PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	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
AUTHORS	Yokomichi, Hiroshi; Mochizuki, Mie; Tsuchida, Akiko; Kojima, Reiji; Horiuchi, Sayaka; Ooka, Tadao; Akiyama, Yuka; Miyake, Kunio; Otawa, Sanae; Shinohara, Ryoji; Inadera, Hidekuni; Yamagata, Zentaro

VERSION 1 – REVIEW

REVIEWER	Ghosh, Debajyoti University of Cincinnati College of Medicine
REVIEW RETURNED	23-Feb-2021

GENERAL COMMENTS	Case-definition: "We asked if physicians had diagnosed the children with AD." The authors should mention if consistent criteria were used for diagnosing AD. For example, mis-diagnosis or over-diagnosis of AD can occur if diagnosis is made by a primary care physician rather than a dermatologist or allergist. If no consistent criteria were followed, then the authors should mention this as a limitation. Statistical procedure: Comparison of birth cohorts according to season by Kaplan-Meier curves and the method of censoring appear to be appropriate. Given the amount of data and the type of analysis performed, the article is suitable for a short report.

REVIEWER	Tay, Yong-Kwang Changi General Hospital
REVIEW RETURNED	24-Feb-2021

GENERAL COMMENTS	1. The authors aimed to compare the incidence of atopic dermatitis in children across birth seasons and climate conditions. 2. Page 4, under Abstract: The conclusion is not clear. Being born in the late autumn to early winter is associated with a risk of developing atopic dermatitis. I will presume that during this period, the duration of sunshine is low. Yet, the authors state that a long sunshine duration is positively correlated with atopic dermatitis. The statements seem to be contradictory. Please clarify. 3. Page 7, line 22: Please delete "medication allergy, urticaria, and/or contact dermatitis" as this is not associated with a genetic predisposition to AD. 4. Page 8, under Results, lines 15-28: It can be concluded that it is the sunshine duration (& not the level of humidity) that determine the

	incidence of AD. This is also stated by the authors in the discussion that there is no clear correlation between humidity and the risk of AD. Please delete the humidity statement in the conclusion. The conclusion should read...Additionally, the highest and lowest incidence of AD is found in residents in regions with a long sunshine duration and short sunshine duration respectively. 5. Page 10, under Discussion, lines 4-7: Please delete "In Mongolia...reducing itchiness from severe AD". 6. Page 10, under Discussion, line 42: Please delete "recent", i.e. "A meta-analysis did not show clear..." 7. Page 10, under Discussion, lines 54-62: Please delete the last paragraph as it is repeated. "Even when considering genetic predisposition...could not theoretically confound the observed associations." 8. Page 11, under Limitations, line 14: Please state the types of AD. 9. Page 14, under References: Please check reference 7, that the pages are complete.

REVIEWER	Magin, Parker University of Newcastle, Discipline of General Practice
REVIEW RETURNED	28-Feb-2021

GENERAL COMMENTS	Temporal and climatic factors associated with incidence of atopic dermatitis are of intrinsic interest and have some practical management implications. The study reported in this manuscript is quite large and appears as though it may have had a good response rate – though this is not reported. The results are interesting, if a little puzzling. But there are a number of limitations of the study, which should be better acknowledged in the manuscript, and some aspects of the manuscript that can be improved. The details of the sample frame and response rate for the wider cohort study and for this nested questionnaire study should be stated. The reliability and validity of the outcome factor (caregivers' recall of physicians' diagnoses) is not discussed. This could also be subject to detection bias. The dichotomization of sunshine duration and humidity means these are quite crude measures. The lack of multivariable analysis is also a limitation. It would have been of interest to have adjusted for confounding and interactions in the relationships between AD and sunlight and humidity. It's currently quite awkward to try to interpret relationships across the multiple Kaplan-Meier curves presented. It's unclear what potential confounding variables were elicited in the questionnaires and could have been used in these analyses. More detail should be provided on the content of the questionnaires and the methodology of invitation to participate in the study. In the manuscript itself, there is insufficient background provided as to previous literature in the area and in a rationale for the importance of this particular study.

REVIEWER	Joseph, Rebecca University of Nottingham
REVIEW RETURNED	01-Mar-2021

GENERAL COMMENTS	This paper uses data from a large birth cohort in Japan to study the association between atopic dermatitis and birth month and local climate conditions in infants. The paper demonstrates a difference in incidence rates of atopic dermatitis according to birth month and the local climate conditions in the first six months of life. These differences are presented clearly in a series of graphs. The results are largely descriptive, and the paper might benefit from presenting additional results and more discussion about potential confounding factors. I have added some specific comments below: 1. It would be useful to include a short description of the climate and seasons in Japan, and if/how this varies across the regions studied. In particular, it would be helpful to know if the four climate categories in the study correspond to particular months or seasons. 2. A summary of the characteristics of the study population would be helpful. This could be a table of baseline characteristics, possibly grouped by birth month and should include any available baseline demographic characteristics (e.g. sex) and the factors reported in the study (climate category, parental history of allergic disease) 3. There is room to present total person-years of follow-up and crude incidence rates, possibly stratified by birth season or even birth month if numbers allow. 4. Be clear about the main study findings in the first paragraph of the discussion (the difference in rates by birth month and season, and by climate conditions). 5. There should be more discussion about confounding factors – in particular, there are likely to be behavioural differences associated with different climates (amount of time spent inside/outside, in heated/air-conditioned rooms, exposure to sunlight and vitamin D levels etc.). Strong conclusions about the link between climate and atopic dermatitis cannot be drawn from the results presented and some of these other possible explanations should be discussed. 6. In Figure 1 it is difficult to distinguish the different lines. Maybe consider using colour as well as patterns. 7. You could include a short description of the distribution of the different centres across Japan. 8. Could you include the numbers remaining in the cohort/ lost to follow-up at each of the data collection time points? 9. The discussion includes a few comments about risk factors, potentially implying causality. These statements are a bit strong given the potential for confounding.

VERSION 1 – AUTHOR RESPONSE

Responses to comments of reviewer #1

2. Case-definition: “We asked if physicians had diagnosed the children with AD.” The authors should mention if consistent criteria were used for diagnosing AD. For example, mis-diagnosis or over-diagnosis of AD can occur if diagnosis is made by a primary care physician rather than a dermatologist or allergist. If no consistent criteria were followed, then the authors should mention this as a limitation.

We appreciate the point of clarifying who diagnosed AD. We could not unify the criteria of diagnosing AD. We have added this issue as a limitation to the revised manuscript.

Line 189: 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

3. Statistical procedure: Comparison of birth cohorts according to season by Kaplan-Meier curves and the method of censoring appear to be appropriate.

We thank the reviewer for agreeing with this procedure.

4. Given the amount of data and the type of analysis performed, the article is suitable for a short report.

This manuscript was transferred to BMJ Open. BMJ Open does not include short report articles. Therefore, we would like to submit our manuscript to BMJ Open as an Original Research article.

Responses to comments of reviewer #2
The authors aimed to compare the incidence of atopic dermatitis in children across birth seasons and climate conditions.
5. Page 4, under Abstract: The conclusion is not clear. Being born in the late autumn to early winter is associated with a risk of developing atopic dermatitis. I will presume that during this period, the duration of sunshine is low. Yet, the authors state that a long sunshine duration is positively correlated with atopic dermatitis. The statements seem to be contradictory. Please clarify.

We thank the reviewer for pointing out that these sentences contradict each other. We apologise that the figure of sunshine duration and humidity associated with the incidence of AD was not correct. Therefore, we have revised the figure and conclusion (see below).

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

Line 37: 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.

Line 196: 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.

6. Page 7, line 22: Please delete "medication allergy, urticaria, and/or contact dermatitis" as this is not associated with a genetic predisposition to AD.

We thank the reviewer for this comment. We have revised the covariates of the analysis.

Line 88: 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.

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.

7. Page 8, under Results, lines 15-28: It can be concluded that it is the sunshine duration (& not the level of humidity) that determine the incidence of AD. This is also stated by the authors in the discussion that there is no clear correlation between humidity and the risk of AD. Please delete the humidity statement in the conclusion. The conclusion should read...Additionally, the highest and lowest incidence of AD is found in residents in regions with a long sunshine duration and short sunshine duration respectively.

We thank the reviewer for the insightful comment. In the corrected crude figure, the level of humidity was associated with the incidence of AD. This association was diminished when other risk factors were considered. We have described this information in the conclusion.

Line 198: 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.

8. Page 10, under Discussion, lines 4-7: Please delete "In Mongolia...reducing itchiness from severe AD".

We would like to discuss the association of incident AD with sunshine duration and humidity. We have deleted the sentence about the rare incidence of AD in Mongolian people. Ultraviolet lighting is sometimes used for treating severe AD. We have added this information to the revised manuscript.

Line 160: Ultraviolet lighting is sometimes used clinically for reducing itchiness from severe AD.19

9. Page 10, under Discussion, line 42: Please delete "recent", i.e. "A meta-analysis did not show clear..."

We thank the reviewer for this advice. We have deleted the word “recent” as suggested.

Line 171: A meta-analysis did not show clear evidence for a protective effect of breast feeding on the incidence of AD.20

10. Page 10, under Discussion, lines 54-62: Please delete the last paragraph as it is repeated. "Even when considering genetic predisposition...could not theoretically confound the observed associations."

In this paragraph, we wished to discuss that the results considering genetic predisposition were similar to the main results. We have changed the sentences to appropriately convey our meaning.

Line 174: 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.

11. Page 11, under Limitations, line 14: Please state the types of AD.

We apologise for our use of terminology. We meant the severity and mechanism of AD. We have changed the following sentence.

Line 193: 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.

12. Page 14, under References: Please check reference 7, that the pages are complete.

This is an article of a BMC web-based journal, and therefore the page number is the article number. The page number is correct for this article.

Responses to comments of reviewer #3

13. Temporal and climatic factors associated with incidence of atopic dermatitis are of intrinsic interest and have some practical management implications. The study reported in this manuscript is quite large and appears as though it may have had a good response rate – though this is not reported. The results are interesting, if a little puzzling.

We thank the reviewer for the interest in our results. The response rate in this study was 79.9% at 3 years of age. We have added this information to the revised manuscript.

Line 113: 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.

14. But there are a number of limitations of the study, which should be better acknowledged in the manuscript, and some aspects of the manuscript that can be improved.

We have added some limitations to the manuscript. We hope that all the limitations are clear to the readers.

Line 189: 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.

15. The details of the sample frame and response rate for the wider cohort study and for this nested questionnaire study should be stated.

We appreciate the reviewer's point. The response rate had decreased by the age of 3 years. We have added the following information to the revised manuscript.

Line 113: 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.

16. The reliability and validity of the outcome factor (caregivers' recall of physicians' diagnoses) is not discussed. This could also be subject to detection bias.

We appreciate the reviewer's suggestion. We agree that there could have been detection bias, which could have changed the incidence of AD. We have discussed this possibility in the limitations section.

Line 190: 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

17. The dichotomization of sunshine duration and humidity means: these are quite crude measures.

We thank the reviewer for the comment. The mean values of sunshine duration and humidity in each region were means from April 2011 to March 2015 from which the studied children were exposed. We adopted cut-off values of 166.1 hours/month for sunshine duration and 68.4% for humidity to divide the studied regions into high/low categories of the meteorological measures when possible. Because there are no cut-off values for high/low sunshine duration and humidity in Japan and we hoped to simply measure the effect of various exposures, we divided the 18 regions by mean values.

18. The lack of multivariable analysis is also a limitation. It would have been of interest to have adjusted for confounding and interactions in the relationships between AD and sunlight and humidity. It's currently quite awkward to try to interpret relationships across the multiple Kaplan-Meier curves presented.

We thank the reviewer for the advice. We have added the results of Cox proportional regression. We have slightly changed the conclusion with the results of the multivariate analysis.

Table 1. Hazard ratios of exposures for atopic dermatitis incidence at age of three years.

Exposure	Crude	Adjusted
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	Ref	Ref
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)

19. It's unclear what potential confounding variables were elicited in the questionnaires and could have been used in these analyses. More detail should be provided on the content of the questionnaires and the methodology of invitation to participate in the study.

The investigation was based on a fill-in questionnaire. We have added an explanation of the question

about the parental history of allergic diseases.

Line 89: The father and mother were asked individually about a history of allergic diseases to determine their experience of each diagnosed disease by a physician.

20. In the manuscript itself, there is insufficient background provided as to previous literature in the area and in a rationale for the importance of this particular study.

We thank the reviewer for the comment. We have added some information to clarify the importance of this study to the Introduction section.

Line 50: 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 data9 10 and metrological data11 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.

Responses to comments of reviewer #4
This paper uses data from a large birth cohort in Japan to study the association between atopic dermatitis and birth month and local climate conditions in infants. The paper demonstrates a difference in incidence rates of atopic dermatitis according to birth month and the local climate conditions in the first six months of life. These differences are presented clearly in a series of graphs. The results are largely descriptive, and the paper might benefit from presenting additional results and more discussion about potential confounding factors. I have added some specific comments below:

We thank the reviewer for the comment. We apologise that the graph of the incidence of AD in relation to sunshine duration and humidity needed to be corrected. We hope that the manuscript is sufficiently improved after addressing the reviewer's comments.

21. It would be useful to include a short description of the climate and seasons in Japan, and if/how this varies across the regions studied. In particular, it would be helpful to know if the four climate categories in the study correspond to particular months or seasons.

We appreciate the reviewer's advice. We have added information of the Japanese sunshine duration and humidity in the various seasons to the revised manuscript.

Line 72: 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.

22. A summary of the characteristics of the study population would be helpful. This could be a table of baseline characteristics, possibly grouped by birth month and should include any available baseline demographic characteristics (e.g. sex) and the factors reported in the study (climate category, parental history of allergic disease)

We thank the reviewer for the suggestion. We have added a table of baseline characteristics.

Line 116: Supplementary table 1 shows characteristics of the participants.

Supplementary table 1. Baseline characteristics of participant and climate data.
Mean (SD) or number (%)
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 (%).

23. There is room to present total person-years of follow-up and crude incidence rates, possibly stratified by birth season or even birth month if numbers allow.

In accordance with the reviewer's advice, we have shown the number of children, person-years, and incidence of AD by birth month and season.

Line 95: The incidence of AD by birth month and season until 3 years of age was calculated.

Line 118: Supplementary Table 2 shows the incidence rate of AD by birth month and season.

Supplementary table 2. Incidence rate of atopic dermatitis to three years of age by birth month.
Timing of birth Number of children Mean person-years Incidence per 100 person-years
Birth month
January 7,762 2.57 4.95
February 6,987 2.59 4.34
March 7,612 2.62 4.21
April 7,721 2.60 4.24
May 8,081 2.61 5.15
June 7,862 2.58 4.54
July 8,909 2.6 4.50
August 10,079 2.59 4.42
September 10,302 2.57 5.01
October 9,457 2.56 5.38
November 7,835 2.55 5.19
December 7,693 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

24. Be clear about the main study findings in the first paragraph of the discussion (the difference in rates by birth month and season, and by climate conditions).

We appreciate the reviewer's advice. We have clearly described the findings of this study in the first paragraph of the Discussion.

Line 139: 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.

25. There should be more discussion about confounding factors – in particular, there are likely to be behavioural differences associated with different climates (amount of time spent inside/outside, in heated/air-conditioned rooms, exposure to sunlight and vitamin D levels etc.). Strong conclusions about the link between climate and atopic dermatitis cannot be drawn from the results presented and some of these other possible explanations should be discussed.

We have further discussed the confounding factors of vitamin D and sunlight strength. We have also added another paragraph on confounding factors to the Discussion.

Line 174: 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.

26. In Figure 1 it is difficult to distinguish the different lines. Maybe consider using colour as well as patterns.

We thank the reviewer for the advice. We have changer the colour in the figure for readability.

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

27. You could include a short description of the distribution of the different centres across Japan.

We could not provide a short description of the different centres. Instead, we have generally described their distribution in Japan.

Line 74: 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.

28. Could you include the numbers remaining in the cohort/ lost to follow-up at each of the data collection time points?

We have described how we followed up the participants in the revised manuscript.

Line 113: 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.

29. The discussion includes a few comments about risk factors, potentially implying causality. These statements are a bit strong given the potential for confounding.

We thank the reviewer for the comment. We have added sentences that imply the causality of our data to the revised manuscript.

Line 143: 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.

Line 179: 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.

VERSION 2 – REVIEW

REVIEWER	Magin, Parker University of Newcastle, Discipline of General Practice
REVIEW RETURNED	25-Apr-2021

GENERAL COMMENTS	The authors have addressed most of my comments. A few issues remain. • The authors have not provided more details of the sample frame of

	the study • The response has elaborated on how the dichotomization of sunshine and humidity were done, but not acknowledged as a limitation of the study that these are quite crude measures

REVIEWER	Joseph, Rebecca University of Nottingham
REVIEW RETURNED	29-Apr-2021

GENERAL COMMENTS	Thank you for resubmitting this paper and responding to the feedback on the earlier draft. I believe the methods are appropriate and the key results are clearly demonstrated and are interesting. From reading the paper, I interpreted the key findings as follows: There is an association between birth season and incidence of atopic dermatitis, which appears to be unrelated to the sunshine duration and humidity in the first six months of life, and which appears to persist for at least the first three years of life. The study also reports an increased incidence of atopic dermatitis associated with both maternal and paternal history of allergic disorders. I think that some further clarification would be useful for readers of the paper. I have made some additional suggestions below (my suggested phrasings are to help illustrate my points, you may be able to improve on what I suggest). 1. Add something to the title to clarify that the climate conditions were based on the months after birth. Perhaps something like "…with birth month, and with sunshine duration and humidity in the first months of life". 2. Similarly, add this information to the "Exposure" section of the abstract. If you have room, you could also mention that these variables were binary. E.g. "Exposure Birth month; mean sunshine duration (short/long) and humidity (high/low) in the first 6 months of life." 3. In the abstract, the first sentence in the results is slightly ambiguous. Perhaps consider the following wording: "Results The highest incidence of atopic dermatitis was in children born in the months of October to December". You could remove ", which may be associated with dry skin and itchiness," from the final sentence in the abstract. 4. Introduction line 4: I would change "causal factors" to something like "factors associated with AD". 5. Page 8, results paragraph 1: this might be clearer if reordered slightly and with a few more comments on the different figures/tables. This is a suggestion: "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 those born in October and December (Supplementary Figure 1). Supplementary Figures 2 and 3 show the results after varying how the months were grouped." 6. Page 9 paragraph 2 (results): "The observed highest and lowest incidence of AD shown in Figures 4 and 4 was…" should this be "Supplementary Figures 4 and 5"? 7. Page 9 paragraph 2 (results): I think the line "The order of accumulated incidence of AD among the seasons did not change from 6 months to 3 years of age" does not necessarily belong to that paragraph and could be moved to the end of paragraph 1 of the

	results. 8. Discussion line 1: add the age limit for clarity, e.g. “the incidence of AD by the age of 3 years…”. 9. Discussion, page 12 paragraph 2: I would remove the last sentence in this paragraph as it seems to go slightly beyond your findings (the sentence starting “These data suggest that strong…”). 10. General comment: make sure it is always clear you are talking about the sunshine/humidity in the first 6 months of life. It is clear in the methods, but it would be helpful to be explicit about it in the results/discussion (e.g. Discussion paragraph 2 line 6 could be “we did not observe a clear correlation between high or low humidity in the first 6 months of life and the risk of AD”).

VERSION 2 – AUTHOR RESPONSE

Responses to the comments of reviewer #3

1. The authors have not provided more details of the sample frame of the study.
We apologise that we did not provide adequate details of the sample frame of this study. We have added the following information to the revised manuscript.

Line 68: “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”

2. The response has elaborated on how the dichotomization of sunshine and humidity were done, but not acknowledged as a limitation of the study that these are quite crude measures.
We appreciate the point of the limitation of dichotomization of sunshine duration and humidity. We have added this limitation to the main text.

Line 194: “Third, dichotomizations of a long/short sunshine duration and high/low humidity were determined by single cut-off values.”

Responses to the comments of reviewer #4
Thank you for resubmitting this paper and responding to the feedback on the earlier draft. I believe the methods are appropriate and the key results are clearly demonstrated and are interesting. From reading the paper, I interpreted the key findings as follows:
There is an association between birth season and incidence of atopic dermatitis, which appears to be unrelated to the sunshine duration and humidity in the first six months of life, and which appears to persist for at least the first three years of life. The study also reports an increased incidence of atopic dermatitis associated with both maternal and paternal history of allergic disorders.
I think that some further clarification would be useful for readers of the paper. I have made some additional suggestions below (my suggested phrasings are to help illustrate my points, you may be able to improve on what I suggest).
We would like to thank the reviewer for understanding and summarizing our results. We have revised our manuscript in accordance with the reviewer’s suggestions.

3. Add something to the title to clarify that the climate conditions were based on the months after birth. Perhaps something like “…with birth month, and with sunshine duration and humidity in the first months of life”.

We would like to thank the reviewer for the advice. We have revised the title as follows.

Title: “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”

4. Similarly, add this information to the “Exposure” section of the abstract. If you have room, you could also mention that these variables were binary. E.g. “Exposure Birth month; mean sunshine duration (short/long) and humidity (high/low) in the first 6 months of life.”

We agree with the reviewer and have added the information as suggested.

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

5. In the abstract, the first sentence in the results is slightly ambiguous. Perhaps consider the following wording: “Results The highest incidence of atopic dermatitis was in children born in the months of October to December”. You could remove “, which may be associated with dry skin and itchiness,” from the final sentence in the abstract.

We appreciate the reviewer’s suggestions. We have modified the abstract in accordance with the reviewer’s comment.

Abstract
“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.”

6. Introduction line 4: I would change “causal factors” to something like “factors associated with AD”.

We would like to thank the reviewer for this suggestion. As mentioned by the reviewer, discussing causality in epidemiology may be difficult. We have changed the text as follows.

Line 51: “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.”

7. Page 8, results paragraph 1: this might be clearer if reordered slightly and with a few more comments on the different figures/tables. This is a suggestion:
“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 those born in October and December (Supplementary Figure 1). Supplementary Figures 2 and 3 show the results after varying how the months were grouped.”

We appreciate your suggestion for clarifying the results. We have changed the following sentences.

Line 122: “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.”

8. Page 9 paragraph 2 (results): “The observed highest and lowest incidence of AD shown in Figures 4 and 4 was…” should this be “Supplementary Figures 4 and 5”?

We apologise for this mistake. We have corrected the figures.

Line 137: “The observed highest and lowest incidence of AD shown in Supplementary Figures 4 and 5 was consistent with that shown in Figure 1.”

9. Page 9 paragraph 2 (results): I think the line “The order of accumulated incidence of AD among the seasons did not change from 6 months to 3 years of age” does not necessarily belong to that paragraph and could be moved to the end of paragraph 1 of the results.

We would like to thank the reviewer for the advice. We have moved this sentence to the end of the first paragraph of the Results.

Line 127: “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 of age.”

10. Discussion line 1: add the age limit for clarity, e.g. “the incidence of AD by the age of 3 years…”.

We agree with the reviewer. We have added the following information.

Abstract
“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.”

Line 140: “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.”

Line 146: “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.”

Line 202: “Births in October to December have the highest incidence of AD until the age of 3 years.”

11. Discussion, page 12 paragraph 2: I would remove the last sentence in this paragraph as it seems to go slightly beyond your findings (the sentence starting “These data suggest that strong…”).

We would like to thank the reviewer for the advice. We have removed this sentence as suggested.

12. General comment: make sure it is always clear you are talking about the sunshine/humidity in the first 6 months of life. It is clear in the methods, but it would be helpful to be explicit about it in the results/discussion (e.g. Discussion paragraph 2 line 6 could be “we did not observe a clear correlation between high or low humidity in the first 6 months of life and the risk of AD”).

We appreciate the reviewer's suggestion. We have carefully reviewed our manuscript.

Line 129: "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."

Line 154: "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."

VERSION 3 – REVIEW

REVIEWER	Joseph, Rebecca University of Nottingham
REVIEW RETURNED	07-Jun-2021

GENERAL COMMENTS	Thank you again for your revisions to this paper and responding to my earlier feedback. I think this is an interesting paper and have no further suggestions to make.