2 of direct sunshine, as measured by a solarimeter. The mean sunshine duration and humidity of the 18 prefectures from April 2011 to March 2015 were 166.1 hours/month and 68.4%, respectively. These values were used as cut-off values for categorising children as being exposed to a long/short sunshine duration and high/low humidity while taking into account their resident area and birth month. For this categorisation, the mean sunshine duration and humidity in the child's resident area over 6 months beginning with the child's birth month were compared with the cut-off values. An example of this categorisation is that a child who was born in April

2011 would be categorised based on meteorological data from April to September 2011.

For considering a child's genetic predisposition to AD, we used a parental history of asthma, allergic rhinitis, pollen allergy, AD, allergic conjunctivitis, and/or food allergy. The father and mother were asked individually about a history of allergic diseases to determine their experience of each diagnosed disease by a physician.

Analyses

The 12 months of the year were categorised into four seasons in three different ways (i.e., starting with January–March, February–April, or March–May). We compared Kaplan–Meier curves of the incidence of AD among seasons by performing log-rank tests. The incidence of AD by birth month and season until 3 years of age was calculated. We also compared the incidence of AD using Kaplan–Meier curves for children who were born in regions with long vs. short sunshine, with high vs. low humidity, and with a long/short sunshine duration and high/low humidity. Because we found a difference in the incidence of AD among birth seasons, we compared this incidence among seasons by strata of children whose parents had a history of allergic disease and those who did not have a history of allergic disease. We performed Cox regression by birth season, humidity and parental history of allergy, which were considered to be risk factors of AD from Kaplan–Meier curves. Data from participants who were lost to follow-up or developed AD after 3 years of age were considered as being censored. We conducted all statistical analyses using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). Kaplan–Meier curves were drawn using RStudio version 1.2.1335 (R Project for Statistical Computing, Vienna, Austria). Two-sided p values of <0.05 were

considered to indicate a significant difference.

Patient and public involvement

Written informed consent was obtained from all participants. Patient consent for publication was not required. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

The number of participants who answered the questionnaire decreased with the child's age. By the ages of 6 months, 1 year, 2 years, and 3 years, 1715 of 100,304 children (response rate for 96.4%), 4505 of 90,549 children (response rate for 87.0%), 7299 of 84,859 children (response rate for 81.5%), and 9704 of 80,176 children (response rate for 77.0%), respectively, had developed AD. Supplementary Table 1 shows the characteristics of the participants. Figure 1 and Supplementary Figures 1–3 show the incidence of AD curves for birth months and seasons. Supplementary Table 2 shows the incidence rate of AD by birth month and season. The highest and lowest incidence of AD was observed in the October to December group and the April to June group, respectively (Figure 1).

We also assessed the incidence of AD among four climate categories, including combinations of a long/short sunshine duration and high/low humidity. High or low sunshine duration was not associated with the incidence of AD (Figure 2), while low humidity was associated with the incidence of AD compared with high humidity (Figure 3). Among the long/short sunshine duration and high/low humidity groups, the short

sunshine duration and low humidity group had a significantly higher incidence of AD than the long sunshine duration and low humidity group (Figure 4).

We also analysed the incidence of AD on the basis of parental history of any allergic disease. Supplementary Figures 4 and 5 show the incidence of AD by birth season, as stratified by parental history of allergic disease. The observed highest and the lowest incidence of AD shown in Figures 4 and 5 was consistent with that shown in Figure 1. The order of accumulated incidence of AD among the seasons did not change from 6 months to 3 years of age.

Table 1 shows the results of Cox proportional regression for risk factors of the incidence of AD. The adjusted hazard ratio showed that birth between October and December and the father's and mother's history of allergy were risk factors of AD in the child.

Table 1. Hazard ratios (95% confidence intervals) of possible factors involved in the incidence of atopic dermatitis at 3 years old.

Factors	Crude hazard ratio (confidence interval)	Adjusted hazard ratio (confidence interval)
Short vs. long sunshine duration	1.03 (0.99, 1.08)	—
Low vs. high humidity	1.06 (1.01, 1.11)	0.99 (0.95, 1.04)
Birth month between January and March	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
Birth month between April and June	Reference	Reference
Birth month between July and September	1.06 (0.99, 1.13)	1.05 (0.98, 1.13)
Birth month between October and December	1.20 (1.12, 1.28)	1.20 (1.12, 1.29)
Father's history of allergy	1.21 (1.16, 1.28)	1.18 (1.12, 1.24)
Mother's history of allergy	1.70 (1.62, 1.78)	1.69 (1.61, 1.77)

DISCUSSION

The current study showed that the incidence of AD was highest when born between October and December, and lowest when born between April and June. Consideration of parental history of allergic disease did not alter this association. Multivariate analysis showed that sunshine duration or humidity was not associated with the incidence of AD.

Potential aetiologies of this association are bacterial infection, dry air, high solar radiation/sunshine hours, and atmospheric pressure. Dry skin and itchiness, which develop into AD, are common in low humidity. In the USA, a higher incidence of AD is associated with indoor heating use and low humidity, ultraviolet exposure, and outdoor temperature.[13] In Japan, a negative correlation between humidity and dermatological visits concerning AD was observed.[14] In our study, we did not observe a clear correlation between high or low humidity and the risk of AD, which suggested that humidity may not be critical for inducing AD.

In Japan, AD shows remittance in 50% of 4-month-old patients before the age of 18 months. However, a previous study reported a high cumulative incidence rate of AD of 30% in children who were younger than 3 years.[15] In mice, low humidity caused a higher cutaneous immune reaction by an increase in Langerhans cells and penetration of allergen.[16] The mean humidity in Japan was 70% in 2016, which is not high compared with other countries.[17] High humidity is clearly associated with a higher incidence of hand, foot and mouth disease with fever, ulcers, and vesicles.[18] Dry and itchy skin are caused by low humidity and

low temperature.[8] However, in this study, there was no effect of high or low humidity on the risk of AD when birth month and parental history of allergic disease were considered (Table 1). Therefore, in the present children, humidity did not appear to be important for inducing AD. Our study also did not suggest that a long sunshine duration induces AD.

Ultraviolet lighting is sometimes used clinically for reducing itchiness from severe AD.[19] However, a long sunshine duration can also cause dry skin, which is a risk factor of AD. Furthermore, heat from a long sunshine duration can cause sweating, leading to itchiness and psychological stress from discomfort, both of which can exacerbate AD. In Japan, humidity is fairly constant. Therefore, we initially suspected that in Japan, itchiness and psychological stress from long duration of sunshine may be a cause of AD in children. However, in contrast to our speculation, a combination of short sunshine duration and low humidity was associated with the highest incidence of AD (Figure 4).

Notably, the association between the incidence rate of AD across birth seasons, sunshine duration, and humidity levels hardly changed from 6 months old to 3 years old (Figures 1 and 4). This finding indicates that environmental factors with an adverse or preventive effect persist through early childhood. Allergic predisposition may not be determined until 6 months of age. Before that age, most infants only drink milk and do not eat allergenic solid products. A meta-analysis did not show clear evidence for a protective effect of breast feeding on the incidence of AD.[20] Our analysis did not examine feeding behaviour of the children.

Confounding factors of our analysis need to be considered. When we considered genetic

predisposition, the following results were the same for children of parents with and without allergic diseases. A high incidence of AD was found in children who were born in October to December (Figure 1, Supplementary figures 4 and 5 and Table 1). Because parents would not expect baby by genetic predisposition, the factor could not have theoretically confounded the observed associations.

Serum vitamin D levels may be involved in the association between birth month and the incidence of AD. Maternal vitamin D supplementation does not affect the risk of AD at 3 years old.[21] However, in an Australian study, a far distance from the equator was associated with a higher prevalence of eczema.[22] Ultraviolet B irradiation decreases inflammation and promotes skin barrier function.[6] Our data showed that birth between April and June was the most protective against the incidence of AD. A high or low prevalence of AD among birth seasons was preserved from 6 months to 3 years old. These data suggest that strong sunlight from birth to 6 months old, rather than sunshine duration, may be associated with the incidence of AD through development of the infant's skin barrier function.

Limitations

Our results are limited by infection not being examined as a potential confounder. Second, we used 6 monthly means of sunshine duration and humidity. Individual experience was not considered. Third, the incidence of AD was reported by caregivers based on the physician's diagnosis. There could have been recall bias of caregivers. Fourth, physicians who diagnosed children included specialists of AD and non-specialists. Physicians might have underdiagnosed AD in infancy because this diagnosis could cause stigma to children and caregivers.[23] Fifth, we were unable to consider details of AD. Because AD can be caused by

several mechanisms, analysis of disease severity may lead a further understanding of its aetiology.

Conclusions

Births in October to December have the highest incidence of AD. This result is consistent when a parental history of allergic disease is considered. A high or low incidence of AD by birth season persists from 6 months through to 3 years in childhood. Although the lowest incidence of AD is found in residents in regions with a long sunshine duration and high humidity in crude data, multivariate analysis shows no association of sunshine duration and humidity with the incidence of AD.

Footnotes

Contributors: All of the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY and MM conceived the study. HY and MM contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, MM, AT, RK, SH, TO, YA, and KM wrote the first draft of the manuscript. All authors contributed to revision of the manuscript. ZY was responsible for data integrity. ZY obtained funding.

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Competing interests: None.

Ethics approval: The protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the Ethics Committees of all participating institutions, in accordance with the ethical guidelines and regulations of the Declaration of Helsinki.

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

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Figure legends

Figure 1. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from January.

Figure 2. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration.

Figure 3. Incidence of atopic dermatitis in regions with a high/low mean humidity.

Figure 4. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity.

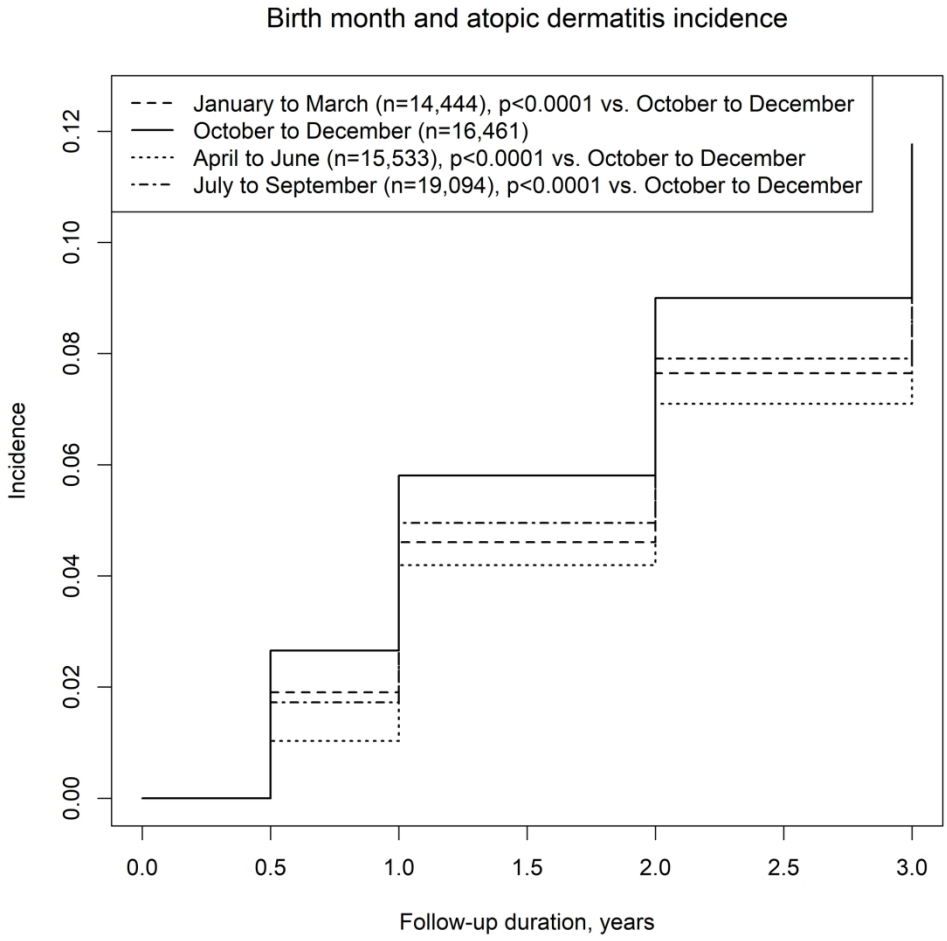
Supplementary Figure 1. Incidence of atopic dermatitis in relation to birth month.

Supplementary Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from February.

Supplementary Figure 3. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from March.

Supplementary Figure 4. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.

Supplementary Figure 5. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.



Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from January.

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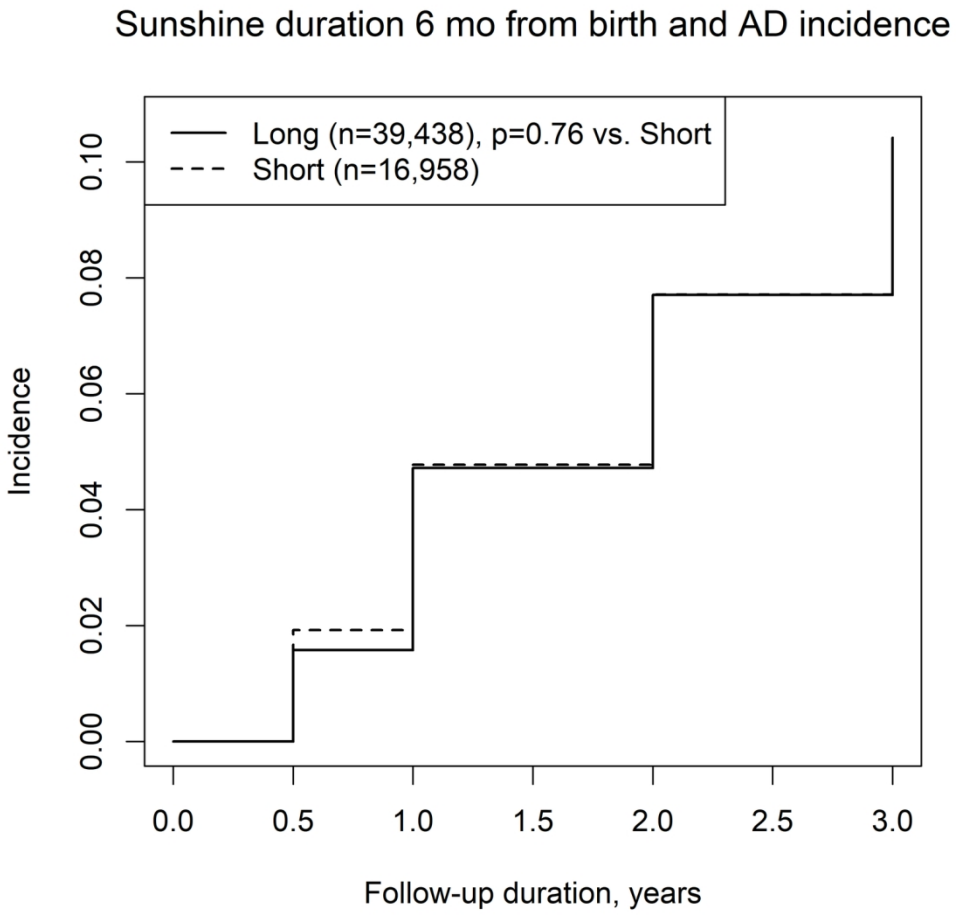

Incidence of atopic dermatitis in regions with a long/short mean sunshine duration.

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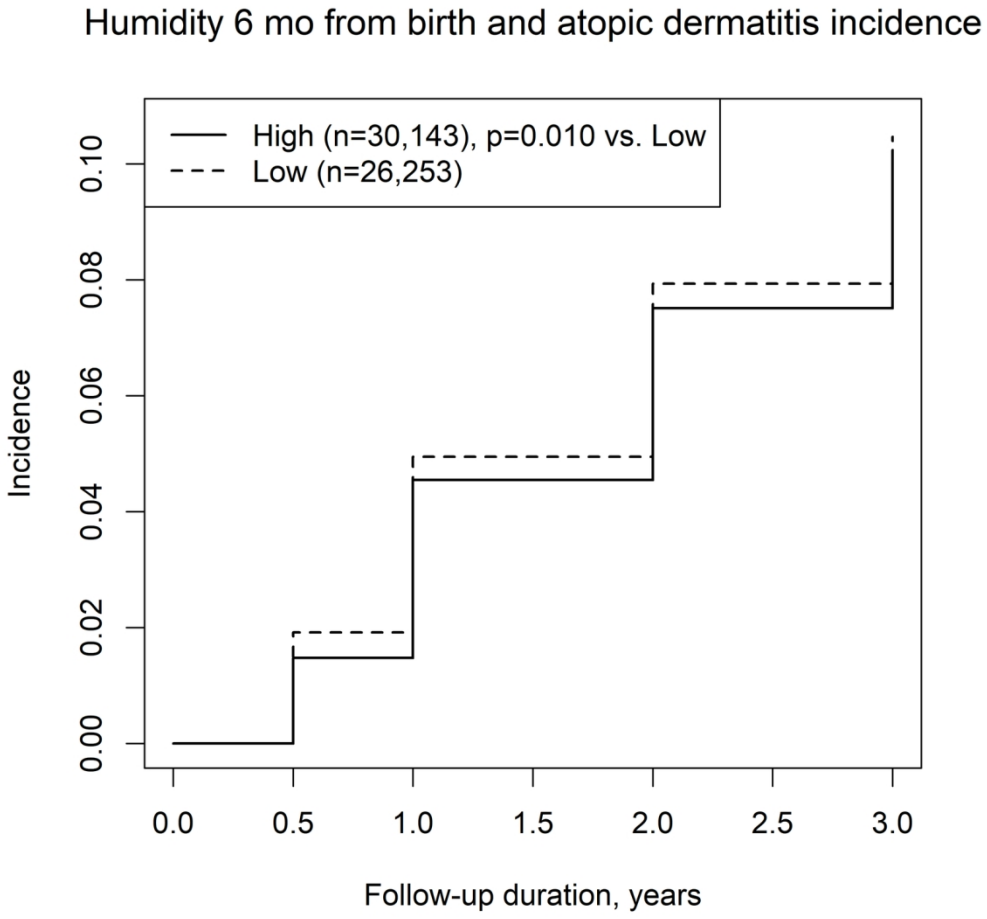
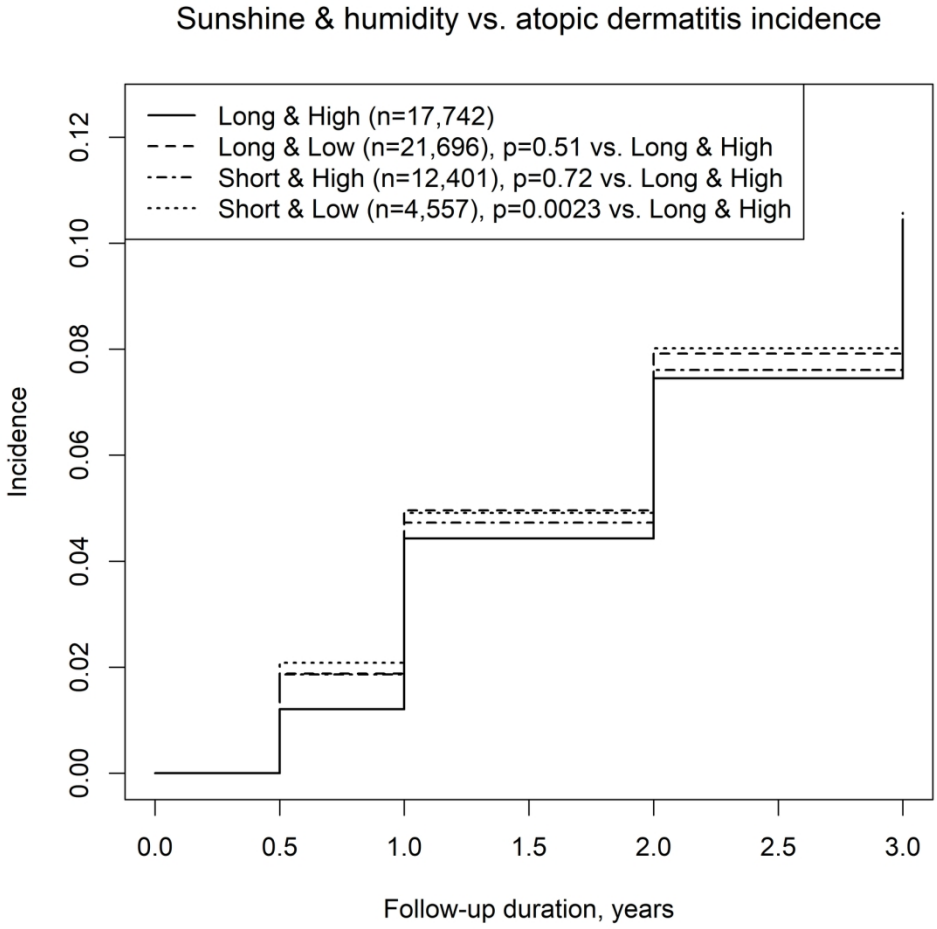


Incidence of atopic dermatitis in regions with a high/low mean humidity.

140x140mm (300 x 300 DPI)



Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity.

163x163mm (300 x 300 DPI)

Supplementary Table 1. Baseline characteristics of participants and climate data.

Characteristic	
Male sex	51,396 (51.3)
Maternal history of allergic disease	49,197 (49.2)
Paternal history of allergic disease	21,327 (21.3)
Sunshine duration, hours/month	169 (26)
Humidity, %	67.3 (5.2)
Climate category for sunshine duration and humidity	
Long and high	15,240 (18.6)
Long and low	31,671 (38.6)
Short and high	19,401 (23.7)
Short and low	15,738 (19.2)

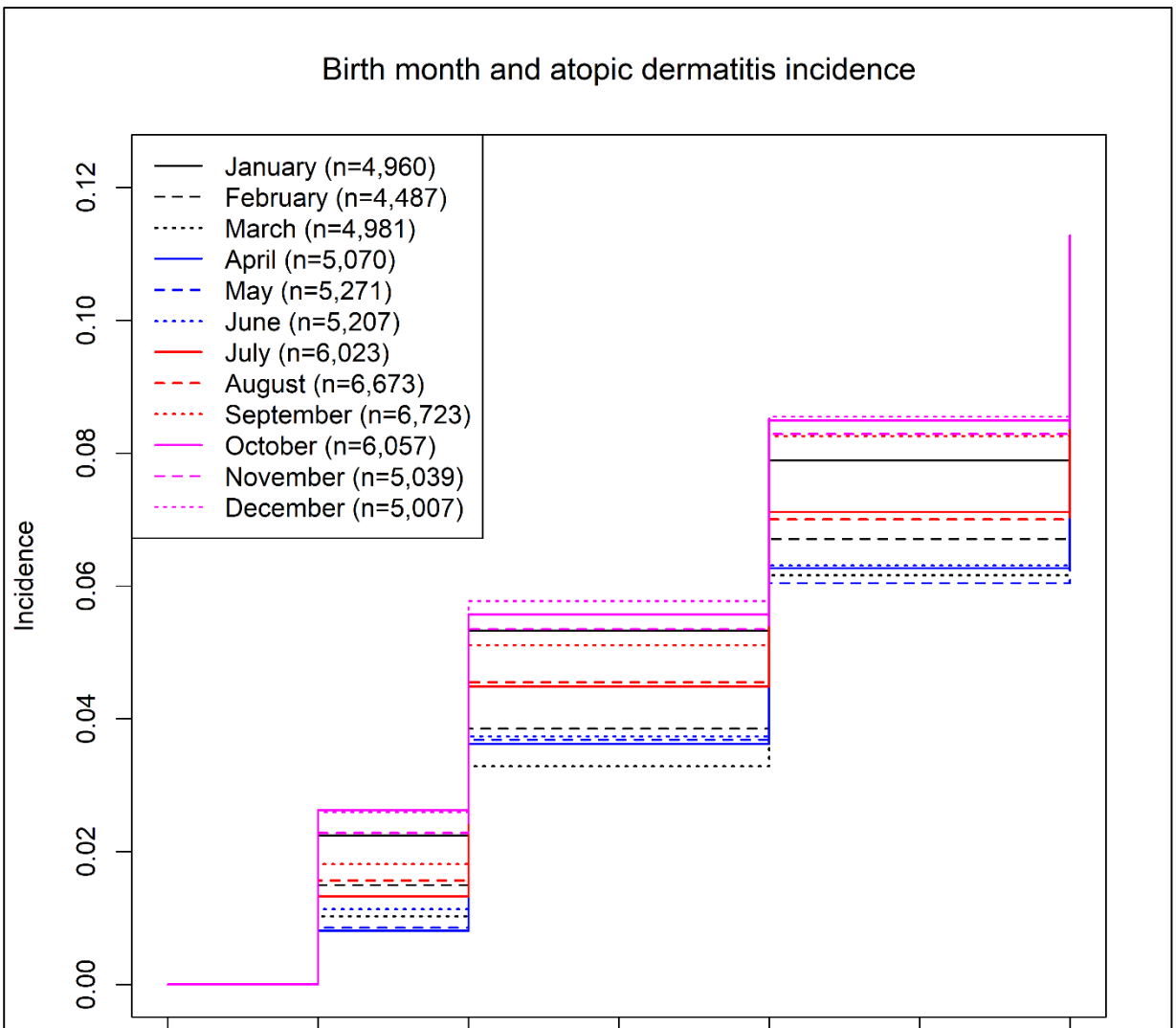
Values are mean (SD) or number (%).

Supplementary Table 2. Incidence rate of atopic dermatitis to 3 years of age by birth month.

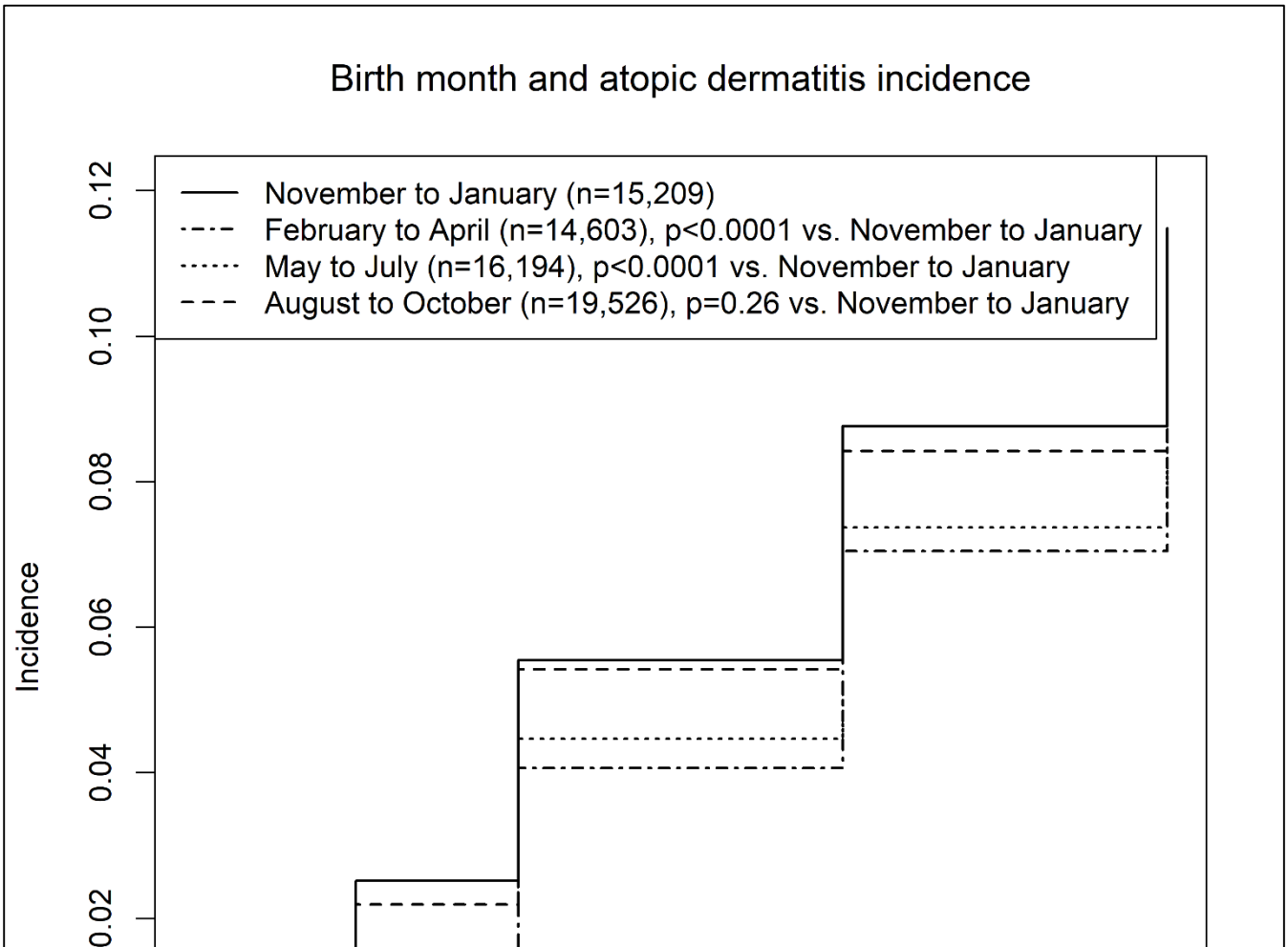
Timing of birth	Number of children	Mean person-years	Incidence per 100 person-years
Birth month			
January	7762	2.57	4.95
February	6987	2.59	4.34
March	7612	2.62	4.21
April	7721	2.60	4.24
May	8081	2.61	5.15
June	7862	2.58	4.54
July	8909	2.6	4.50
August	10,079	2.59	4.42
September	10,302	2.57	5.01
October	9457	2.56	5.38
November	7835	2.55	5.19
December	7693	2.55	5.21
Season			
January to March	22,361	2.59	4.50
April to June	23,664	2.60	4.31
July to September	29,290	2.59	4.65
October to December	24,985	2.55	5.27

1

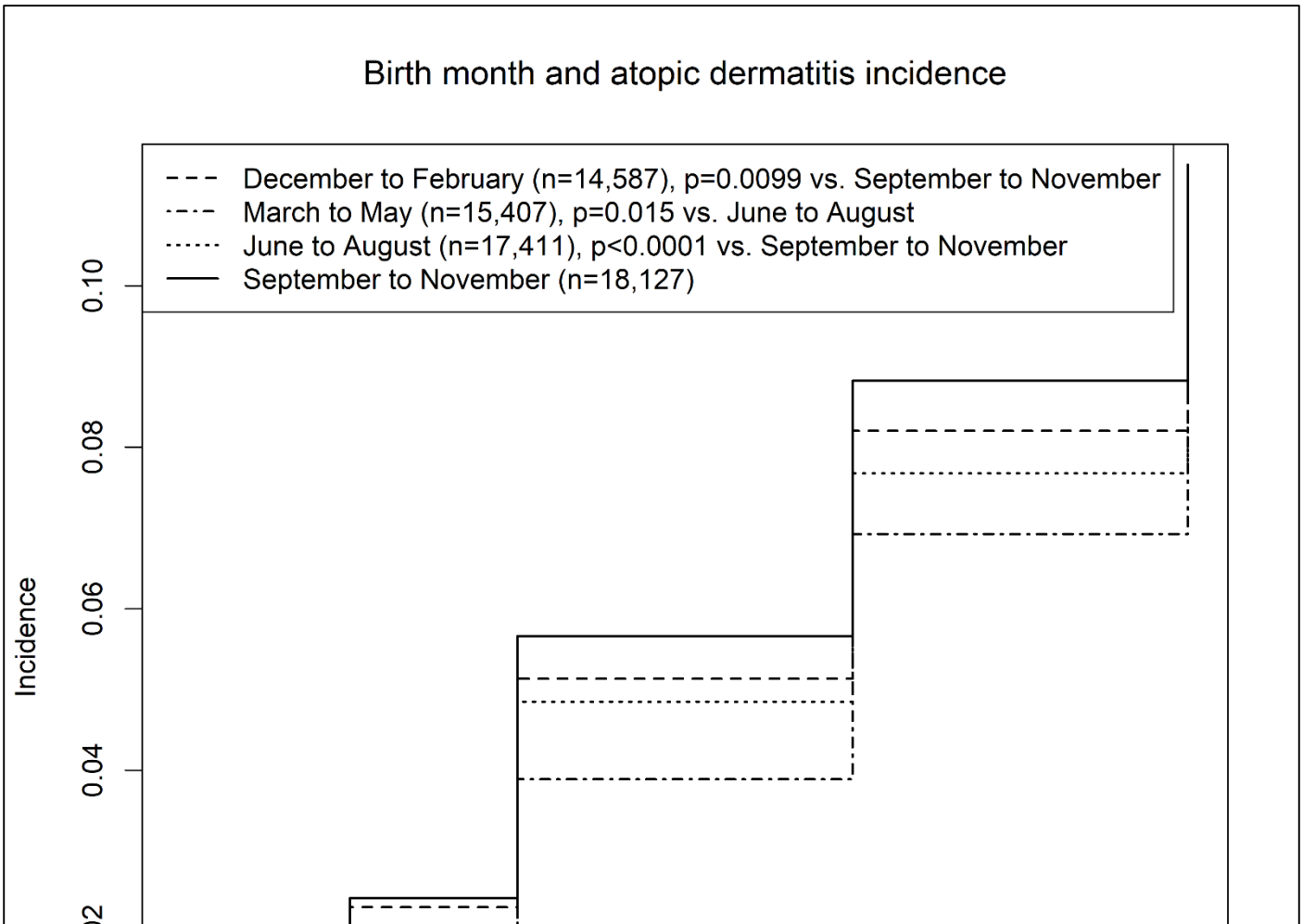
Supplementary Figure 1. Incidence of atopic dermatitis in relation to birth month.



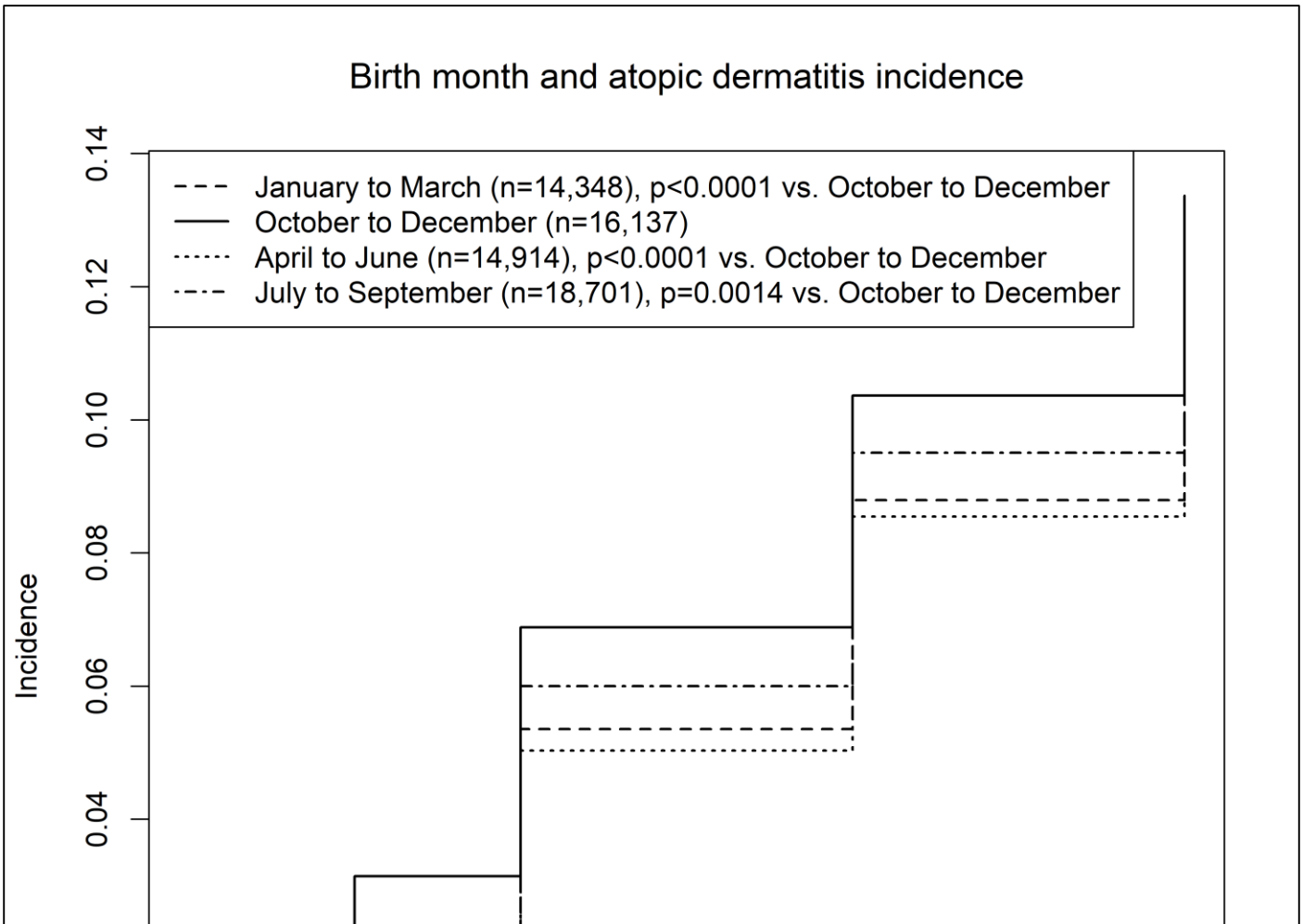
Supplementary Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from February.



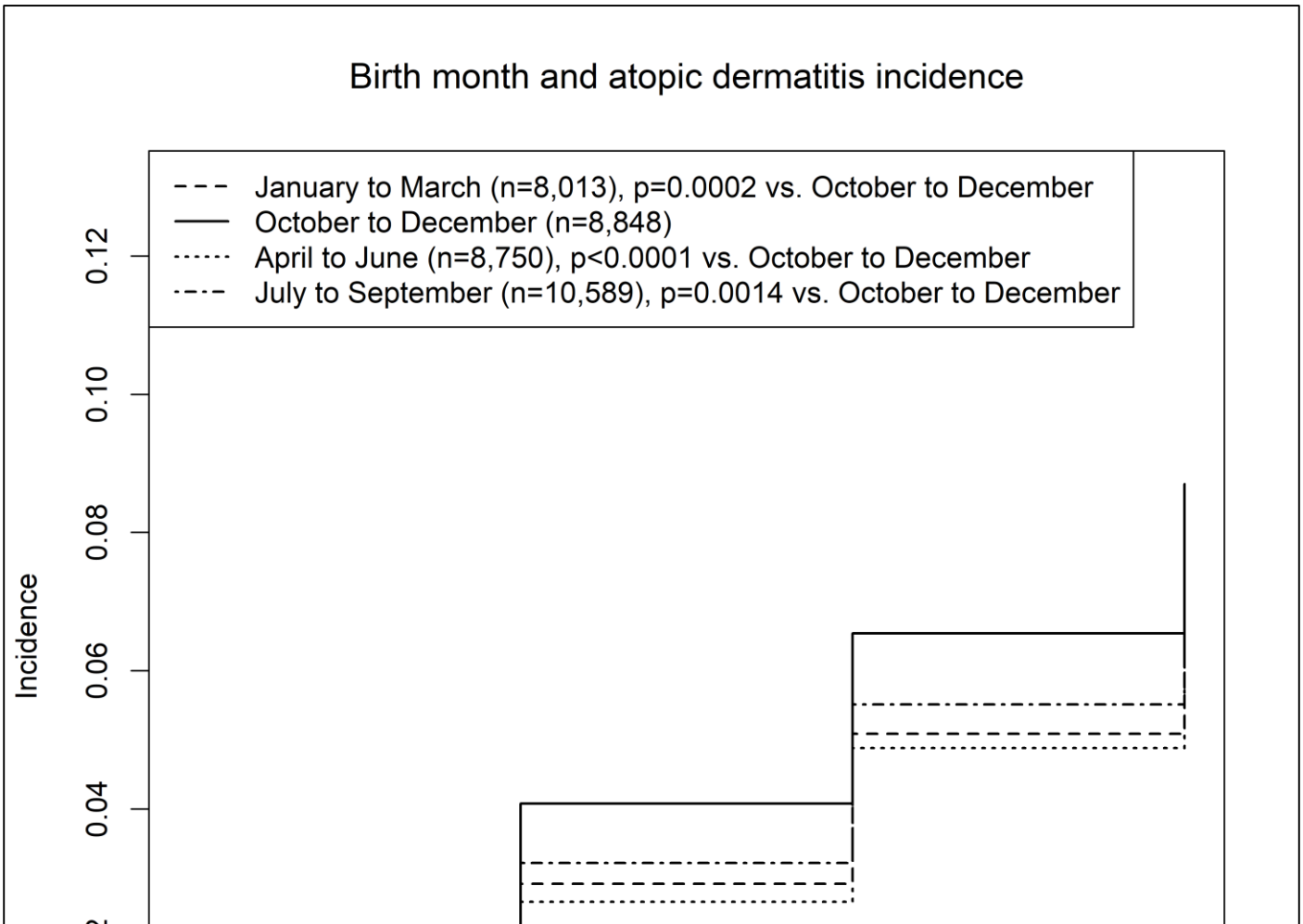
Supplementary Figure 3. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from March.



Supplementary Figure 4. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.



Supplementary Figure 5. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	7, 8
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supplementary table 1
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figures 1-4, Supplementary figures 1-3, Table 1
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary figures 4 and 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10–12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

Association of the incidence of atopic dermatitis until 3 years old with birth month and with sunshine duration and humidity in the first 6 months of life: Japan Environment and Children's Study

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Secondary Subject Heading:	Paediatrics, Epidemiology, Public health, Genetics and genomics
Keywords:	Paediatric dermatology < DERMATOLOGY, EPIDEMIOLOGY, Community child health < PAEDIATRICS, PREVENTIVE MEDICINE, Paediatric clinical genetics & dysmorphology < GENETICS, IMMUNOLOGY

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Original research

Association of the incidence of atopic dermatitis until 3 years old with birth month and with sunshine duration and humidity in the first 6 months of life: Japan Environment and Children's Study

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ABSTRACT

Objective To compare the incidence of atopic dermatitis in children aged from 6 months to 3 years across birth seasons and climate conditions.

Design Cohort study.

Setting Fifteen regional centres across Japan.

Participants A total of 100,304 children born from 2011 to 2014.

Exposure Birth month, and mean sunshine duration (short/long) and humidity (high/low) in the first 6 months of life.

Primary outcome measure Incidence of atopic dermatitis.

Results The highest incidence of atopic dermatitis was in children born in the months of October to December. The lowest incidence of atopic dermatitis was in the months of April to June and in periods with a long duration of sunshine and high humidity. Low humidity was significantly associated with a higher incidence of atopic dermatitis. However, this significant difference disappeared when the birth season and parental history of allergic disease were considered in multivariate analysis.

Conclusions In Japan, being born in the late autumn to early winter months is associated with a risk of developing atopic dermatitis until the age of 3 years. Sunshine duration and humidity from birth to 6 months of age are not associated with the incidence of atopic dermatitis.

Strengths and limitations of this study

- Six-monthly meteorological data were used, corresponding to individual children.
- The parental history of allergic disease was considered.
- A history of bacterial infection was not considered theoretically as a confounder.
- Metrological data of children's residence were not individual but averaged.
- The severity of atopic dermatitis was not analysed.

INTRODUCTION

Approximately 10%–20% of children have atopic dermatitis (AD).[1 2] Many genetic and environmental factors may be associated with the incidence and aggravation of AD.[3] An epidemiological investigation identifying factors associated with AD would be helpful for reducing the number of child patients who suffer from this disease from infancy.

Possible environmental factors of AD include seasonal climate conditions, chemical irritants, bacterial colonisation, psychological stress,[4] and birth month.[4] Among environmental factors, being born from autumn to winter in the northern hemisphere increases the risk of developing AD, while birth from spring to summer may decrease the incidence of AD.[5] The mechanism of this association could be confounded by prevailing seasonal viruses, airborne natural antigens, or sunshine duration and humidity, which could be related to psychological stress, dry skin, and itchiness. Exposure to ultraviolet may improve skin barrier performance,[6] and may reduce the risk of developing AD.[7] Low humidity may be related to a high incidence of AD.[8] Relating birth cohort data[9-12] and metrological data[13] may help answer the question of how birth month is associated with the incidence of AD. Therefore, this study aimed to investigate how birth month is associated with the incidence of AD.

METHODS

Measures

Details on the Japan Environment and Children's Study (JECS) project are published elsewhere.[9] Approximately 100,000 expecting mothers who lived in designated study areas were recruited over 3 years from January 2011. Participating children were followed until they reached 13 years old. Exposure to environmental factors was assessed by chemical analyses of bio-specimens (blood, cord blood, urine, breast milk, and hair), household environment measurements, and computational simulations using monitoring data and questionnaires. One of the JECS' priority outcomes was immune system disorders (allergic diseases).[9] The JECS comprises a cohort of 104,062 children born from 2011 to 2014 in 15 Regional Centres covering 18 prefectures across Japan.[14] We used the JECS data "jecs-ta-20190930-qsn" for generating questionnaires, which were sent to caregivers by post when their children were aged 6 months, 1 year, 2 years, and 3 years. We asked if physicians had diagnosed the children with AD.

In Japan, sunshine duration almost peaks on 21 June (the summer solstice) and is at its shortest on 21 December (the winter solstice). Humidity, which is lowest in winter, rises proportionally with a rise in sunshine duration to summer. Sunshine duration varies depending on regions from approximately 125 to 180 hours/month. Humidity also varies depending on region and month from approximately 50% to 80% in Japan. Therefore, sunshine duration and humidity of the 18 studied prefectures from the northern to southern regions of Japan varied. Overall in Japan, among seasons, summer has the longest sunshine duration and highest humidity, and winter has the shortest sunshine duration and lowest humidity.

We collected climate condition data per prefecture and month from the Japan Meteorological Agency website.[13] The sunshine duration was defined as hours with ≥120 Watt/m^2 of direct sunshine, as measured by a solarimeter. The mean sunshine duration and humidity of the 18 prefectures from April 2011

to March 2015 were 166.1 (standard deviation: 45.4) hours/month and 68.4% (standard deviation: 7.6%), respectively. These values were used as cut-off values for categorising children as being exposed to a long/short sunshine duration and high/low humidity while taking into account their resident area and birth month. For this categorisation, the mean sunshine duration and humidity in the child's resident area over 6 months beginning with the child's birth month were compared with the cut-off values. An example of this categorisation is that a child who was born in April 2011 would be categorised on the basis of meteorological data from April to September 2011.

For considering a child's genetic predisposition to AD, we used a parental history of asthma, allergic rhinitis, pollen allergy, AD, allergic conjunctivitis, and/or food allergy. The father and mother were asked individually about a history of allergic diseases to determine their experience of each diagnosed disease by a physician.

Analyses

The 12 months of the year were categorised into four seasons in three different ways (i.e., starting with January to March, February to April, or March to May). We compared Kaplan–Meier curves of the incidence of AD among seasons by performing log-rank tests. The incidence of AD by birth month and season until 3 years of age was calculated. We also compared the incidence of AD using Kaplan–Meier curves for children who were born in regions with long vs. short sunshine, with high vs. low humidity, and with a long/short sunshine duration and high/low humidity. Because we found a difference in the incidence of AD among birth seasons, we compared this incidence among seasons by strata of children whose parents

had a history of allergic disease and those who did not have a history of allergic disease. We performed Cox regression by birth season, humidity, and parental history of allergy, which were considered to be risk factors of AD from Kaplan–Meier curves. Data from participants who were lost to follow-up or developed AD after 3 years of age were considered as being censored. We conducted all statistical analyses using SAS statistical software version 9.4 (SAS Institute, Cary, NC, USA). Kaplan–Meier curves were drawn using RStudio version 1.2.1335 (R Project for Statistical Computing, Vienna, Austria). Two-sided p values of <0.05 were considered to indicate a significant difference.

Patient and public involvement

Written informed consent was obtained from all participants. Patient consent for publication was not required. Patients or the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

RESULTS

The number of participants who answered the questionnaire decreased with the child's age. By the ages of 6 months, 1 year, 2 years, and 3 years, 1715 of 100,304 children (response rate: 96.4%), 4505 of 90,549 children (response rate: 87.0%), 7299 of 84,859 children (response rate: 81.5%), and 9704 of 80,176 children (response rate for 77.0%), respectively, had developed AD. Supplementary Table 1 shows the characteristics of the participants. The highest and lowest incidence of AD was observed in the October to December group and the April to June group, respectively (Figure 1). The overall incidence per 100 person-

years varied from 5.27 (October to December) to 4.31 (April to June) (Supplementary Table 2). By month, the highest incidence was in children born in October and December (Supplementary Figure 1). Supplementary Figures 2 and 3 show the results after varying how the months were grouped. The order of accumulated incidence of AD among the seasons did not change much from 6 months to 3 years old.

We also assessed the incidence of AD among four climate categories, including combinations of a long/short sunshine duration and high/low humidity, in the first 6 months of life. High or low sunshine duration was not associated with the incidence of AD (Figure 2), while low humidity was associated with the incidence of AD compared with high humidity (Figure 3). Among the long/short sunshine duration and high/low humidity groups, the short sunshine duration and low humidity group had a significantly higher incidence of AD than the long sunshine duration and low humidity group (Figure 4).

We also analysed the incidence of AD based on parental history of any allergic disease. Supplementary Figures 4 and 5 show the incidence of AD by birth season, as stratified by parental history of allergic disease. The observed highest and lowest incidence of AD shown in Supplementary Figures 4 and 5 was consistent with that shown in Figure 1.

Table 1 shows the results of Cox proportional regression for risk factors of the incidence of AD. The adjusted hazard ratio showed that birth between October and December and the father's and mother's history of allergy were risk factors of AD until the age of 3 years in the child.

Table 1. Hazard ratios (95% confidence intervals) of possible factors involved in the incidence of atopic dermatitis until 3 years old.

Factors	Crude hazard ratio (confidence interval)	Adjusted hazard ratio (confidence interval)
Short vs. long sunshine duration	1.03 (0.99, 1.08)	—
Low vs. high humidity	1.06 (1.01, 1.11)	0.99 (0.95, 1.04)
Birth month between January and March	1.02 (0.95, 1.09)	1.02 (0.95, 1.09)
Birth month between April and June	Reference	Reference
Birth month between July and September	1.06 (0.99, 1.13)	1.05 (0.98, 1.13)
Birth month between October and December	1.20 (1.12, 1.28)	1.20 (1.12, 1.29)
Father's history of allergy	1.21 (1.16, 1.28)	1.18 (1.12, 1.24)
Mother's history of allergy	1.70 (1.62, 1.78)	1.69 (1.61, 1.77)

DISCUSSION

The current study showed that the incidence of AD until the age of 3 years was highest when children were born between October and December and lowest when they were born between April and June. Consideration of parental history of allergic disease did not alter this association. Multivariate analysis showed that sunshine duration or humidity was not associated with the incidence of AD.

Potential aetiologies of this association are bacterial infection, dry air, high solar radiation/sunshine hours, and atmospheric pressure. Dry skin and itchiness, which develop into AD, are common in low humidity. In the USA, a higher incidence of AD is associated with indoor heating use and low humidity, ultraviolet exposure, and outdoor temperature.[15] In Japan, a negative correlation between humidity and dermatological visits concerning AD was observed.[16] In our study, we did not observe a clear correlation between high or low humidity in the first 6 months of life and the risk of AD, which suggested that humidity

is not critical for inducing AD.

In Japan, AD shows remittance in 50% of 4-month-old patients before the age of 18 months. However, a previous study reported a high cumulative incidence rate of AD of 30% in children who were younger than 3 years.[17] In mice, low humidity caused a higher cutaneous immune reaction by an increase in Langerhans cells and penetration of allergen.[18] The mean humidity in Japan was 70% in 2016, which is not high compared with other countries.[19] High humidity is clearly associated with a higher incidence of hand, foot and mouth disease with fever, ulcers, and vesicles.[20] Dry and itchy skin are caused by low humidity and low temperature.[8] However, in this study, there was no effect of high or low humidity on the risk of AD when birth month and parental history of allergic disease were considered (Table 1). Therefore, in the present children, humidity did not appear to be important for inducing AD. Our study also did not suggest that a long sunshine duration induces AD.

Ultraviolet lighting is sometimes used clinically for reducing itchiness from severe AD.[21] However, a long sunshine duration can also cause dry skin, which is a risk factor of AD. Furthermore, heat from a long sunshine duration can cause sweating, leading to itchiness and psychological stress from discomfort, both of which can exacerbate AD. In Japan, humidity is fairly constant. Therefore, we initially suspected that in Japan, itchiness and psychological stress from a long duration of sunshine may be a cause of AD in children. However, in contrast to our speculation, a combination of short sunshine duration and low humidity was associated with the highest incidence of AD (Figure 4).

Notably, the association between the incidence rate of AD across birth seasons, sunshine duration,

and humidity levels hardly changed from 6 months to 3 years old (Figures 1 and 4). This finding indicates that environmental factors with an adverse or preventive effect persist through early childhood. Allergic predisposition may not be determined until 6 months of age. Before that age, most infants only drink milk and do not eat allergenic solid products. A meta-analysis did not show clear evidence for a protective effect of breast feeding on the incidence of AD.[22] Our analysis did not examine feeding behaviour of the children.

Confounding factors of our analysis need to be considered. When we considered genetic predisposition, we found a high incidence of AD in children who were born in October to December, regardless of whether their parents had allergic diseases (Figure 1, Supplementary Figures 4 and 5, and Table 1). Because parents do not plan the birth month of a newborn with a genetic predisposition to AD, this factor could not have theoretically confounded the observed associations.

Serum vitamin D levels may be involved in the association between birth month and the incidence of AD. Maternal vitamin D supplementation does not affect the risk of AD at 3 years old.[23] However, in an Australian study, a far distance from the equator was associated with a higher prevalence of eczema.[24] Ultraviolet B irradiation decreases inflammation and promotes skin barrier function.[6] Our data showed that birth between April and June was the most protective period against the incidence of AD. A high or low prevalence of AD among birth seasons was preserved from 6 months to 3 years old.

Limitations

Our study has the following limitations. First, our results are limited by infection not being examined as a potential confounder. Second, we used 6 monthly means of sunshine duration and humidity. Individual

experience was not considered. Third, dichotomizations of a long/short sunshine duration and high/low humidity were determined by single cut-off values. Fourth, the incidence of AD was reported by caregivers based on the physician's diagnosis. There could have been recall bias of caregivers. Fifth, physicians who diagnosed children included specialists of AD and non-specialists. Physicians might have underdiagnosed AD in infancy because this diagnosis can cause stigma to children and caregivers.[25] Sixth, we were unable to consider details of AD. Because AD can be caused by several mechanisms, analysis of disease severity may lead to a further understanding of its aetiology.

Conclusions

Births in October to December have the highest incidence of AD until the age of 3 years. This result is consistent when a parental history of allergic disease is considered. A high or low incidence of AD by birth season persists from 6 months through to 3 years in childhood. Although the lowest incidence of AD is found in residents in regions with a long sunshine duration and high humidity in crude data, multivariate analysis shows no association of sunshine duration and humidity with the incidence of AD.

Footnotes

Contributors: All the authors agreed with the manuscript's results and conclusion and approved the final version of the manuscript. HY and MM conceived the study. HY and MM contributed to the design of the study and interpretation of the data analyses. HY analysed the data. HY, MM, AT, RK, SH, TO, YA, and KM wrote the first draft of the manuscript. SH, OS, RS, HI, and ZY contributed to data collection. All authors contributed to revision of the manuscript. ZY was responsible for data integrity. ZY obtained funding.

Funding: This work was supported by the Ministry of the Environment, Japan.

Competing interests: None.

Ethics approval: The protocol was approved by the Ministry of the Environment's Institutional Review Board on Epidemiological Studies (no. 100910001) and by the Ethics Committees of all participating institutions, in accordance with the ethical guidelines and regulations of the Declaration of Helsinki.

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

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Figure legends

Figure 1. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from January.

Figure 2. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration.

Figure 3. Incidence of atopic dermatitis in regions with a high/low mean humidity.

Figure 4. Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity.

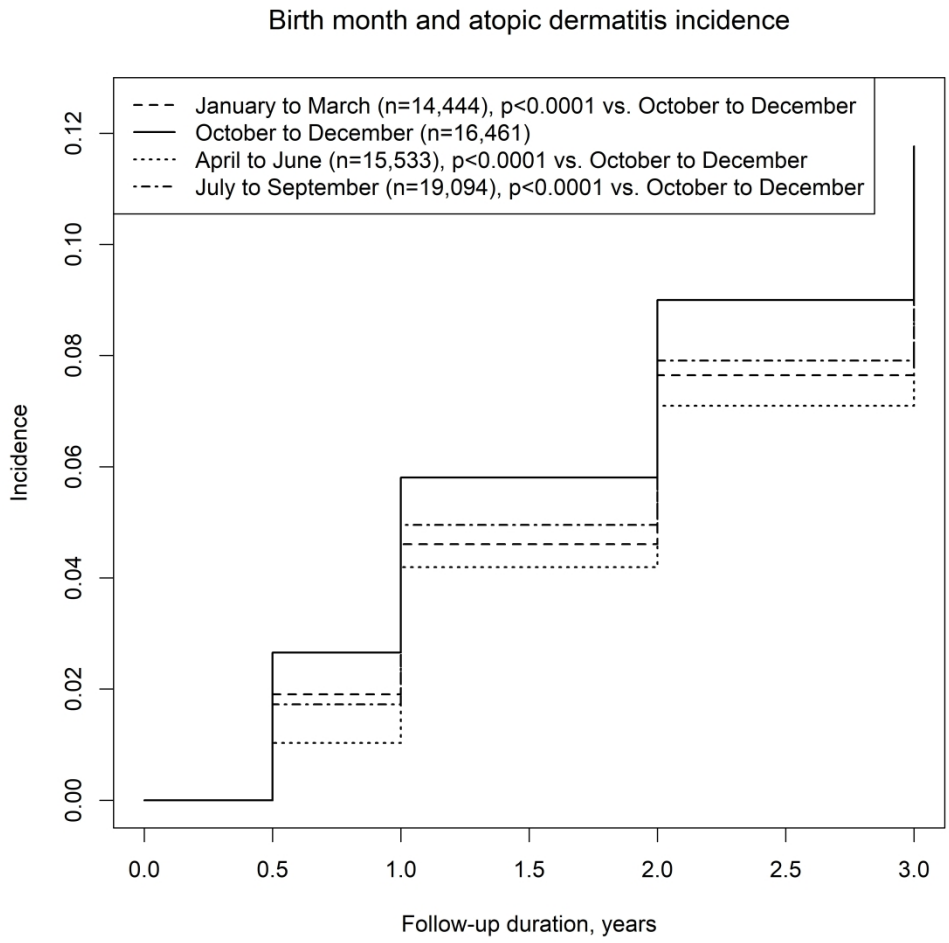
Supplementary Figure 1. Incidence of atopic dermatitis in relation to birth month.

Supplementary Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from February.

Supplementary Figure 3. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from March.

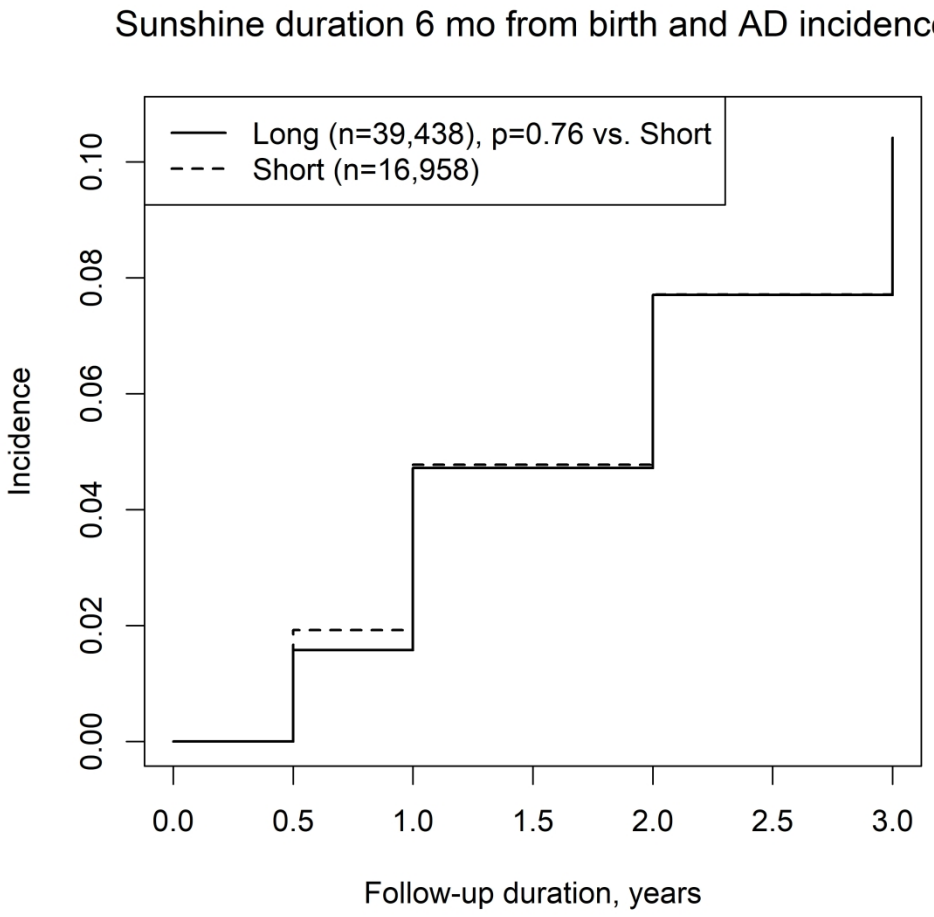
Supplementary Figure 4. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.

Supplementary Figure 5. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.



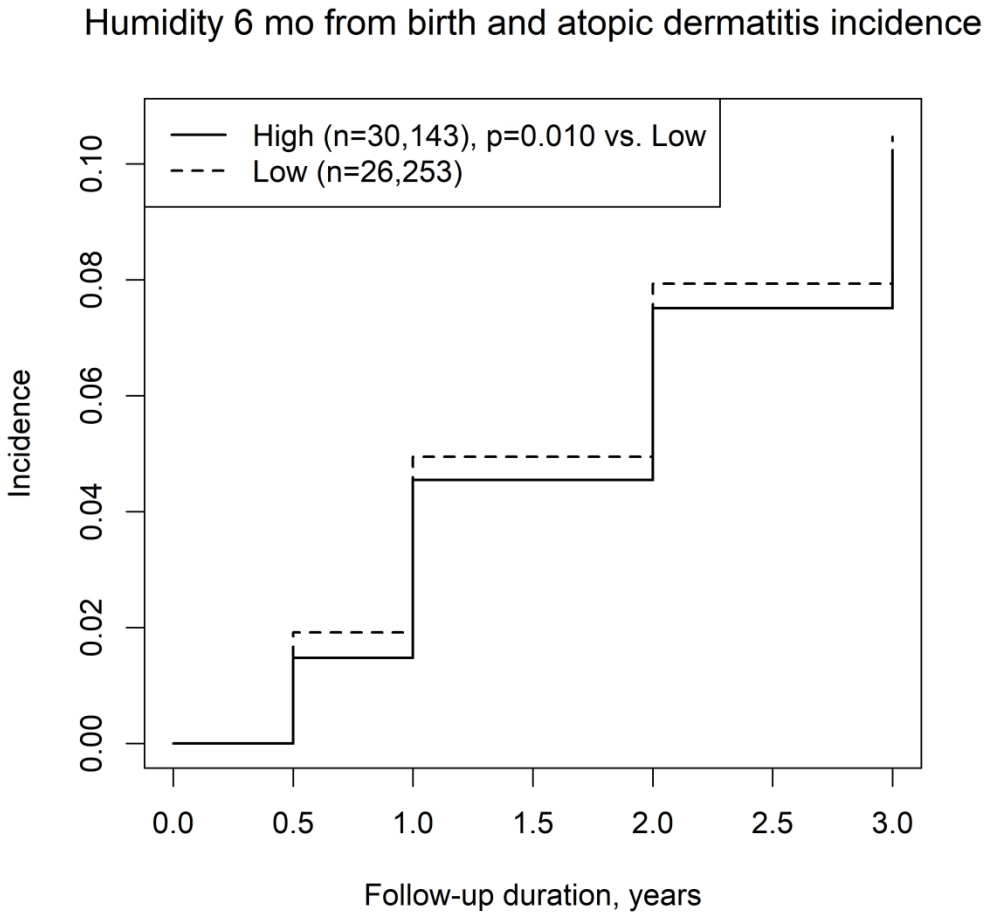
Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from January.

185x185mm (560 x 560 DPI)



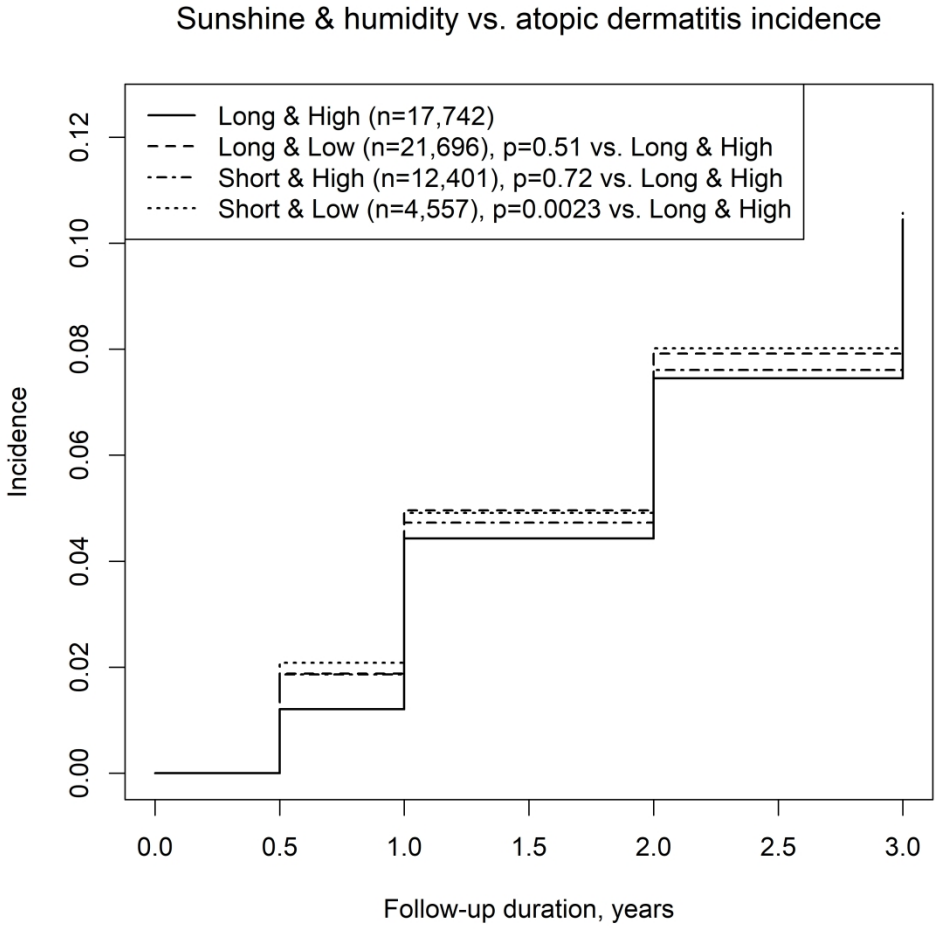
Incidence of atopic dermatitis in regions with a long/short mean sunshine duration.

140x140mm (560 x 560 DPI)



Incidence of atopic dermatitis in regions with a high/low mean humidity.

140x140mm (560 x 560 DPI)



Incidence of atopic dermatitis in regions with a long/short mean sunshine duration and high/low mean humidity.

163x163mm (560 x 560 DPI)

Supplementary Table 1. Baseline characteristics of participants and climate data.

Characteristic	
Male sex	51,396 (51.3)
Maternal history of allergic disease	49,197 (49.2)
Paternal history of allergic disease	21,327 (21.3)
Sunshine duration, hours/month	169 (26)
Humidity, %	67.3 (5.2)
Climate category for sunshine duration and humidity	
Long and high	15,240 (18.6)
Long and low	31,671 (38.6)
Short and high	19,401 (23.7)
Short and low	15,738 (19.2)

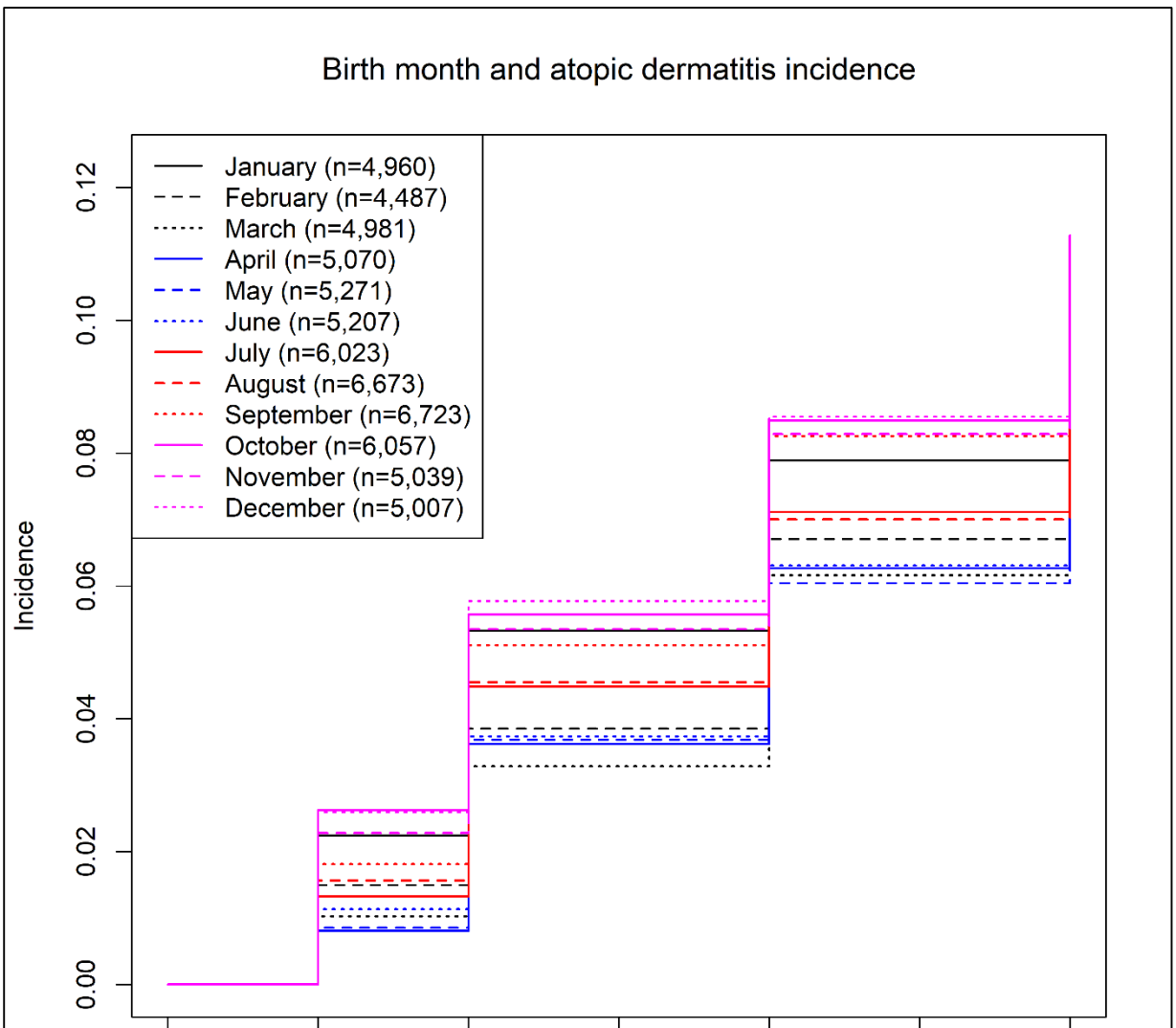
Values are mean (SD) or number (%).

Supplementary Table 2. Incidence rate of atopic dermatitis to 3 years of age by birth month.

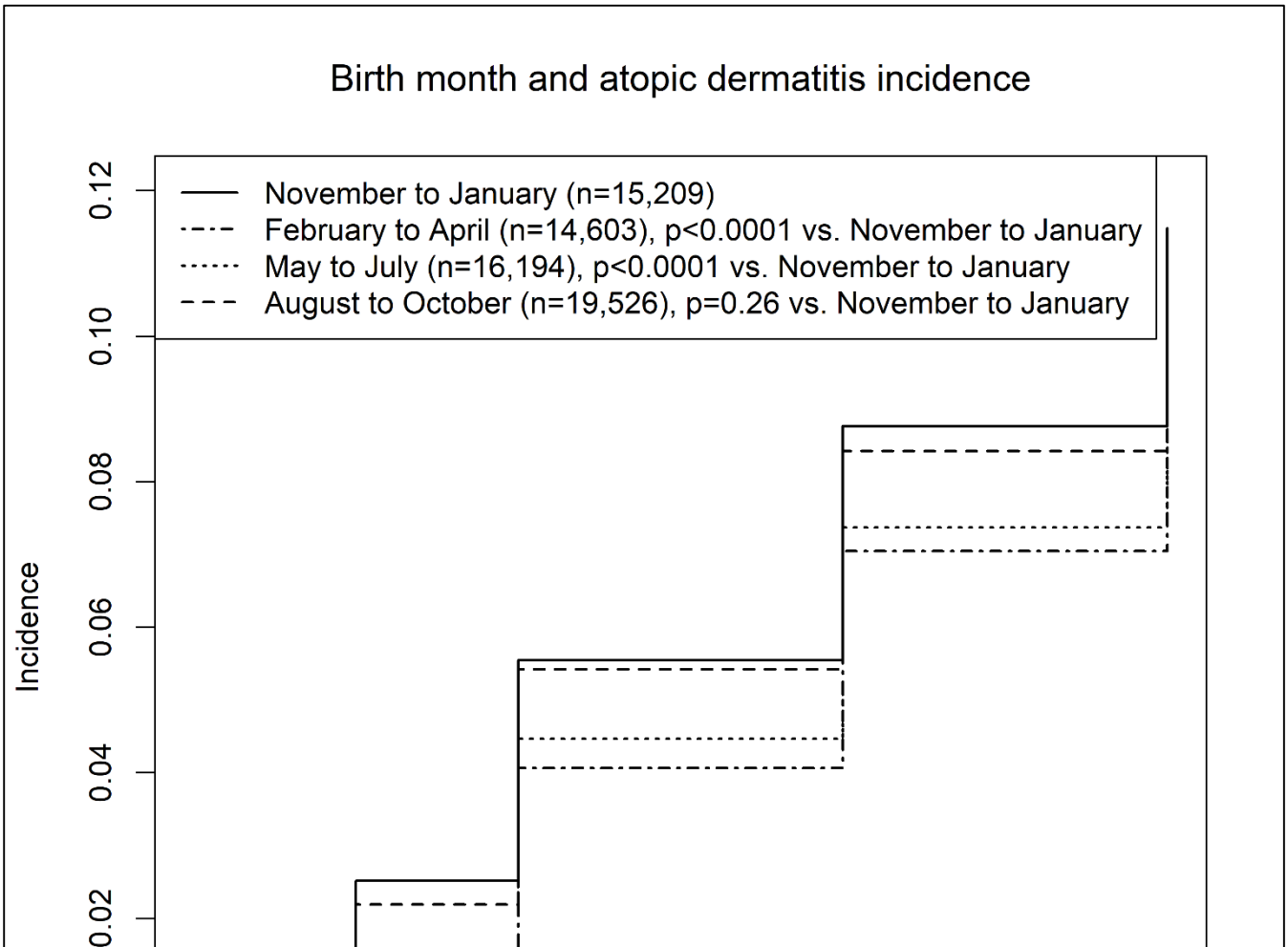
Timing of birth	Number of children	Mean person-years	Incidence per 100 person-years
Birth month			
January	7762	2.57	4.95
February	6987	2.59	4.34
March	7612	2.62	4.21
April	7721	2.60	4.24
May	8081	2.61	5.15
June	7862	2.58	4.54
July	8909	2.6	4.50
August	10,079	2.59	4.42
September	10,302	2.57	5.01
October	9457	2.56	5.38
November	7835	2.55	5.19
December	7693	2.55	5.21
Season			
January to March	22,361	2.59	4.50
April to June	23,664	2.60	4.31
July to September	29,290	2.59	4.65
October to December	24,985	2.55	5.27

1

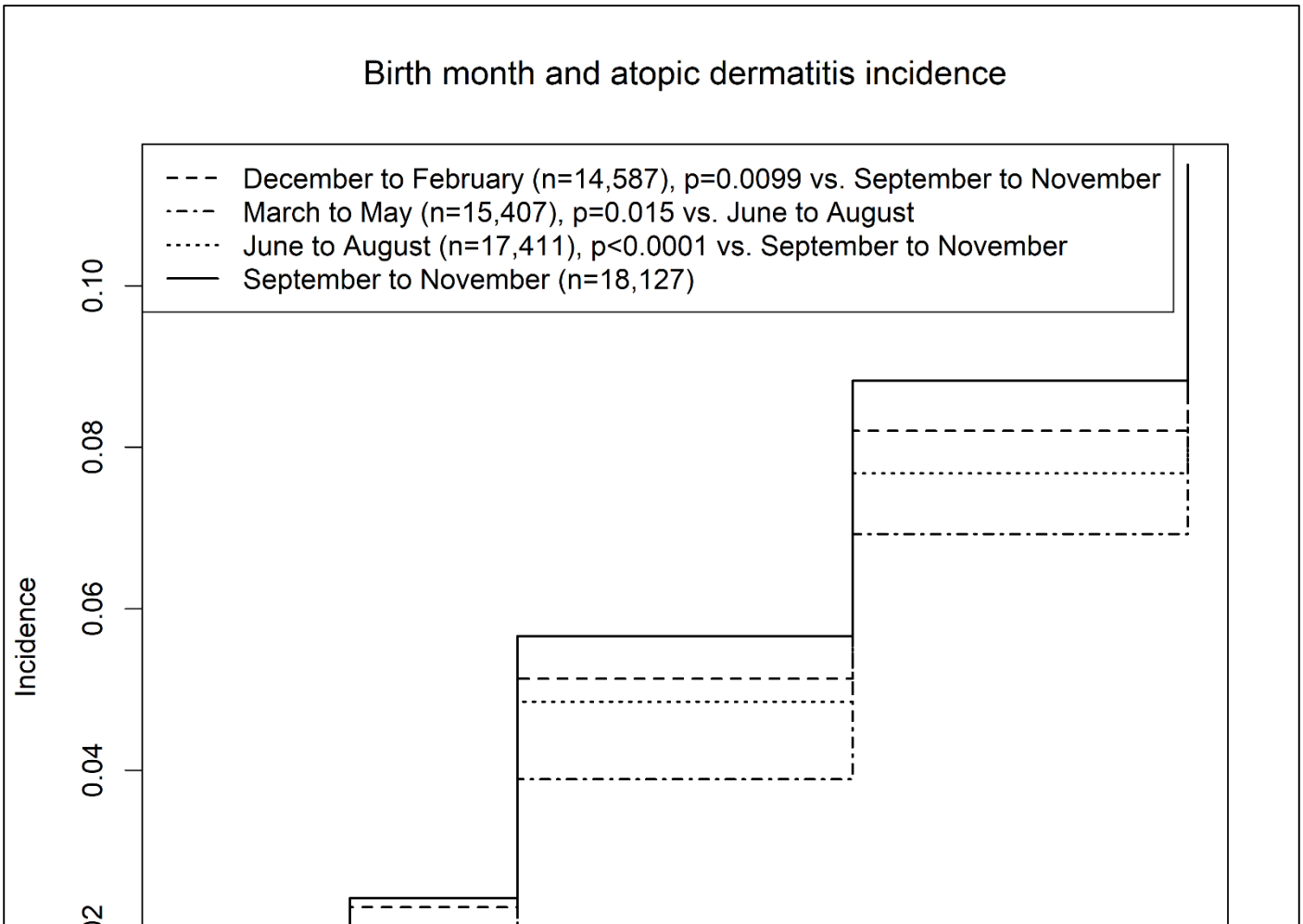
Supplementary Figure 1. Incidence of atopic dermatitis in relation to birth month.



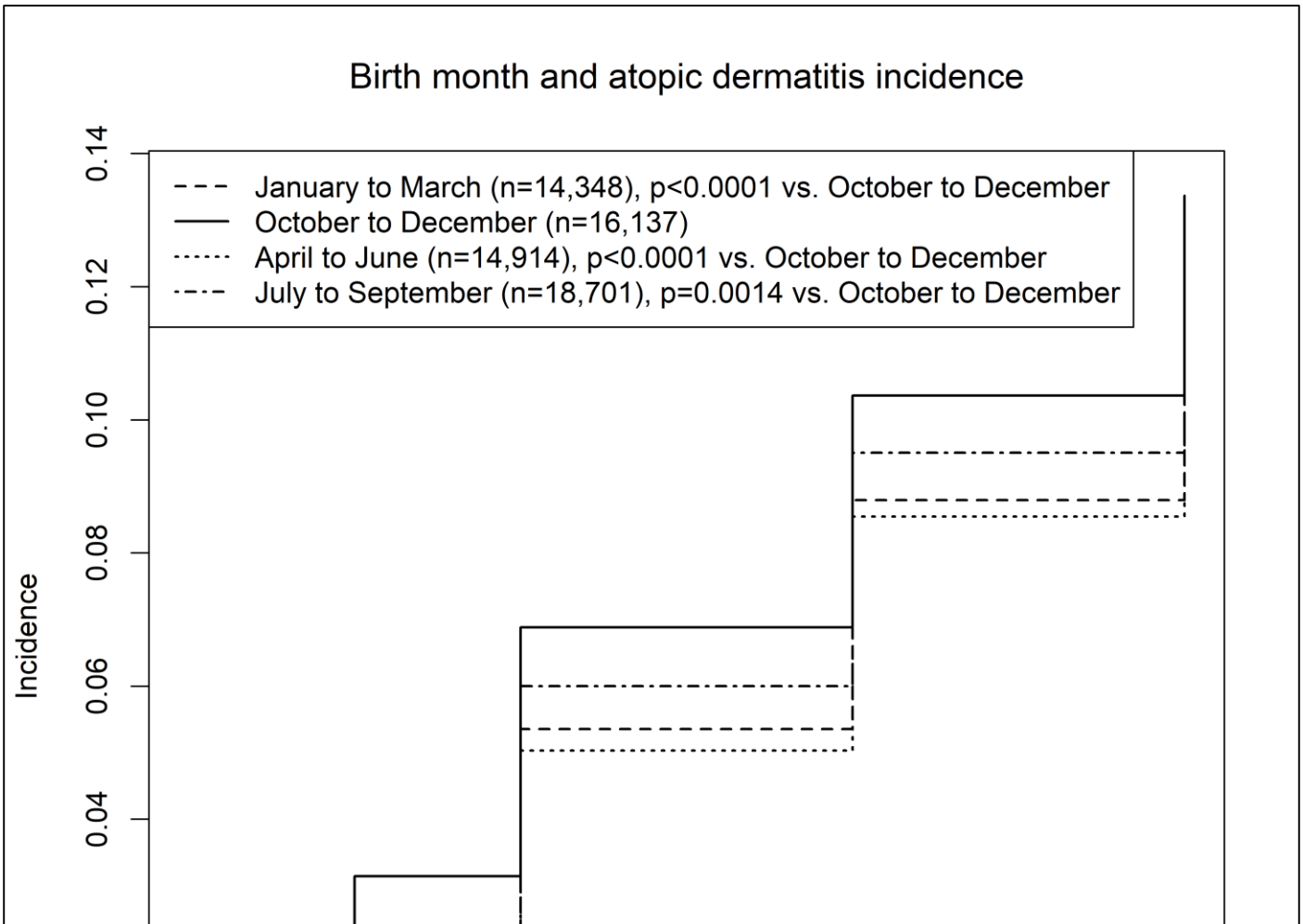
Supplementary Figure 2. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from February.



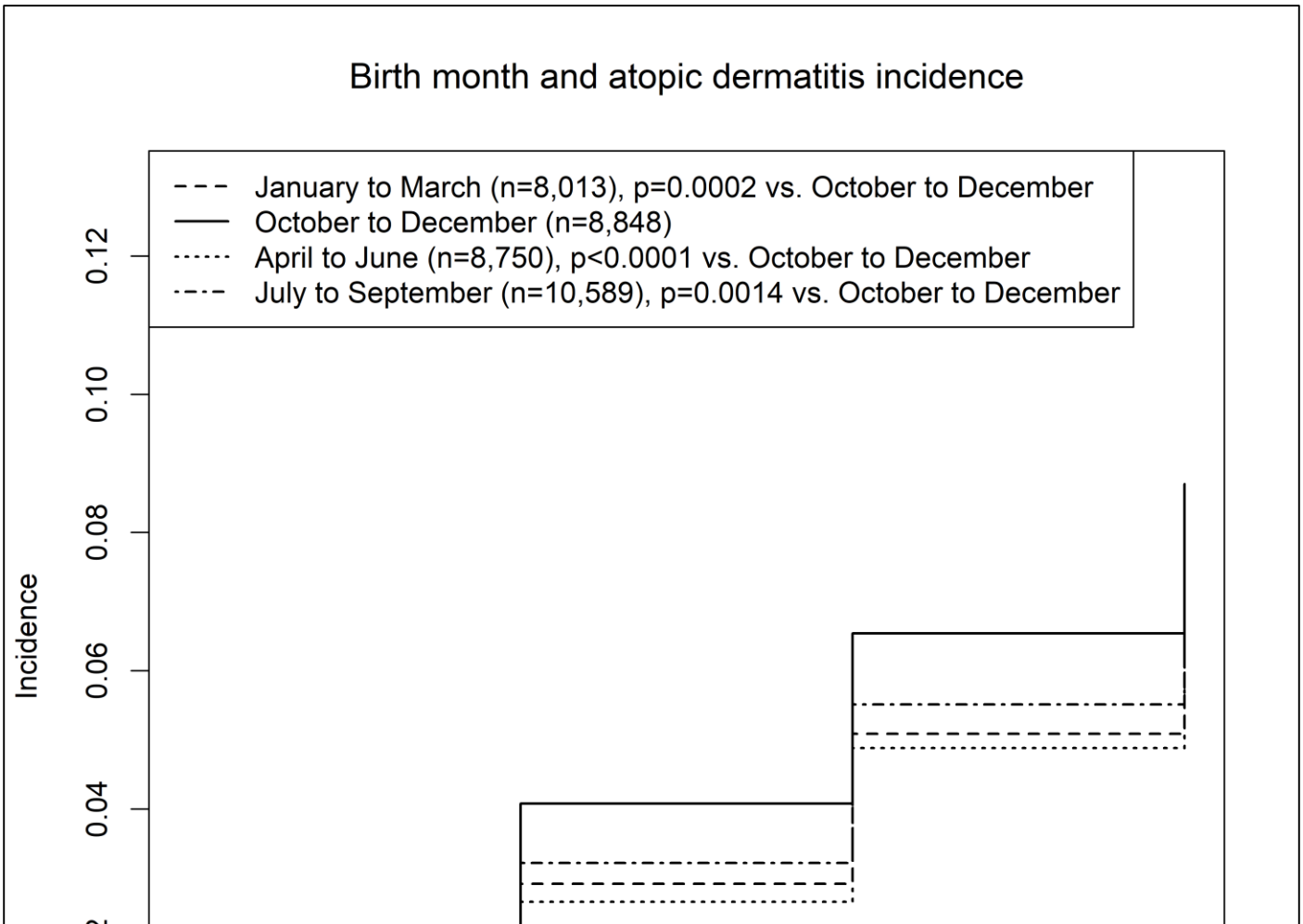
Supplementary Figure 3. Birth season and incidence of atopic dermatitis in a Japanese birth cohort with the seasons starting from March.



Supplementary Figure 4. Birth season and incidence of atopic dermatitis in children whose parents had a history of allergic disease.



Supplementary Figure 5. Birth season and incidence of atopic dermatitis in children whose parents had no history of allergic disease.



STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	5
Methods			
Study design	4	Present key elements of study design early in the paper	7-8
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	6
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	6-7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	6-7
Bias	9	Describe any efforts to address potential sources of bias	7
Study size	10	Explain how the study size was arrived at	6
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	6-7
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	7-8
		(*b*) Describe any methods used to examine subgroups and interactions	7-8
		(*c*) Explain how missing data were addressed	7
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	Not Applicable
		(*e*) Describe any sensitivity analyses	7
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	8
		(b) Give reasons for non-participation at each stage	7-8
		(c) Consider use of a flow diagram	Not Applicable
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	Supplementary table 1
		(b) Indicate number of participants with missing data for each variable of interest	8
Outcome data	15*	Report numbers of outcome events or summary measures	8
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	Figures 1-4, Supplementary figures 1-3, Table 1
		(*b*) Report category boundaries when continuous variables were categorized	6-7
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	Not Applicable
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	Supplementary figures 4 and 5
Discussion			
Key results	18	Summarise key results with reference to study objectives	10
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	12-13
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	10–12
Generalisability	21	Discuss the generalisability (external validity) of the study results	11-12
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	14

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.