Original Article | Annals of Dermatology 2023;35(1):11-22 • https://doi.org/10.5021/ad.21.268

Prenatal Maternal Risk Factors Contributing to Atopic Dermatitis: A Systematic Review and Meta-Analysis of Cohort Studies

Hong Cui[1,2], Zhijuan Mu[1,2]

[1]Department of Dermatology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, Tianjin, [2]National Clinical Research Center for Chinese Medicine Acupuncture and Moxibustion, Tianjin, China

Received December 22, 2021
Revised July 6, 2022
Accepted October 12, 2022

Corresponding Author
Hong Cui
Department of Dermatology, First Teaching Hospital of Tianjin University of Traditional Chinese Medicine, No.88 Changling Road, Xiqing District, Tianjin 300381, China
Tel: +86-022-27987678
Fax: +86-022-27987678
E-mail: hongtcm123@outlook.com
https://orcid.org/0000-0003-1242-6167

Background: The gestational risk factors predispose to the manifestation of early childhood atopic dermatitis (AD).
Objective: We evaluated the association between modifiable and non-modifiable gestational and prenatal risk factors that affect the AD prevalence in children.
Methods: We performed the systematic review and meta-analysis of cohort studies (n=27) in PubMed and EMBASE (2000~2021). A meta-analysis was performed using random-effects models to estimate pooled odds ratios (OR) or hazard ratio (HR). We performed a systematic review according to Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guidelines and summarized cohort studies investigating gestational and prenatal risk factor those predispose to AD in off spring. Leading modifiable and non-modifiable were identified through ORs. Meta-analysis using the random effect model was also conducted to provide an overall estimate for several significant factors.
Results: Among the non-modifiable risk factors gestational diabetes (7.2, 95% confidence interval [CI]: 1.4~34.5), maternal history of allergy (2.14, 95% CI: 1.54~2.97) and prenatal history of eczema (2.46, 95% CI: 1.0~5.8) were found as major determining risk factors in early manifestation of AD in children. Further, maternal exposure to industrial products (1.89, 95% CI: 1.10~3.16), exposure to antibiotics during pregnancy (3.59, 95% CI: 1.19~10.85) and passive smoking during pregnancy (2.60, 95% CI: 1.11~6.1) are leading causes of early AD manifestation.
Conclusion: Conclusively, both genetic and environmental factors play a pivotal role in early manifestation of AD. The better managing the environmental factors during gestational phase to the least can help curtail the prevalence of AD in children.

Keywords: Atopic dermatitis, Gestational, Prenatal, Risk factors

INTRODUCTION

Atopic dermatitis (AD) is common non-communicable inflammatory skin diseases manifested by itching and recurrent eczematous lesions[1,2], skin inflammation, skin barrier abnormality and increase chances of skin infection[3]. It is one of the leading cause of skin related global burden affecting health-related quality of life (HRQoL)in both adults and children[4]. According to estimates, the prevalence of AD is highest in children ranging from 10% to 20%[5] compared to 2.1%~8.1% among adults[6]. A group of dermatologists put the prevalence of AD at 30.48% in infants aging 1 to 12 months and 12.94% in 1 to 7 years old children[7]. It may also predispose to asthma, hay fever and food allergy, infections and cardiovascular risk[8].

The etiology of AD is poorly understood and literature mainly puts the burden on genetic factors, immunological factors[9] and lifestyle issues[10,11]. The filaggrin protein is located on chromosome 1q21.3 and its modifications are identified as major contributing factor in AD onset and progression and asthma[12,13]. The major role of flaggerin is to maintain skin barrier functions[14]. More than

34 loci have been identified as predisposing factors in AD, among which overexpression of EMSY, mutations in docking protein 2 (DOK2), CD200 receptor 1, LoF mutations in caspase recruitment domain-containing protein (CARD14) are linked with AD[15–17]. Socioeconomic position, demographics, smoking patterns, diet, alcohol exposure, weight gain, allergy history and even season of birth play a vital role in clinical manifestation of AD[18].

Considering the importance of genetic and ecological factors combined, it is imperative to notice what maternal and gestational factors during pregnancy play their part in manifestation of AD. This review aims to provide the data from the cohort studies relating to the maternal factors during pregnancy those affect the onset of AD in offspring.

MATERIALS AND METHODS

Search strategy and selection criteria

This review comprises of an extensive and systematic literature search from PubMed (2000~present) and Cochrane library (2000~present). Preferred Reporting Item for Systematic Review and Meta-Analyses (PRISMA) guidelines were followed for the conduction of this review[19]. Both PubMed and Cochrane library were searched in the first week of August 2021. Search terms were based on the Mesh terms where necessary and free text [For instance (prenatal OR antenatal OR gestational OR maternal OR pregnancy) AND ("atopic dermatitis" OR "eczema" OR "allergic disease*" OR "atopic disease*" OR "allergic disorder*")] (Complete search terms are provided as Supplementary Data). Selection criteria was further narrowed by restricting the search to cohort studies that are published in English language after 2000. The titles and abstracts of the finalized articles were screened based on the pre-existing criteria. Two independent researchers reviewed full-texts articles that qualifies for the selection criteria. Any inclusion conflict was settled through discussion among the study team. The protocols for this review are registered with PROSPERO (registration number: XXX12345678901). The software RevMan 5.2 and STATA version 14.0 (College Station, TX, USA) were used to construct the meta-analysis. Ethical approvals were not required as this systematic review and meta-analysis does not involve any direct participation of human. The cohort studies based on the association of any pre-existing maternal condition(s) that is/are manifested into AD in newborn were included in this systematic review. If the same research had duplicate reports, only the most recent one was included in the meta-analysis.

Data collection and analysis

1) Selection of studies

Two researchers independently performed the study selection procedure the same time. Duplicate papers and unqualified literatures were removed by sifting through the abstracts and articles. Full-text articles were then screened for further exclusion. Excluded studies were compiled in a table with a reason for exclusion written in front. Any conflict was resolved through discussion. Details of the study selection procedure are shown in Fig. 1 (PRSIMA table).

2) Data extraction

Two independent researchers extracted the required data from all the included studies on first author's name, publication year, study location, study design, maternal infection, children's allergic disorder information, sample size, effect size and 95% confidence interval (CI), and adjusted or matched varieties. Disagreements about study information were resolved through discussing with a third author.

3) Quality assessment of included studies

Newcastle–Ottawa Scale (NOS) recommended by Cochrane Collaboration assessed the quality of the included studies. This scale consists of 8 items evaluating the quality of observational cohort studies in terms of selection, comparability, and outcome. Differences in opinion were resolved by discussion or consultation with a third author.

Data synthesis and statistical analysis

1) Data synthesis

We conducted a meta-analysis to generate pooled odds ratios (ORs) and 95% CI for the association between maternal infection during pregnancy and asthma or eczema in offspring using RevMan 5.3.5 and STATA version 12.0.

2) Assessment of heterogeneity

Heterogeneity was assessed by the I^2 test. The value of I2 ranges from 0% to100%. with 0% to 40% indicating no important heterogeneity, 40% to 60% indicating moderate heterogeneity, 60% to 90% indicating substantial heterogeneity, and >90% indicating considerable heterogeneity. If $I^2 \geq 50\%$, the reasons for the high heterogeneity was searched and a random-effects model for data analysis were used.

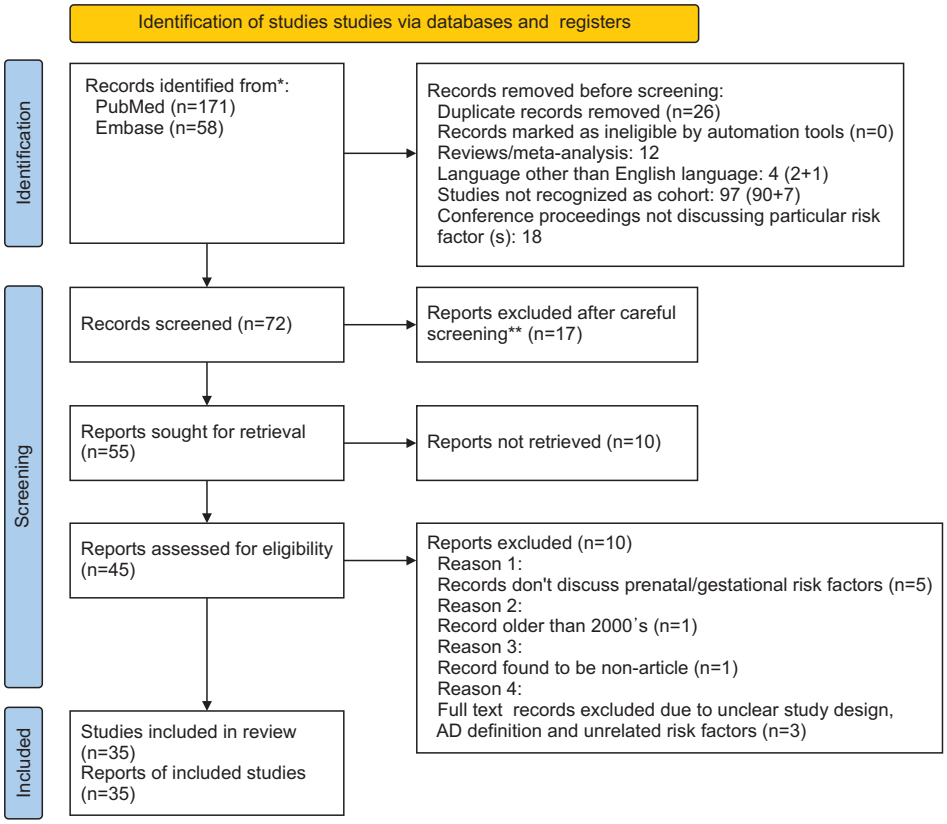

Fig. 1. PRISMA flow diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). †If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

3) Assessment of publication bias

A funnel plot was used to evaluate publication bias if more than 10 studies are included. Relative risk from each study is plotted against their variance. Asymmetrical appearance of the plot indicates the presence of publication bias. Egger test was used to test the asymmetry of the funnel plot. The result was classified based on the Cochrane Handbook for Systematic Reviews of Interventions.

4) Sensitivity analysis

The sensitivity analysis was performed to assess whether the sample size and missing data impact the results of the review. If there are adequate studies (no less than 3 studies), we conducted a sensitivity analysis to check the robustness of conclusions and assess the impact of methodological quality.

RESULTS

Literature search

We have searched the PubMed and Embase databases for related search terms (Supplementary Data) that yielded 171 and 58 records respectively. Duplicates, review articles/meta-analysis, and inconclusive conference proceedings were removed. Only the cohort studies published in English language were selected for further analysis. 72 records were finalized for screening of which 45 were found to be eligible for final analysis. In total, 27 studies were included in the meta-analysis. The PRISMA flow diagram is presented in Fig. 1.

Study characteristics

The retrospective and prospective cohort studies those discuss the prenatal and gestational risk factors in pregnant women that affect the manifestation and/or occurrence of AD in offspring were included in the review. The age of mother(s) was not specified, though studies discussing the age as an isolated risk factor for AD were included. The included 27 studies encompass 327, 364 individuals (pregnant mother/kid) form 13 different countries. Both modifiable and non-modifiable risk factors were included in the study. The minimum age detected for diagnosis of AD was 6 months and maximum was observed to be at 18 years (Table 1)[20-54]. OR and hazards ratio were used to draw a forest plot. Multiple factors from one study were also included in the forest plot. Quality assessment using the NOS scale revealed 70% of the studies have score more than 6.

Table 1. Tabulated characteristics of thirty-five included studies

Reference (year)	Country	Sample size (n)	Study design	Risk of AD development manifested in OR (95% CI)	AD diagnosis age in children	Study goal	Modifiable/ non-modifiable
Bertelsen et al. (2014)[44]	Norway	40,614	Questionnaire	0.859 (0.807~0.914)	6 months	Association between consumption of probiotic milk in pregnancy and childhood AD	Modifiable
Chiu et al. (2015)[45]	Taiwan	164 mother–child pairs	Questionnaire	0.12 (0.02~0.63)	4 years	Relationship between maternal vitamin D levels and AD in early age	Modifiable
Chen et al. (2018)[21]	China	1,056 pregnant women	Interview/ medical records	2.22 (1.07~4.58)	24 months	The link between Prenatal exposure to perfluoroalkyl and perfluoroalkyl substances and childhood AD	Modifiable
Chang et al. (2016)[38]	Republic of Korea	973 mother-baby dyads	Questionnaires	1.31 (1.02~1.69)	5 years	Prenatal maternal distress association with AD in offspring	Non-modifiable
		1,531 mother-baby dyads		1.85 (1.06~3.25)			Non-modifiable
Celik et al. (2019)[20]	Turkey	84 AD children, 56 normal children	Questionnaire	2.60 (1.11~6.1)	24 Months	Mothers exposure to fermented food/exposure to passive smoking and chances of childhood eczema	Modifiable
Carson (2013)[30]	Denmark	411 Kids	Interview	1.44 (1.05~1.99)	First seven years of life	Alcohol intake with history of asthma and childhood AD	Modifiable
Drucker et al. (2019)[31]	United States of America	13,269	Questionnaires	1.23 (1.05~1.43)	10-17 years of age	Association between maternal pre-pregnancy BMI, gestational weight gain, and offspring AD	Modifiable
Gazibara et al. (2016)[46]	The Netherlands	3,019 mothers and their children	Questionnaires	0.97 (0.50~1.87)	Until the age of 4 years	Associations of maternal and fetal 25-hydroxyvitamin D levels with childhood AD	Modifiable
Wadonda-Kabondo et al. (2004)[35]	United Kingdom	14,541 mothers 14 062 children	Questionnaires and clinical assessments	1.69 (1.47~1.95)	42 months	Association of parental eczema, hay fever, and asthma with AD in infancy	Non-modifiable

Table 1. Continued 1

Reference (year)	Country	Sample size (n)	Study design	Risk of AD development manifested in OR (95% CI)	AD diagnosis age in children	Study goal	Modifiable/ non-modifiable
Mukherjee et al. (2018)[47]	United Kingdom	1,456 mother–child pairs	Interviews and examinations	0.4 (0.2~0. 8)	18 years of age	Breastfeeding modifies the effect of smoking during pregnancy on eczema	Modifiable
Renz-Polster et al. (2005)[48]	United States of America	8,953 births	Electronic medical records	0.90 (0.7~1.16)	Children aged 3–10 years	The effects of C-section/Vaginal delivery on AD	Modifiable
Wegienka et al. (2015)[49]	United States of America	1,258 women	Interviews, a clinic visit with a study physician and results from biological and environmental samples	0.69 (0.44~1.08)	2 years	Antibiotics and vaginal antifungal use during pregnancy and its effects on childhood eczema	Modifiable
Goudarzi et al. (2018)[50]	Japan	3,296 mother–child pairs	Asthma and Allergies in Childhood (ISAAC) questionnaires	0.97 (0.94~0.99)	Up to 7 years	Pre-pregnancy BMI and risk of eczema at 7 years	Non-Modifiable
Taylor-Robinson et al. (2016)[43]	United Kingdom	14,499 children	-	1.52 (1.31~1.76)	Up to 5 years	Pre-pregnancy BMI and risk of eczema at 7 years	Non-Modifiable
Korhonen et al. (2018)[51]	Finland	Atopic kids: 202 Non-atopic kids: 333	Blood and cord sample collection	0.43 (0.23~0.80)	5 years	Enterovirus infection in pregnancy and AD risk in children	Non-Modifiable
Zulyniak et al. (2020)[52]	Canada	2,160 mother-infant pairs	Semi-quantitative food-frequency questionnaire (FFQ)	0.65 (0.55~0.76)	1 year	Plant-based diet and its association with AD	Modifiable
Deng et al. (2016)[24]	China	2,598 pre-school children	Questionnaire	1.54 (1.14~2.09)	6 years	Maternal exposure to outdoor air pollution and links with childhood AD	Modifiable
Kumar et al. (2009)[32]	United States of America	680 children	Medical record review	7.2 (1.4~34.5)	3.2±2.3 years	Gestational diabetes and risk of childhood AD	Non-Modifiable
Gao et al. (2019)[34]	China	976 mother–child pairs	Questionnaires	3.59 (1.19~10.85) 2.14 (1.54~2.97)	12 months	Influence of prenatal and early-life exposures on food allergy and eczema in infancy	Modifiable Non-modifiable

Table 1. Continued 2

Reference (year)	Country	Sample size (n)	Study design	Risk of AD development manifested in OR (95% CI)	AD diagnosis age in children	Study goal	Modifiable/ non-modifiable
				1.38 (1.00~1.91) 1.81 (1.17~2.80)			Non-modifiable Modifiable
Wang et al. (2013)[42]	Taiwan	24,200 mother–newborn pairs	Questionnaires	1.64 (1.44~1.87)	3 years of age	Maternal employment and AD in children	Non-modifiable
Hersoug et al. (2008)[41]	Denmark	31,471 mother–child pairs	Interview	1.03 (0.81~1.301)	18 months of age	Maternal employment in child-care institutions and the risk of AD in the offspring	Non-modifiable
Miyake et al. (2013)[27]	Japan	1,354 Japanese mother–child pairs	Diet history questionnaire	1.42 (0.93~2.17)	23~29 months	Maternal fat intake and risk of AD	Modifiable
Rucci et al. (2016)[28]	Netherlands	4,976 subjects	ISAAC-based questionnaires	1.21 (1.07~1.37)	6 years	Maternal fatty acid levels during pregnancy, childhood lung function and risk of AD	Modifiable
Leermakers et al. (2013)[29]	Netherlands	2,976 mothers	Food frequency questionnaire	1.17 (1.00~1.38)	4 years	Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood	Modifiable
Elbert et al. (2017)[37]	Netherlands	5,205 children	Questionnaire	1.15 (1.02~1.29)	5 years	Gestational psychiatric symptoms and risk of childhood AD	Non-modifiable
Wang et al. (2016)[36]	Taiwan	24,200 mother–newborn pairs	Questionnaire	1.42 (1.21~1.66)	3 years	Maternal psychologic problems increased the risk of childhood AD	Non-modifiable
Rada et al. (2020)[40]	United States	4,044 mothers 4,813 off springs	Questionnaire	1.06 (0.76~1.47)	Born between 1987 and 1995*	Night shift work surrounding pregnancy and offspring risk of AD	Non-modifiable
Lu et al. (2017)[26]	China	2,598 children	Questionnaire	1.26 (1.09~1.46)	3~6 years	Perinatal exposure to traffic-related air pollution and eczema in preschool children	Modifiable
Timm et al. (2017)[53]	Denmark	62,560 mother–child pairs	Questionnaires	1.45 (1.19~1.76)	18 months	Prenatal antibiotics and AD risk	Modifiable

Table 1. Continued 3

Reference (year)	Country	Sample size (n)	Study design	Risk of AD development manifested in OR (95% CI)	AD diagnosis age in children	Study goal	Modifiable/ non-modifiable
Lu et al. (2017)[26]	China	2,598 children	Questionnaire	1.26 (1.09~1.46)	3~6 years	Perinatal exposure to traffic-related air pollution and eczema in preschool children	Modifiable
Timm et al. (2017)[53]	Denmark	62,560 mother–child pairs	Questionnaires	1.45 (1.19~1.76)	18 months	Prenatal antibiotics and AD risk	Modifiable
Just et al. (2012)[25]	United States of America	407	Questionnaires	1.52 (1.21~1.91)	24 months of age.	Prenatal exposure to butyl benzyl phthalate and early eczema	Modifiable
Kurzius-Spencer et al. (2005)[33]	United States of America	744 pregnant women	Questionnaires/ blood samples	2.46 (1.0~5.8)	12 months	Prenatal factors associated with the development of eczema	Non-modifiable
Lee et al. (2021)[23]	Republic of Korea	738 mother–child pairs	Questionnaires/ blood samples	1.83 (1.00~3.38)	6-month	Prenatal heavy metal exposures and atopic dermatitis	Modifiable
Wen et al. (2009)[22]	Taiwan	863 mother infant pairs	ISAAC questionnaire	1.89 (1.10~3.16)	5-year	Prenatal perfluorooctanoic acid exposure and early onset AD	Modifiable
McKeever et al. (2001)[54]	United Kingdom	29,238 children	Questionnaire	0.70 (0.64~0.76)	2 years	Siblings, multiple births, and the incidence of allergic disease	Non-modifiable
Mommers et al. (2010)[39]	Netherlands	2,319 children	Questionnaire	1.42 (0.84~2.39)	2 years	Timing of infection and development of wheeze, eczema, and atopic sensitization	Non-modifiable

AD: atopic dermatitis, OR: odds ratio, CI: confidence interval, HR: hazards ratio, RR: relative risk, BMI: body mass index, C-Section: cesarean delivery, PUFA: polyunsaturated fatty acids. *Questionnaires were completed in 2004.

The modifiable gestational/prenatal risk factors and association with AD

The analysis of the studies revealed that AD is associated with various modifiable gestational/prenatal risk factors. Among the 27 included reports, 20 had highlighted the modifiable gestational risk factors. The ingestion and/or exposure to different industrial pollutants during pregnancy was found to be greatest modifiable risk factor(s) that predisposes to AD in off springs. Mothers with exposure to passive smoking had higher risk of developing AD in their kids (2.60, 95% CI 1.11~6.1)[20]. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances raised the risk for childhood AD (2.22, 95% CI 1.07~4.58)[21]. It was followed by prenatal perfluorooctanoic acid (1.89, 95% CI 1.10~3.16)[22] and heavy metal exposure (1.83, 95% CI 1.00~3.38) during pregnancy that raises the chances of AD in kids[23]. Other prominent modifiable risk factors are maternal exposure to outdoor air pollution (1.54, 95% CI 1.14~2.09)[24], prenatal exposure to butyl benzyl phthalate (1.52, 95% CI 1.21~1.91)[25], and 1st trimester exposure to NO_2 in 1st trimester (1.26, 95% CI 1.09~1.46) (Fig. 2)[26].

Dietary habits and patterns during pregnancy were found as second leading cause of AD risk in children.

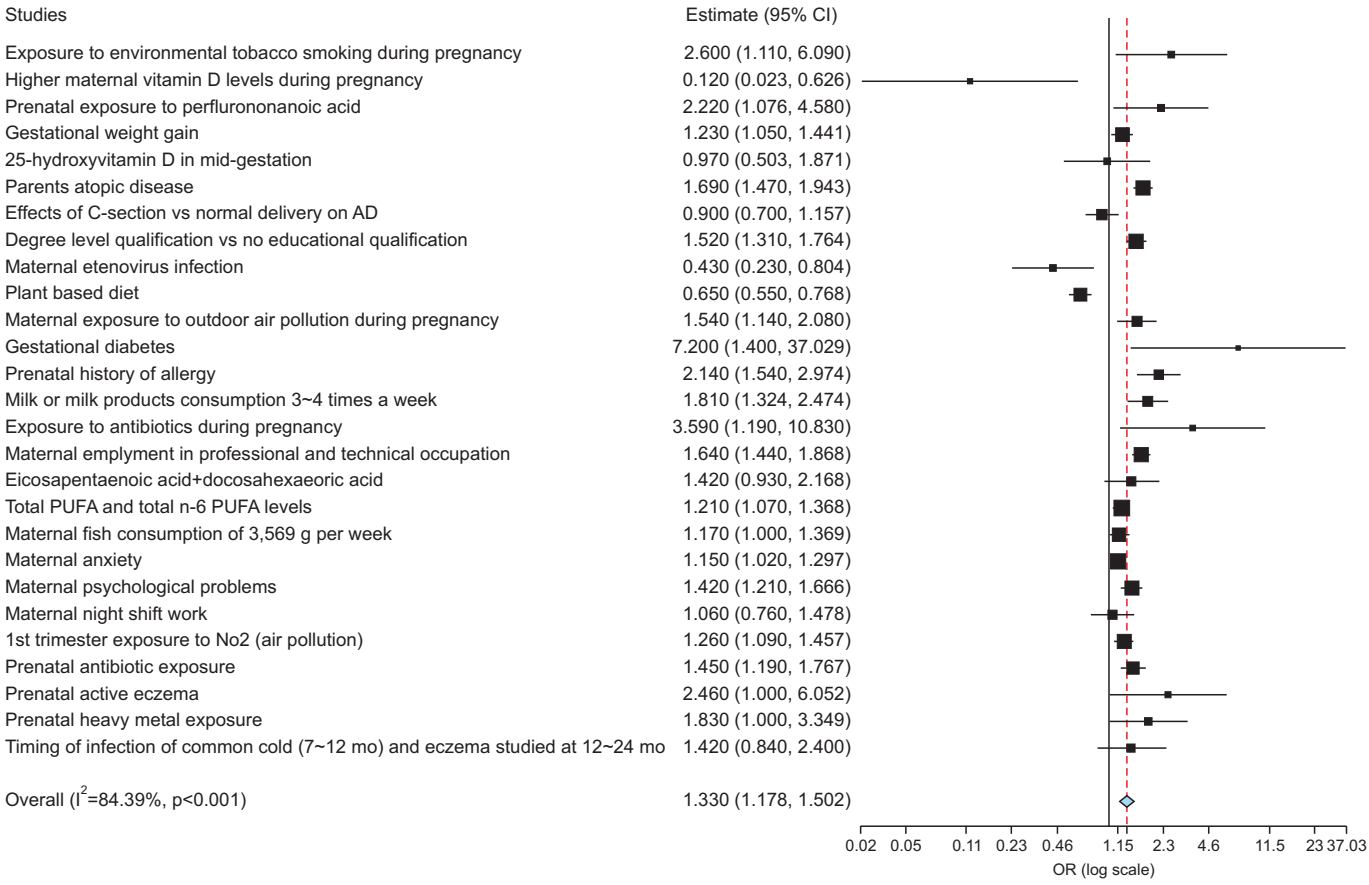

Fig. 2. Pooled ORs from meta-analyses representing modifiable/non-modifiable factors gestational/prenatal risk factors for the predisposition of AD in children. The analysis was performed using RevMan 5.3.5 and STATA version 12.0. Both modifiable and non-modifiable maternal factors play a decisive role in manifestation of AD in offspring. Gestational diabetes and maternal exposure to antibiotics during pregnancy remain a key factor for AD risk in immediate children. AD: atopic dermatitis; OR: odds ratio.

Maternal fat intake during pregnancy (eicosapentaenoic acid+docosahexaenoic acid) (1.42, 95% CI 0.93~2.17)[27], higher maternal total polyunsaturated fatty acids (PUFA) and total n-6 PUFA levels (1.21, 95% CI 1.07~1.37)[28] are also linked with raised risk of AD in newborns. Further, higher maternal fatty fish consumption of around 35~69 g per week (1.17, 95% CI 1.00~1.38)[29], alcohol intake in pregnancy (1.44, 95% CI 1.05~1.99)[30], higher maternal pre-pregnancy body mass index and gestational weight gain (1.23, 95% CI 1.05~1.43)[31] are dietary risk factors associated with higher risk of AD (Fig. 2).

The non-modifiable gestational/prenatal risk factors and association with AD

The most important non-modifiable gestational risk factors associated with the prevalence of AD in newborn is gestational diabetes (7.2, 95% CI 1.4~34.5)[32], followed by prenatal eczema in pregnancy (2.46, 95% CI 1.0~5.8)[33] and prenatal history of allergy (2.14, 95% CI 1.54~2.97)[34]. Another study also pointed at the parents history of eczema, asthma, hay fever and associated risk of AD in offspring (1.69, 95% CI 1.47~1.95)[35]. Furthermore, children of mothers suffering from mental disorders such as maternal psychological disorder (1.42, 95% CI 1.21~1.66)[36], maternal anxiety (1.15, 95% CI 1.02~1.29)[37], distress mothers suffering from distress (1.85, 95% CI 1.06~3.25), depression during pregnancy (1.31, 95% 1.02~1.69)[38] had an increases risk of developing AD.

Timing of first infection of common cold (7~12 months) and eczema in kids diagnosed at 12~24 months (1.42, 95% CI 0.84~2.39)[39] is related. The pattern of life during gestational period seems to play a vital role in determining the degree of risk of AD in offspring. For instance, maternal night shift work (1.06, 95% CI 0.76~1.47)[40], mothers employed in child-care institutions (1.03, 95% CI 0.81~1.301)[41], mothers with professional or technical occupation (1.64, 95% CI 1.44~1.87)[42],

season of birth (1.38, 95% CI 1.00~1.91), and degree-level qualifications (1.52 95% CI 1.31~1.76)[43], predisposes to AD in children (Fig. 2).

DISCUSSION

The results of this meta-analysis of cohort studies focusing on the prenatal factors that increase the risk of childhood eczema suggest that both modifiable and non-modifiable factors are important in AD predisposition. The broader understanding of this meta-analysis revealed that exposure to industrial hazards and outdoor air pollution in pregnant mothers is the largest group of risk modifiable factors that raises the risk of AD in young kids. Previous studies have also highlighted eczema as an environmental disease[55,56]. In addition to environmental factors, dietary factors also play a significant role. The consumption of fatty diet in prenatal phase remains a second largest group of factors in the context. Our results are in line with the previous animal[57] and human data[58]. Furthermore, life patterns, obesity and alcohol consumption during pregnancy phase are other important causes of childhood AD. Correspondingly, previous studies have associated reduction in weight with improved treatment outcomes in AD patients[59]. Our analysis suggested that other factors such as consumption of probiotic milk in pregnancy, higher levels of maternal vitamin D, deficiency in vitamin D at mid-gestational period, effects of gestational smoking and breastfeeding on AD, cesarean delivery and plant based diet does not significantly affect the outcomes in childhood AD.

Similarly, among group of non-modifiable risk factors gestational diabetes and prenatal eczema/allergies understandably remain a key determining factor of childhood AD. There is abundant data available suggesting the key role and association of asthma and other allergies with childhood eczema[60]. Mother's psychological state, depression and anxiety is second largest non-modifiable group of risk factors predisposing to childhood AD. Interestingly there is a shared genetic liability between major depressive disorders and AD[61]. Furthermore, mother's occupation and pattern of work life style was revealed as another vital predisposing factor. It is also interesting to notice that even season of birth of autumn/winter play a significant role in AD manifestation in young kids. Mother's exposure to passive smoking invariably affects the emergence of AD in kids. Interestingly, the manifestation of AD in adolescents is also affected by second-hand smoking[62].

Our results showed that maternal risk factors during pregnancy period play a decisive role in manifestation of AD in off spring. A set of both modifiable and non-modifiable risk factors are associated with predisposition of AD. Namely, mother's exposure to industrial substances, antibiotics use and passive smoking during pregnancy are leading causes of AD early risk. Similarly parental allergy history, prenatal eczema mother's psychological state determines the predisposition of AD in children. Both environmental and genetic factor in gestational period play a diverse and intricate role in manifestation of AD in off spring. Further studies are required clarify the mechanisms and ways to manage the modifiable factors to the least.

SUPPLEMENTARY MATERIALS

Supplementary data can be found via http://anndermatol.org/src/sm/ad-21-268-s001.pdf.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

FUNDING SOURCE

None.

DATA SHARING STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ORCID

Hong Cui, https://orcid.org/0000-0003-1242-6167
Zhijuan Mu, https://orcid.org/0000-0001-7257-2903

REFERENCES

1. Nomura T, Wu J, Kabashima K, Guttman-Yassky E. Endophenotypic variations of atopic dermatitis by age, race, and ethnicity. J Allergy Clin Immunol Pract 2020;8:1840-1852.
2. Langan SM, Irvine AD, Weidinger S. Atopic dermatitis. Lancet

2020;396:345-360. Erratum in: Lancet 2020;396:758.
3. McAleer MA, Flohr C, Irvine AD. Management of difficult and severe eczema in childhood. BMJ 2012;345:e4770.
4. Blome C, Radtke MA, Eissing L, Augustin M. Quality of life in patients with atopic dermatitis: disease burden, measurement, and treatment benefit. Am J Clin Dermatol 2016;17:163-169.
5. Deckers IA, McLean S, Linssen S, Mommers M, van Schayck CP, Sheikh A. Investigating international time trends in the incidence and prevalence of atopic eczema 1990-2010: a systematic review of epidemiological studies. PLoS One 2012;7:e39803.
6. Barbarot S, Auziere S, Gadkari A, Girolomoni G, Puig L, Simpson EL, et al. Epidemiology of atopic dermatitis in adults: results from an international survey. Allergy 2018;73:1284-1293.
7. Li H, Zhang Z, Zhang H, Guo Y, Yao Z. Update on the pathogenesis and therapy of atopic dermatitis. Clin Rev Allergy Immunol 2021;61:324-338.
8. Silverberg JI. Comorbidities and the impact of atopic dermatitis. Ann Allergy Asthma Immunol 2019;123:144-151.
9. Ma Y, Wang W, Devarakonda T, Zhou H, Wang XY, Salloum FN, et al. Functional analysis of molecular and pharmacological modulators of mitochondrial fatty acid oxidation. Sci Rep 2020;10:1450.
10. Olesen AB, Ellingsen AR, Olesen H, Juul S, Thestrup-Pedersen K. Atopic dermatitis and birth factors: historical follow up by record linkage. BMJ 1997;314:1003-1008.
11. Løset M, Brown SJ, Saunes M, Hveem K. Genetics of atopic dermatitis: from DNA sequence to clinical relevance. Dermatology 2019;235:355-364.
12. Baurecht H, Hotze M, Brand S, Büning C, Cormican P, Corvin A, et al. Genome-wide comparative analysis of atopic dermatitis and psoriasis gives insight into opposing genetic mechanisms. Am J Hum Genet 2015;96:104-120. Erratum in: Am J Hum Genet 2015;97:933.
13. Luukkonen TM, Kiiski V, Ahola M, Mandelin J, Virtanen H, Pöyhönen M, et al. The value of FLG Null mutations in predicting treatment response in atopic dermatitis: an observational study in Finnish patients. Acta Derm Venereol 2017;97:456-463.
14. Palmer CN, Irvine AD, Terron-Kwiatkowski A, Zhao Y, Liao H, Lee SP, et al. Common loss-of-function variants of the epidermal barrier protein filaggrin are a major predisposing factor for atopic dermatitis. Nat Genet 2006;38:441-446.
15. Elias MS, Wright SC, Remenyi J, Abbott JC, Bray SE, Cole C, et al. EMSY expression affects multiple components of the skin barrier with relevance to atopic dermatitis. J Allergy Clin Immunol 2019;144:470-481. Erratum in: J Allergy Clin Immunol 2020;145:723.
16. Mucha S, Baurecht H, Novak N, Rodríguez E, Bej S, Mayr G, et al. Protein-coding variants contribute to the risk of atopic dermatitis and skin-specific gene expression. J Allergy Clin Immunol 2020;145:1208-1218.
17. Peled A, Sarig O, Sun G, Samuelov L, Ma CA, Zhang Y, et al. Loss-of-function mutations in caspase recruitment domain-containing protein 14 (CARD14) are associated with a severe variant of atopic dermatitis. J Allergy Clin Immunol 2019;143:173-181.e10.
18. Nutten S. Atopic dermatitis: global epidemiology and risk factors. Ann Nutr Metab 2015;66 Suppl 1:8-16.
19. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
20. Celik V, Beken B, Yazicioglu M, Ozdemir PG, Sut N. Do traditional fermented foods protect against infantile atopic dermatitis. Pediatr Allergy Immunol 2019;30:540-546.
21. Chen Q, Huang R, Hua L, Guo Y, Huang L, Zhao Y, et al. Prenatal exposure to perfluoroalkyl and polyfluoroalkyl substances and childhood atopic dermatitis: a prospective birth cohort study. Environ Health 2018;17:8.
22. Wen HJ, Chen PC, Chiang TL, Lin SJ, Chuang YL, Guo YL. Predicting risk for early infantile atopic dermatitis by hereditary and environmental factors. Br J Dermatol 2009;161:1166-1172.
23. Lee S, Park SK, Park H, Lee W, Kwon JH, Hong YC, et al. Prenatal heavy metal exposures and atopic dermatitis with gender difference in 6-month-old infants using multipollutant analysis. Environ Res 2021;195:110865.
24. Deng Q, Lu C, Li Y, Sundell J, Dan Norbäck. Exposure to outdoor air pollution during trimesters of pregnancy and childhood asthma, allergic rhinitis, and eczema. Environ Res 2016;150:119-127.
25. Just AC, Whyatt RM, Perzanowski MS, Calafat AM, Perera FP, Goldstein IF, et al. Prenatal exposure to butylbenzyl phthalate and early eczema in an urban cohort. Environ Health Perspect 2012;120:1475-1480.
26. Lu C, Deng L, Ou C, Yuan H, Chen X, Deng Q. Preconceptional and perinatal exposure to traffic-related air pollution and eczema in preschool children. J Dermatol Sci 2017;85:85-95.
27. Miyake Y, Tanaka K, Okubo H, Sasaki S, Arakawa M. Maternal fat intake during pregnancy and wheeze and eczema in Japanese infants: the Kyushu Okinawa Maternal and Child Health Study. Ann Epidemiol 2013;23:674-680.
28. Rucci E, den Dekker HT, de Jongste JC, Steenweg-de-Graaff J, Gaillard R, Pasmans SG, et al. Maternal fatty acid levels during pregnancy, childhood lung function and atopic diseases. The Generation R

Study. Clin Exp Allergy 2016;46:461-471.
29. Leermakers ET, Sonnenschein-van der Voort AM, Heppe DH, de Jongste JC, Moll HA, Franco OH, et al. Maternal fish consumption during pregnancy and risks of wheezing and eczema in childhood: the Generation R Study. Eur J Clin Nutr 2013;67:353-359.
30. Carson CG. Risk factors for developing atopic dermatitis. Dan Med J 2013;60:B4687.
31. Drucker AM, Pope EI, Field AE, Qureshi AA, Dumas O, Camargo CA Jr. Association between maternal pre-pregnancy body mass index, gestational weight gain, and offspring atopic dermatitis: a prospective cohort study. J Allergy Clin Immunol Pract 2019;7:96-102.e2.
32. Kumar R, Ouyang F, Story RE, Pongracic JA, Hong X, Wang G, et al. Gestational diabetes, atopic dermatitis, and allergen sensitization in early childhood. J Allergy Clin Immunol 2009;124:1031-1038.e1-4.
33. Kurzius-Spencer M, Halonen M, Carla Lohman I, Martinez FD, Wright AL. Prenatal factors associated with the development of eczema in the first year of life. Pediatr Allergy Immunol 2005;16:19-26.
34. Gao X, Yan Y, Zeng G, Sha T, Liu S, He Q, et al. Influence of prenatal and early-life exposures on food allergy and eczema in infancy: a birth cohort study. BMC Pediatr 2019;19:239.
35. Wadonda-Kabondo N, Sterne JA, Golding J, Kennedy CT, Archer CB, Dunnill MG. Association of parental eczema, hayfever, and asthma with atopic dermatitis in infancy: birth cohort study. Arch Dis Child 2004;89:917-921.
36. Wang IJ, Wen HJ, Chiang TL, Lin SJ, Guo YL. Maternal psychologic problems increased the risk of childhood atopic dermatitis. Pediatr Allergy Immunol 2016;27:169-176.
37. Elbert NJ, Duijts L, den Dekker HT, de Jong NW, Nijsten TE, Jaddoe VW, et al. Maternal psychiatric symptoms during pregnancy and risk of childhood atopic diseases. Clin Exp Allergy 2017;47:509-519.
38. Chang HY, Suh DI, Yang SI, Kang MJ, Lee SY, Lee E, et al. Prenatal maternal distress affects atopic dermatitis in offspring mediated by oxidative stress. J Allergy Clin Immunol 2016;138:468-475.e5.
39. Mommers M, Thijs C, Stelma F, Penders J, Reimerink J, van Ree R, et al. Timing of infection and development of wheeze, eczema, and atopic sensitization during the first 2 yr of life: the KOALA birth cohort study. Pediatr Allergy Immunol 2010;21:983-989.
40. Rada S, Strohmaier S, Drucker AM, Eliassen AH, Schernhammer ES. Night shift work surrounding pregnancy and offspring risk of atopic disease. PLoS One 2020;15:e0231784.
41. Hersoug LG, Benn CS, Simonsen JB, Kamper-Jørgensen M, Linneberg A. Maternal employment in child-care institutions and the risk of infant wheeze and atopic dermatitis in the offspring. Pediatr Allergy Immunol 2008;19:688-695.
42. Wang IJ, Wen HJ, Chiang TL, Lin SJ, Chen PC, Guo YL. Maternal employment and atopic dermatitis in children: a prospective cohort study. Br J Dermatol 2013;168:794-801.
43. Taylor-Robinson DC, Williams H, Pearce A, Law C, Hope S. Do early-life exposures explain why more advantaged children get eczema? Findings from the U.K. Millennium Cohort Study. Br J Dermatol 2016;174:569-578.
44. Bertelsen RJ, Brants©¡ter AL, Magnus MC, Haugen M, Myhre R, Jacobsson B, et al. Probiotic milk consumption in pregnancy and infancy and subsequent childhood allergic diseases. J Allergy Clin Immunol 2014;133:165-171.e1-e8.
45. Chiu CY, Huang SY, Peng YC, Tsai MH, Hua MC, Yao TC, et al. Maternal vitamin D levels are inversely related to allergic sensitization and atopic diseases in early childhood. Pediatr Allergy Immunol 2015;26:337-343.
46. Gazibara T, den Dekker HT, de Jongste JC, McGrath JJ, Eyles DW, Burne TH, et al. Associations of maternal and fetal 25-hydroxyvitamin D levels with childhood lung function and asthma: the Generation R Study. Clin Exp Allergy 2016;46:337-346.
47. Mukherjee N, Sutter TR, Arshad SH, Holloway JW, Zhang H, Karmaus W. Breastfeeding duration modifies the effect of smoking during pregnancy on eczema from early childhood to adolescence. Clin Exp Allergy 2018;48:1688-1697.
48. Renz-Polster H, David MR, Buist AS, Vollmer WM, O'Connor EA, Frazier EA, et al. Caesarean section delivery and the risk of allergic disorders in childhood. Clin Exp Allergy 2005;35:1466-1472.
49. Wegienka G, Havstad S, Zoratti EM, Kim H, Ownby DR, Johnson CC. Combined effects of prenatal medication use and delivery type are associated with eczema at age 2 years. Clin Exp Allergy 2015;45:660-668.
50. Goudarzi H, Konno S, Kimura H, Araki A, Miyashita C, Itoh S, et al. Contrasting associations of maternal smoking and pre-pregnancy BMI with wheeze and eczema in children. Sci Total Environ 2018;639:1601-1609.
51. Korhonen L, Seiskari T, Lehtonen J, Puustinen L, Surcel HM, Haapala AM, et al. Enterovirus infection during pregnancy is inversely associated with atopic disease in the offspring. Clin Exp Allergy 2018;48:1698-1704.
52. Zulyniak MA, de Souza RJ, Shaikh M, Ramasundarahettige C, Tam K, Williams N, et al. Ethnic differences in maternal diet in preg-

nancy and infant eczema. PLoS One 2020;15:e0232170. Erratum in: PLoS One 2021;16:e0246481.
53. Timm S, Schlünssen V, Olsen J, Ramlau-Hansen CH. Prenatal antibiotics and atopic dermatitis among 18-month-old children in the Danish National Birth Cohort. Clin Exp Allergy 2017;47:929-936.
54. McKeever TM, Lewis SA, Smith C, Collins J, Heatlie H, Frischer M, et al. Siblings, multiple births, and the incidence of allergic disease: a birth cohort study using the West Midlands general practice research database. Thorax 2001;56:758-762.
55. Luschkova D, Zeiser K, Ludwig A, Traidl-Hoffmann C. Atopic eczema is an environmental disease. Allergol Select 2021;5:244-250.
56. Guo M, Wei L, Yan H, Duan Z, Niu Z, Xiao C. Exposure to ambient air pollution during trimesters of pregnancy and childhood allergic diseases in Wuhan, China. Int J Environ Health Res 2022;32:1962-1972.
57. Kong WS, Tsuyama N, Inoue H, Guo Y, Mokuda S, Nobukiyo A, et al. Long-chain saturated fatty acids in breast milk are associated with the pathogenesis of atopic dermatitis via induction of inflammatory ILC3s. Sci Rep 2021;11:13109.
58. Gio-Batta M, Sjöberg F, Jonsson K, Barman M, Lundell AC, Adlerberth I, et al. Fecal short chain fatty acids in children living on farms and a link between valeric acid and protection from eczema. Sci Rep 2020;10:22449.
59. Jung MJ, Kim HR, Kang SY, Kim HO, Chung BY, Park CW. Effect of weight reduction on treatment outcomes for patients with atopic dermatitis. Ann Dermatol 2020;32:319-326.
60. Ali Z, Jemec GBE, Ulrik CS. Associations between maternal and environmental exposures on atopic disease in the offspring of mothers with asthma. Immun Inflamm Dis 2021;9:862-870.
61. Cao H, Li S, Baranova A, Zhang F. Shared genetic liability between major depressive disorder and atopic diseases. Front Immunol 2021;12:665160.
62. Jing D, Li J, Tao J, Wang X, Shan S, Kang X, et al. Associations of second-hand smoke exposure with hand eczema and atopic dermatitis among college students in China. Sci Rep 2020;10:17400.