

Original Article

The Association Between Season of Birth and Atopic Dermatitis in the Northern Hemisphere: A Systematic Review and Meta-Analysis

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What is already known about this topic? Atopic dermatitis (AD) is a prevalent chronic skin condition. Although several risk factors for AD have been proposed over the years, it is unknown whether season of birth can affect the risk of developing AD.

What does this article add to our knowledge? This meta-analysis shows that fall and winter birth in the Northern hemisphere was associated with a slightly increased risk of AD, but also indicate that more research is needed to support a cause-effect relationship.

How does this study impact current management guidelines? If prophylactic treatment aiming at improving the skin barrier can reduce the risk of AD, this could be of particular value in children born during the fall and winter on the Northern hemisphere.

BACKGROUND: Cold and dry climate negatively affects skin barrier functions. This could explain the higher incidence of atopic dermatitis (AD) in Northern countries distant from the equator, as well as the general worsening of AD in Northern European winter months. Although it has been suggested that fall and winter birth is associated with AD, this remains unknown.

OBJECTIVES: To examine whether the prevalence of AD is associated with season of birth.

METHODS: We conducted a systematic review and meta-analysis. Two reviewers independently searched 3 databases. Study quality was assessed using a Newcastle-Ottawa scale. Study heterogeneity was assessed with Cochrane Q and I² statistics. Odds ratios with 95% CIs were calculated. Publication bias was assessed using funnel plots.

RESULTS: The systematic review identified 23 relevant articles of which 9 articles were included in the meta-analysis. Among a total of 726,378 children aged 0 to 12 years, the overall pooled

prevalence of AD was 12.9%. The pooled prevalence of AD was 15.4% (95% CI, 12.1%-19.1%), 14.9% (95% CI, 12.0%-18.1%), 12.7% (95% CI, 10.2%-15.4%), and 13.7% (95% CI, 10.8%-17.0%), among children born in the fall, winter, spring, and summer, respectively. AD was significantly associated with fall (odds ratio, 1.16; 95% CI, 1.06-1.28; *P* = .0018) and winter (odds ratio, 1.15; 95% CI, 1.04-1.27; *P* = .0076) birth compared with spring birth.

CONCLUSIONS: Although a positive and significant association was observed between being born in fall and winter and developing AD on the Northern hemisphere, there is a need for additional and better-designed studies to understand the effect of seasonal changes on the risk of AD. © 2019 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2019;■:■-■)

Key words: Atopic dermatitis; Birth season; Climate; Pediatric; Risk

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Abbreviations used
AD- atopic dermatitis
OR- odds ratio
UV- ultraviolet

INTRODUCTION

Atopic dermatitis (AD) is a chronic relapsing pruritic inflammatory skin condition that normally begins in early childhood.^{1,2} Filaggrin gene mutations are associated with xerosis and are a strong risk factor for AD.^{3,4} However, certain climatic factors including low temperatures and ambient humidity may also negatively affect skin barrier functions,⁵ and at least in part explain the higher incidence of AD in countries on the Northern hemisphere that are located distant from the equator, and the dramatic worsening of AD in some patients during winter months.⁶⁻¹³ We recently observed a dramatic increase in the incidence of AD in infants born during the fall and winter months in Denmark.⁶ Thus, we performed a systemic review and meta-analysis to examine whether the prevalence of pediatric AD is generally associated with season of birth.

METHODS

Literature search

A literature search was performed by 2 independent reviewers (M.C. and F.A.) on April 21, 2018, using the databases PubMed, Embase, and Web of Science (see [Figure E1](#) in this article's Online Repository at www.jaci-inpractice.org). Search terms included ("atopic dermatitis" OR "atopic eczema" OR "children eczema" OR "flexural eczema") AND ("season" OR "seasonal" OR "climate" OR "birth" OR "month"). All articles were screened and included/excluded on the basis of title and abstract. Articles were included in the analysis if they contained data on AD incidence or prevalence according to season or month of birth. If only months were given, the spring was classified by the months March-April-May, summer by the months June-July-August, autumn by the months September-October-November, and winter by the months December-January-February. If inclusion criteria could not be determined on the basis of title or abstract, the article was included for full-text screening. No restrictions were placed on date or language of publication. If data were duplicated in more than 1 study, data only from the most recent or comprehensive study were included. Authors of relevant articles without extractable data from text or tables were queried for more comprehensive data. Articles were excluded if they lacked an abstract or only assessed atopy. If there was doubt about inclusion or exclusion of an article, consensus was achieved through discussion between the 2 screeners and the senior author (see [Figure E2](#) in this article's Online Repository at www.jaci-inpractice.org). Data extraction was done by 2 individual authors. The study design, method of establishing the AD diagnosis, the country of origin, and data on the participants' age and sex were collected for each included study. The search process was performed according to Preferred Reporting Items of Systematic reviews and Meta-analyses guidelines (see [Figure E1](#)).¹⁴

Study quality was assessed using an adapted version of Newcastle-Ottawa scale for cross-sectional studies, because all studies identified were cross-sectional. Studies with an adapted Newcastle-Ottawa scale score of 7 or more were considered to be of high quality.¹⁵

Statistical analysis

The possible association between AD and being born during, respectively, the fall, winter, or summer was examined with spring as the reference. Sensitivity analyses were performed for studies from Europe and Asia. Odds ratios (ORs) with 95% CIs were estimated. Study heterogeneity was assessed with Cochrane Q and I^2 statistics. For all analyses, random-effect models (DerSimonian-Laird) were used. Publication bias was assessed using funnel plots (see [Figure E3](#) in this article's Online Repository at www.jaci-inpractice.org). All statistical tests were performed using StatsDirect version 3 (StatsDirect Ltd, Cheshire, UK).

RESULTS

In total, 11,474 articles were identified. After title and abstract screening, 11,292 articles were excluded and the remaining 182 full-text manuscripts were reviewed (see [Figure E1](#)). A total of 23 articles met the inclusions criteria for the systematic review.¹⁶⁻³⁸

Quantitative analysis

Nine articles contained sufficient quantitative data to be included in the meta-analysis ([Table 1](#)).³⁰⁻³⁸ Studies came from 6 countries, and all from the Northern Hemisphere: China (n = 1), Denmark (n = 2), Japan (n = 2), Slovak Republic (n = 1), Taiwan (n = 1), and the United Kingdom (n = 2). The quantitative analysis included a total of 726,378 children aged 0 to 12 years, of which 93,890 (12.9%) had a diagnosis of AD. Studies had Newcastle-Ottawa scale scores of 6,^{30,32,35} 7,³³ 8,^{31,37,38} and 9.^{34,36}

AD diagnosis was assessed by questionnaires in 6 of 9 studies. In these 6 questionnaire studies, 1 study used the International Study for Asthma and Allergies in Childhood (ISAAC) questionnaire,³⁷ 2 studies used modified ISAAC questionnaires,^{35,38} and 1 study used a nonvalidated questionnaire together with objective scoring according to the SCORing Atopic Dermatitis index.³² Of the 2 remaining studies that used the questionnaire, 1 study used a questionnaire with the query "did your child ever have a physician-diagnosed AD?"³⁴ and 1 study used the question "has the child ever had eczema?"³⁰ The remaining 3 studies relied on physician examination for AD diagnosis,^{31,33,36} based on a modified Hanifin and Rajka,³³ *International Classification of Diseases, Tenth Revision* code from a claims data set³⁶; 1 study did not specify the criteria used for defining AD.³¹ In 4 of 9 studies, children were diagnosed before age 2 years,³¹⁻³⁴ and in 1 study before age 5 years.³⁶ The remaining 4 studies included children from various ages ranging between 3 and 12 years.^{30,35,37,38}

Between-study heterogeneity was high in all analyses, with Cochrane Q statistic P values less than .05 and I^2 values greater than 75% for all analyses. The random-effects weighted mean prevalence of AD was highest among children born in the fall (15.4%; 95% CI, 12.1%-19.1%) ([Figure 1](#)) followed by winter (14.9%; 95% CI, 12.0%-18.1%), summer (13.7%; 95% CI, 10.8%-17.0%), and spring (12.7%; 95% CI, 10.2%-15.4%).

A significant association was found between AD and fall birth (OR, 1.16; 95% CI, 1.06-1.28; $P = .0018$), winter birth (OR, 1.15; 95% CI, 1.04-1.27; $P = .0076$), but not summer birth (OR, 1.04; 95% CI, 0.95-1.13; $P = .4085$) when spring birth was used as the reference ([Figure 2](#)). Four of 9 studies showed a significant association between AD and fall birth: Dunlop et al³² (OR, 2.02; 95% CI, 1.13-3.52), Kuzume and Kusu³³ (OR, 1.84; 95% CI, 1.39-2.43), Egeberg et al³⁶ (OR, 1.11; 95% CI, 1.09-1.13), and Cai et al³⁸ (OR, 1.16; 95% CI, 1.02-1.31).

TABLE I. Studies with an adapted NOS score of ≥ 7 were considered to be of high quality

Reference	Country	Participant age (y)	Sex of AD cases (female/male)	Study design	Assessment of AD	Prevalence of AD% (n/n _{total})	NOS scale (score)
Anderson et al, ³⁰ 1981	United Kingdom	12	Not given	Prospective cohort	History of AD reported by parent by answering the question “Whether the child had ever had eczema?”	5.9 (325/5548)	6
Arshad et al, ³¹ 1993	United Kingdom	0-2	67/59	Prospective cohort	Diagnosed by doctor and based on the presence of chronic or chronically relapsing, itchy dermatitis (lasting more than 6 wk) with characteristic morphology (areas of scaly, erythematous, pruritic lesions) and distribution (face, postauricular area, scalp extensor surface of extremities, and flexural creases)	10.7 (126/1174)	8
Dunlop et al, ³² 2006	Slovak Republic	0-1	90/116	Prospective cohort	At age 1 y, the birth cohort underwent a standardized clinical evaluation consisting of a questionnaire completed by the mother along with physical examination of the child. Physical examinations were performed by allergists who underwent training in the assessment of AD based on the SCORAD index. A case of AD represented a child whose physical examination yielded a SCORAD index of >2 or whose mother reported a physician diagnosis of AD	15.6 (206/1325)	6
Kuzume and Kusu, ³³ 2007	Japan	0-1	264/366	Prospective cohort	The diagnosis of AD was made according to the criteria of Leung, ³⁹ which modified the definition of AD presented by Hanifin and Rajka	29.5 (630/2136)	7
Wen et al, ³⁴ 2011	Taiwan	0-2	18/25	Prospective cohort	Based on response to question: “Did your child ever have a physician-diagnosed atopic dermatitis?”	5.9 (43/730)	9
Kahr et al, ³⁵ 2014	Denmark	3-9	460/445	Retrospective cohort	Children with AD were identified by a confirmatory response to the following questions: “Has your child ever had eczema in the folds of the elbows and knees? Questions were adopted and modified from ISAAC	14.4 (905/6270)	6
Egeberg et al, ³⁶ 2016	Denmark	0-5	315,112/ 326,722 (not given for AD cases)	Prospective birth cohort	Danish National Patient Register—The primary end point was the first occurrence of AD in childhood between age 0 and 5 y. An algorithm for identification of children with AD in the Danish population was collaboratively developed by specialists in dermatology, allergology, pharmacoepidemiology, and biostatistics. The algorithm was based on combinations of ICD codes (L20, L308C), disease-specific dispensed prescribed medication (ATC D07, D11AH), and selected exclusion criteria	12.7 (85,743/673,614)	9
Sasaki et al, ³⁷ 2016	Japan	6-12	1506/1666	Cross-sectional	ISAAC—Current eczema was defined as a positive response to the following 3 questions: “Has your child ever had an itchy rash which was coming and going for at least 6 months?” “Has your child had this itchy rash at any time in the past 12 months?” and “Has this itchy rash at any time affected any of the following places: folds of the elbows, behind the knees, in front of the ankles, under the buttocks, or around the neck, ears, or eyes?”	13.4 (3174/23,662)	8

(continued)

TABLE I. (Continued)

Reference	Country	Participant age (y)	Sex of AD cases (female/male)	Study design	Assessment of AD	Prevalence of AD% (n/n _{total})	NOS scale (score)
Cai et al, ³⁸ 2017	China	4-6	Not given	Cross-sectional	Questions about childhood eczema were derived from ISAAC. A diagnosis was based on a confirmatory response to the following question: "Has your child ever had eczema (an itchy rash that was coming and going for at least 6 months)?" (ever) or "Has your child had eczema at any time in the last 12 months?" (past year). The original ISAAC questionnaire did not include the word "eczema" in the questions with respect to childhood eczema but was added with a specific description (an itchy rash that was coming and going for at least 6 mo)	23.6 (4371/11,919)	8

ATC, Anatomical Therapeutic Chemical Classification System; ICD, International Classification of Diseases; ISAAC, International Study of Asthma and Allergies in Childhood; NOS, Newcastle-Ottawa scale; SCORAD, SCORing Atopic Dermatitis.

Three of 9 studies showed significant association between AD and winter birth: Dunlop et al³² (OR, 1.97; 95% CI, 1.32-2.97), Kuzume and Kusu³³ (OR, 1.80; 95% CI, 1.36-2.37), and Egeberg et al³⁶ (OR, 1.10; 95% CI, 1.08-1.13).

Dunlop et al³² also showed a significant association between AD and summer birth (OR, 1.82; 95% CI, 1.19-2.79) compared with spring birth.

A sensitivity analysis restricted to European and Asian studies, respectively, showed positive but nonsignificant associations between AD and summer birth (OR, 1.05; 95% CI, 0.90-1.22; $P = .5473$), fall birth (OR, 1.12; 95% CI, 0.99-1.27; $P = .0738$), and winter birth (OR, 1.15; 95% CI, 0.98-1.35; $P = .0948$). In Asian studies, a significant association was observed for fall birth (OR, 1.27; 95% CI, 1.02-1.57; $P = .0335$), but not for summer birth (OR, 1.06; 95% CI, 0.89-1.27; $P = .5122$) or winter birth (OR, 1.20; 95% CI, 0.96-1.49; $P = .1069$).

Qualitative analysis

A total of 14 studies were included in the qualitative analysis examining 676,867 individuals in total and including 47,467 with AD. In 6 of these studies, fall or winter birth was associated with the highest AD prevalence,^{17-20,23,29} whereas 3 identified summer birth as being associated with AD^{24,25,27} and 5 showed no association with season of birth (see Table E1 in this article's Online Repository at www.jaci-inpractice.org).^{16,21,22,26,28}

DISCUSSION

Main findings

This systematic review and meta-analysis examined whether certain seasons of birth were associated with an increased occurrence of AD. Included studies contained a high cumulative number of children, but were performed only on the Northern hemisphere and only contained European and Asian study participants. We found that the risk of developing AD was slightly increased in children born during the fall or winter when compared with spring, in the quantitative analysis, but mixed results in the qualitative analysis.

We identified surprisingly few studies that could be included in the qualitative analysis, which increased the risk of a random finding. Importantly, the association between AD and fall/winter birth tended to be present in studies that found high AD prevalence estimates,^{32,33,36,38} whereas studies with lower prevalence estimates of AD did not show significant associations.^{30,31,34,35} Because it is possible that the high prevalence studies unintentionally included more unspecific eczemas into the AD group making the diagnosis less specific, these observations should be interpreted carefully. We chose to include studies that did not provide absolute data and hence could be included in the meta-analysis to limit the risk of bias. Although some studies supported the finding from the meta-analysis, the findings from the meta-analysis were only supported in part. Moreover, the association between AD and season of birth was generally much weaker than other risk factors included in the analyses of included studies, for example, parental atopy. Although Kuzume and Kusu³³ (29.5%) has a remarkable increased prevalence compared with the other included studies, and Wen et al³⁴ (5.9%) had a remarkable reduced prevalence, the other studies show similar prevalence, and no influence on the results.

A priori, we expected to observe a higher prevalence of AD in children born during fall and winter when compared with spring

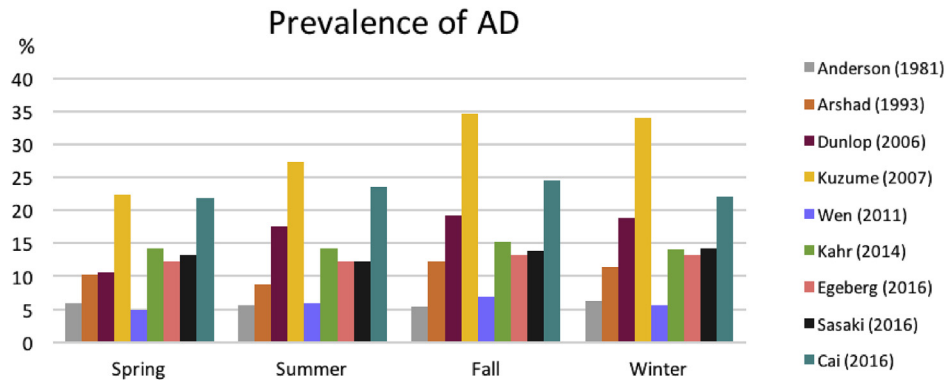


FIGURE 1. Prevalence of AD by birth season in studies included in the quantitative analysis.

and summer. Accordingly, we recently observed a 3% to 5% increased prevalence of pediatric AD at age 18 months in Danish children born in late fall and early winter compared with spring and summer months.⁶ The Danish winters are normally cold, which lead to increased use of indoor heating. Both cold temperatures and low ambient humidity negatively affect the skin barrier, in turn leading to reduced skin hydration and lipid formation as well as increased reactivity to skin irritants.^{7,40} Accordingly, there is an increased number of dermatologist visits for AD as well as use of topical corticosteroids and calcineurin inhibitors over the winter in Denmark,¹³ and a similar increased incidence rate of health care consumption related to AD in Norway during the winter and spring.⁴¹ Interestingly, Japanese patients with AD with common Filaggrin gene mutations reported the highest AD severity in winter months, whereas those without Filaggrin gene mutations experienced worsening in the summer months, indicating genetic predisposition to worsening.⁴²

Based on the scope of the systematic review and the included studies, it was not possible to examine possible factors that could explain a seasonal effect on the risk of AD. However, we here discuss some relevant factors. The dramatic reduction in ultraviolet (UV) irradiation during dark winters on the Northern hemisphere may negatively influence skin barrier functions as suberythemogenic doses of UVB decrease inflammation and enforce skin barrier performance.¹¹ Indeed, a recent study from Australia showed that babies with the highest amount of UV exposure had the lowest risk of developing AD, whereas vitamin D supplementation had no effect.⁴³ A questionnaire study from Korea reinforced this impression as children with the highest number of hours spent outside had the lowest occurrence of AD. Interestingly, cord blood vitamin D levels did not associate with occurrence of AD at age 7 years in Danish children,⁴⁴ and vitamin D supplementation during the third trimester of pregnancy did not affect the risk of AD in Danish children when examined at age 3 years.⁴⁵ These data support that factors associated with UV exposure, but not related to vitamin D synthesis, can reduce the risk of AD. A previous study from Australia identified a latitude-dependent gradient with a higher prevalence of AD in children born more far from the equator,⁴⁶ which we suggested was explained by improved skin barrier functions rather than vitamin D synthesis.⁴⁷ Although the factors discussed here at least in theory could affect the risk of AD in children, there is a need of studies that include such variables to identify possible etiological factors.

Other factors could explain the increased risk of AD in children born during the fall or winter on the Northern hemisphere. Although little is known about the skin barrier function in neonates born during different seasons, immune activity in cord blood and airways is increased in Danish children born during fall and winter.⁴⁸ It has also been shown that the expression of nearly one-fourth of human genes differs according to the time of the year, with many immune genes being more active in the cold and dark winters near the poles.⁴⁹ The increased immune activity could at least in theory increase the risk of developing inflammatory condition such as AD because the immune system here is increased to fight off infections. A strong association between other diseases and season of birth has also been identified.⁵⁰ Interestingly, variations in genes encoding IL-1 β and IL-4 were recently associated with winter birth,⁵¹ and expression of these cytokines is increased in the skin of individuals with AD. Also, postnatal methylation of 92 GpGs was associated with season of birth in children from 2 birth cohorts, and 20 were associated with allergic outcomes.⁵² Although many patients with AD do not have allergic disease, AD is indeed part of the atopic disease spectrum. It may therefore be relevant that IgE levels are significantly increased in individuals who are born in the fall and that an association also has been observed for asthma and season of birth.⁵³ For asthma, a higher risk has been associated with summer birth, although a higher risk has also been identified for winter births, and likely due to infections.^{21,54,55} Air pollution, which has been associated with AD,⁵⁶ is often worse in cold winters, partly due to entrapment from overcast weather, but also due to increased emission from vehicles and household heating. It is important to remember that genetic factors as well as family history of atopy among participants in the included studies may strongly increase the risk of AD,^{31,32,34,37} and that any random uneven overrepresentation across birth months may affect the risk estimates.

Study strengths included the higher number of included studies and individuals as well as a fair representation of studies from both Europe and Asia. Study quality was rated to be overall good. Study limitations included that the AD diagnoses mostly were based on questionnaires and sometimes unspecific AD definitions, which potentially may result in misclassification. Accordingly, the prevalence of AD was markedly different in the included studies, which seemed to affect the associations. Moreover, we would expect the association between AD and fall/winter birth to be strongest in infants, but several studies

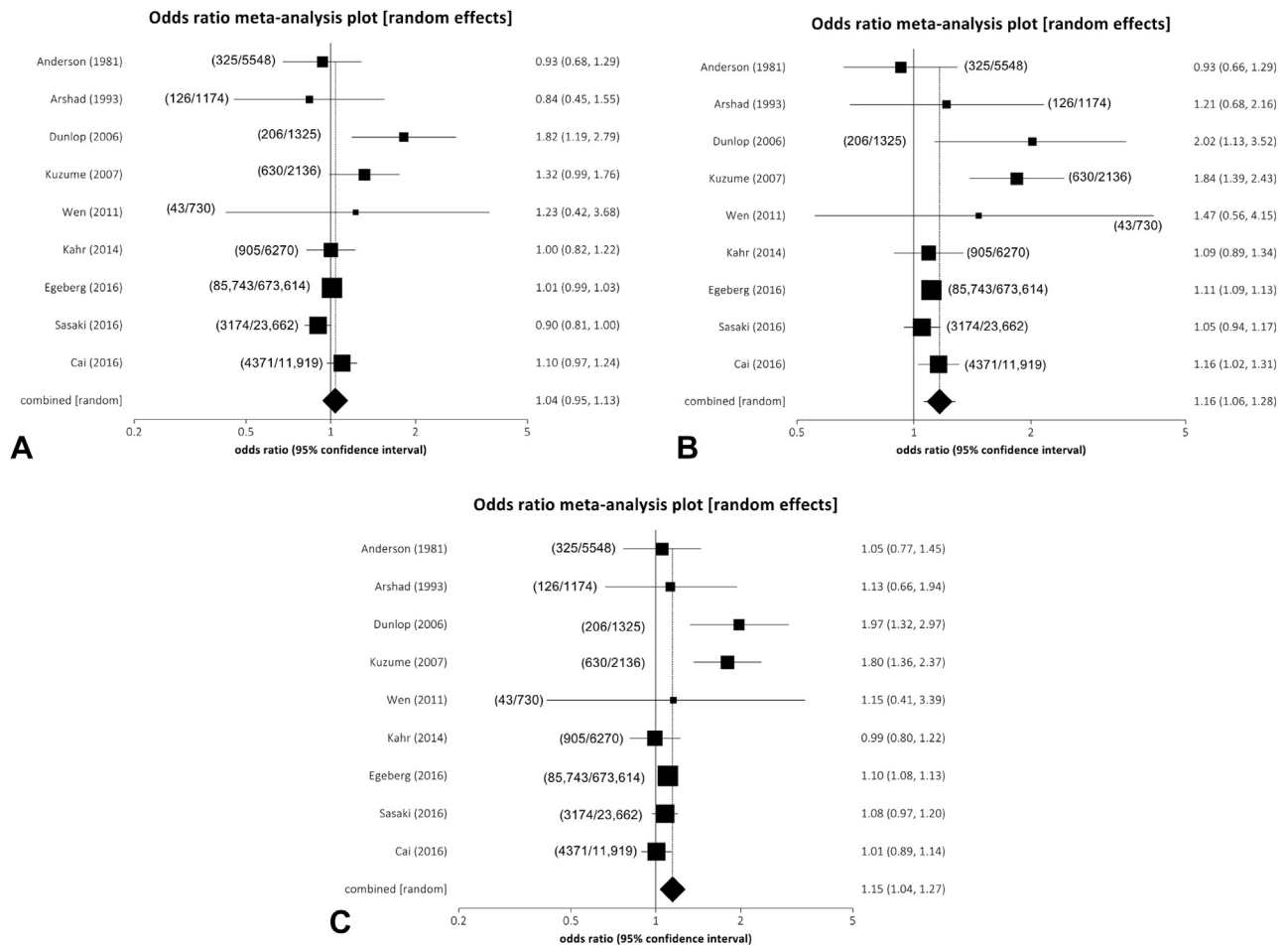


FIGURE 2. The forest plots show the association between AD and being born during summer (A), fall (B), and winter (C), respectively, compared with spring as reference. Number of AD cases and total sample size are added for each study (ADcases/Ntotal).

included much older children, hence allowing other exposures to mask the effect of season. Because no studies were identified from Australia, Africa, and North/South America, the findings cannot be generalized. Also, there is need of studies from the Southern hemisphere to support a genuine relationship with season of birth. Finally, only 9 studies were included in the meta-analysis, which increases the risk of a random finding.

CONCLUSIONS

In this systematic review and meta-analysis of 9 studies, we identified a weakly positive association between developing AD and being born in the fall and winter, but also identified important methodological concerns and limitations. There is a need for additional and better- designed studies to understand the effect of seasonal changes on the risk of AD.

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TABLE E1. Characteristics of studies included in the qualitative analysis only

Reference	Country	Participant age (y)	Sex of AD cases (female/male)	Study design	Assessment of AD	N total	n total AD cases	Main findings
Beck and Hagdrup, ^{E1} 1987	Denmark	0-41	106/104	Retrospective cohort	Not given	210	210	Among 210 patients with AD, the risk of having house-dust mite allergy was increased in patients born between May and November (RR, 1.49; 95% CI, 1.22-2.17)
Meffert et al, ^{E2} 1990	Germany	NA	NA	Case-control	Diagnosis of AD was based on clinical examination and history	448,288	4,040	There was a higher prevalence of AD among individuals born during August to October (9.1%). The prevalence of AD was lower in persons born from March to July (8.1%) (with the exception of May)
Schaferer et al, ^{E3} 1993	Germany	5-6	NA	Cross-sectional	Personal history (by questionnaire) and personal examination (no further information)	1,066	235	No association was observed between AD and month of birth
Karachaliou et al, ^{E4} 1995	Greece	2.5-30	NA	Retrospective cohort	Diagnosis given by physician	1,755	350	More patients with AD were born in July and August compared with all other months of the year (RR, 1.40; 95% CI, 1.11-1.17; $P < .001$)
Olesen et al, ^{E5} 1997	Denmark	6-7	204/199	Prospective birth cohort	Diagnosis of AD given by a doctor, noted as a specialist	7,862	403	No association was observed between AD and season of birth
Aoki et al, ^{E6} 1998	Japan	0-31	4,641/5,515	Prospective cohort	Based on Japanese Dermatological Association Criteria for the diagnosis AD	10,156	10,156	The prevalence of AD in children <1 y was significantly lower, compared with expected for each month, among those born in March and April ($P < .001$) and higher in those born between October and November ($P < .001$)
Chew et al, ^{E7} 1998	Singapore	6-15	NA	Retrospective cohort	ISAAC Questionnaire	NA	NA	Two periods (March-May and September-November) had the highest AD prevalence, with exceptions in few birth years
Kusunoki et al, ^{E8} 1999	Japan	7-15	34/30	Cross-sectional	AD was defined by Hanifin and Rajka	33,725	74	Those born in October to December had the highest prevalence of AD (OR, 1.22; 95% CI, 1.01-1.34; $P < .0001$) and those born in April to June had the lowest prevalence (OR, 0.79; 95% CI, 0.71-0.88; $P < .0001$). Reference season was the 3 other seasons combined. The AD prevalence reached a minimum for children born in May (5.2%; OR, 0.77; 95% CI, 0.65-0.92; $P = .003$) and a maximum for children born in November (7.6%; OR, 1.20; 95% CI, 1.03-1.39; $P = .017$) The reference month was not given

Saitoh et al, ^{E9} 2001	Japan	12-13	391/364	Cross-sectional	AD was defined by Hanifin and Rajka	755	211	No association was observed between AD and season of birth
Chang et al, ^{E10} 2013	Taiwan	7-15	NA	Retrospective cohort	ICD-9-CM codes	NA	NA	No association was observed between AD and season of birth
Kusunoki et al, ^{E11} 2013	Japan	7-15	NA	Cross-sectional	The parents were asked the following questions: (1) has your child ever had eczema; and (2) if so, at what age was it initially observed? Those who answered “yes” to question (1) and those who answered “age within 6 months after birth” to question (2) were regarded as having eczema for 6 mo	13,179	NA	Children born between September and February, compared with children born in March-August, had a significantly higher prevalence (11.4%; OR, 1.51; 95% CI, 1.34-1.69; $P = .0001$) of AD diagnosed before the age of 6 mo. For March-August, the prevalence was 7.9%
Hwang et al, ^{E12}	Korea	6-13	NA	Cross-sectional	Korean version of ISAAC questionnaire	3,344	209	The prevalence of AD was higher in children born in the winter (adjusted OR, 1.24; 95% CI, 1.03-1.49; $P = .024$) than in summer. The prevalence of AD for “symptoms in the recent year” and season of birth showed a nonsignificant association (OR, 1.24; 95% CI, 0.88-1.75; $P = .223$)
Kuo et al, ^{E13} 2016	Taiwan	0-20	16,459/ 14,778	Case-control	ICD-9-CM codes	156,185	31,237	The AD prevalence varied by birth month, with the highest prevalence in summer-born babies. Compared with participants born in May, those born in December (OR, 1.17; 95% CI, 1.10-1.25) had the highest risk of AD followed by those born in October (OR, 1.15; 95% CI, 1.08-1.22) and those born in November (OR, 1.13; 95% CI, 1.06-1.20)
Sargsyan et al, ^{E14} 2018	Armenia	Mean age, 2.5	147/195	Retrospective cohort	Diagnosis given by physicians	342	342	The association between birth season and AD severity showed that being born in the winter was significantly associated with a lower risk of severe AD compared with birth in the spring (OR, 0.2; 95% CI, 0.06-0.64; $P = .007$) and summer (OR, 0.29; 95% CI, 0.09-0.93; $P = .04$)

ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; ISAAC, International Study of Asthma and Allergies in Childhood; RR, relative risk; NA, not applicable/available.

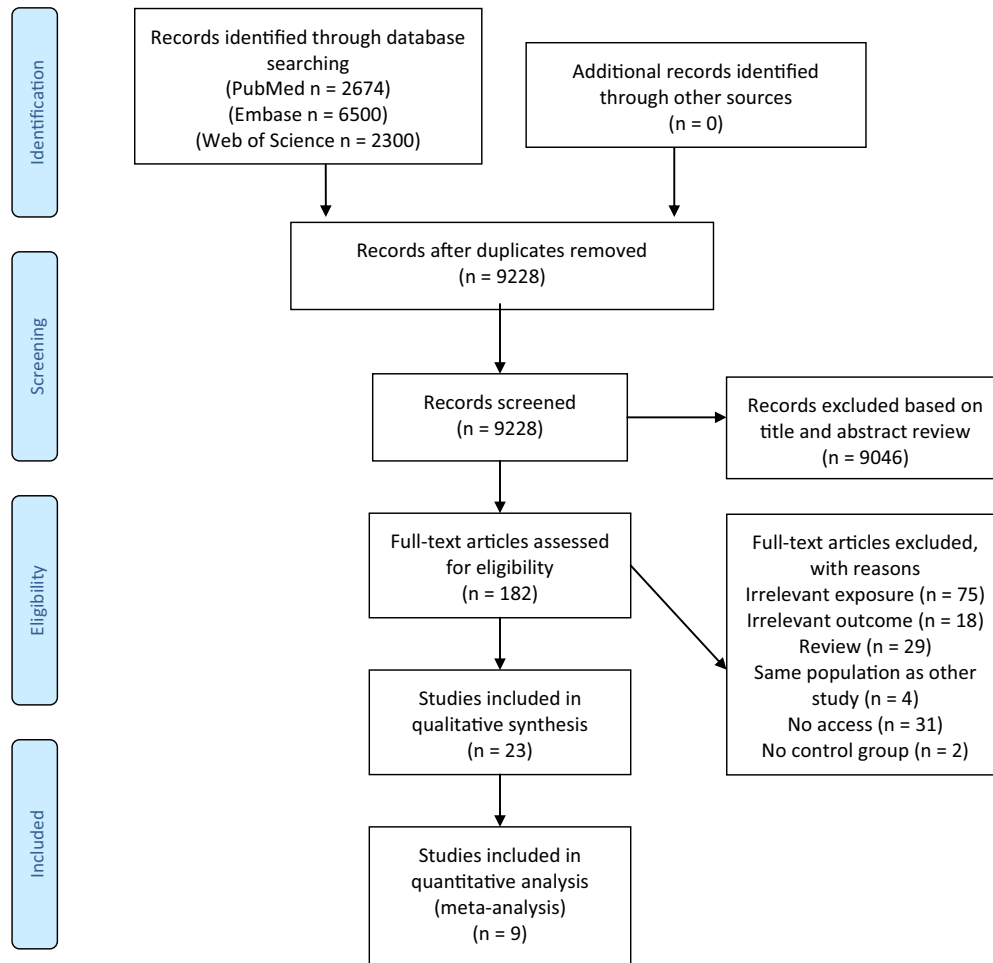


FIGURE E1. The Preferred Reporting Items of Systematic reviews and Meta-analyses flow diagram.

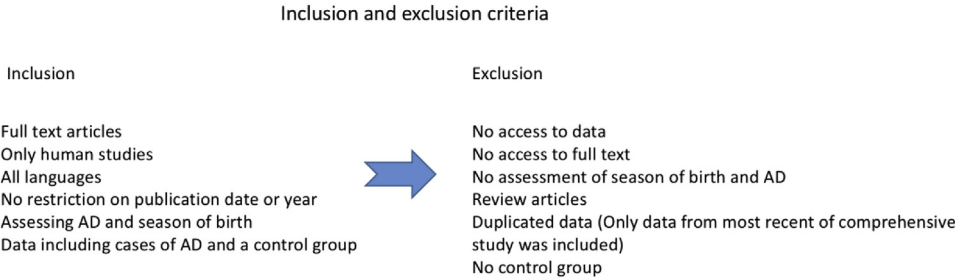


FIGURE E2. Inclusion and exclusion criteria.

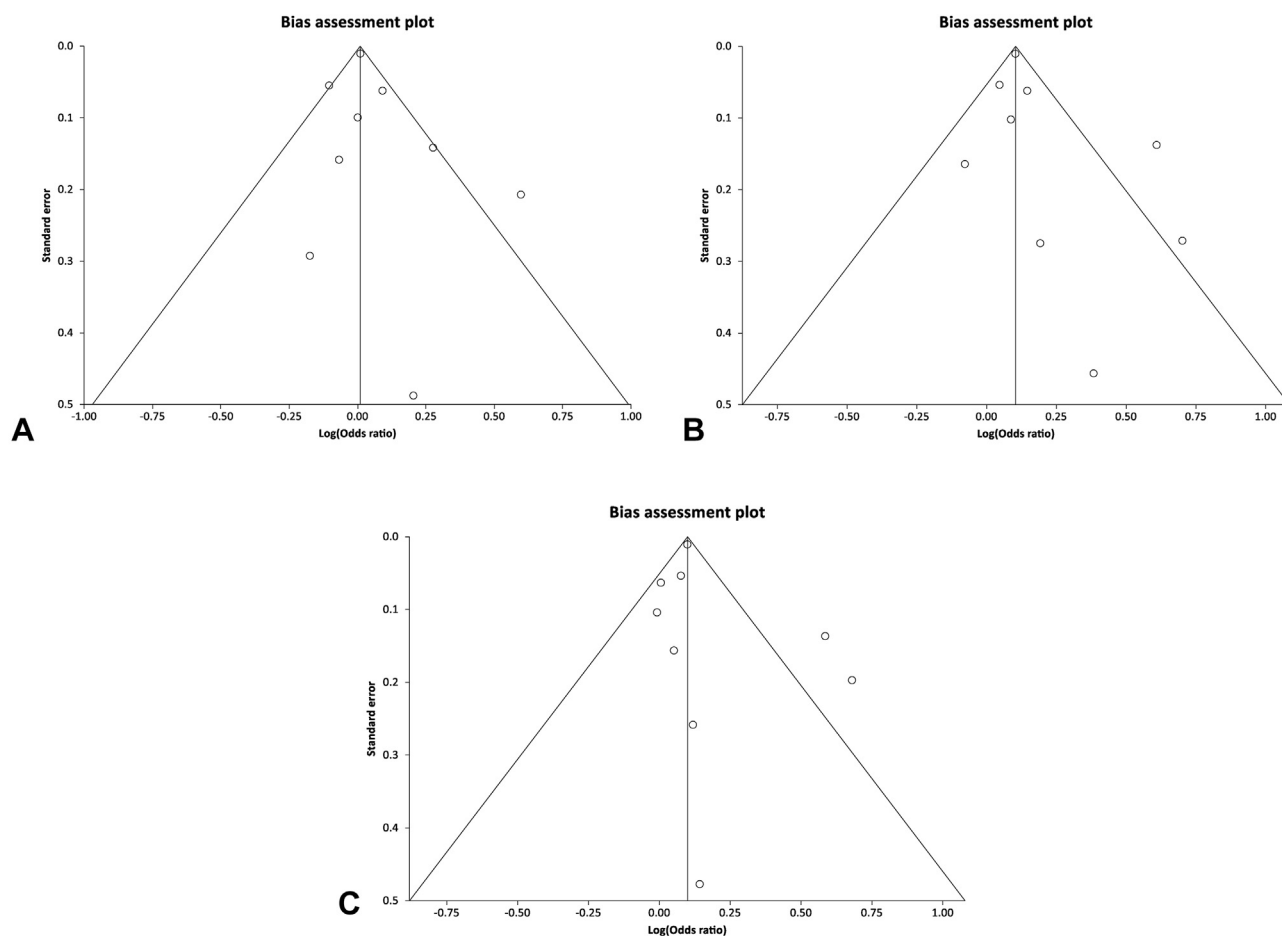


FIGURE E3. The forest plots show bias assessment plot for the studies included in the quantitative analyses, divided into seasons: summer (A), fall (B), and winter (C), respectively, compared with spring as reference.

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