

Associations of demographics, aggravating factors, comorbidities, and treatments with atopic dermatitis severity in China: A national cross-sectional study

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Abstract

Background: Atopic dermatitis (AD) is a chronic inflammatory skin disorder impacting populations worldwide, although its clinical characteristics and patient demographics remain uncharacterized in China. The aim of this study was to investigate the demographics, comorbidities, aggravating factors, and treatments in AD patients across different age groups in China.

Methods: This cross-sectional study included Chinese AD patients from 205 hospitals spanning 30 provinces. Patients completed dermatologist-led surveys of general medical history, comorbidities, AD-related aggravating factors, and medications. Two-level mixed-ordered logistic regression was used to evaluate aggravating factors.

Results: Overall, 16,838 respondents were included in the final analysis (age 30.9 ± 24.1 years). The proportion of severe AD was the highest in patients with AD onset at ≥ 60 years (26.73%). Allergic rhinitis and hypertension were the most common atopic and metabolism-related non-atopic comorbidities, respectively. AD severity was significantly associated with chronic urticaria, food allergies, and diabetes. Aggravating factors including foods, seasonal changes, and psychological factors were also linked to AD severity. The cross-sectional survey implied that severe AD may be related to the undertreatment of effective systemic or topical interventions.

Conclusion: To enhance the management of AD, it is crucial to consider both aggravating factors and the increased utilization of systemic immunotherapy.

Registration: ClinicalTrials.gov Identifier: NCT05316805, CORNERSTONE

Keywords: Atopic dermatitis; Comorbidity; Demographics; Risk factors; Therapeutics

Introduction

Atopic dermatitis (AD) is a common chronic inflammatory skin disease characterized by recurrent pruritic eczematous lesions.^[1] AD has long been considered a disease in children, with prevalence rates reaching 25%.^[2] However, increasing evidence suggests that AD also presents in adults, with estimated prevalence rates of 2.1–4.9% worldwide, with persistent child- and adult-onset forms.^[3–5]

Recent epidemiological studies have shown that AD diagnoses have increased since the early 2000s in industrialized

countries,^[3,6–10] inflicting significant burdens on both patients and healthcare systems. In particular, its prevalence in China has steadily increased across age groups over the past three decades.^[11–14] Nevertheless, the current state, clinical features, and treatment of AD in China are seldom reported, with the large majority of studies focusing on pediatric cases, and only a limited number of reports on adult AD. Despite differences in clinical manifestations and demographic characteristics between children and adults, a thorough analysis of patients with AD across all age groups is lacking.^[6,15,16] Therefore, comprehensive, real-world data for clinical characteristics,

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Chinese Medical Journal 2024;137(XX)

Received: 19-07-2023; Online: 03-03-2024 Edited by: Yuanyuan Ji

Access this article online

Quick Response Code:



Website:

www.cmj.org

DOI:

10.1097/CM9.0000000000003042

aggravating factors, and comorbidities of AD in patients from different age groups across China could help unify efforts to manage this disease and greatly benefit patients. This cross-sectional study is based on data extracted from the national registry of the China Type II Inflammatory Skin Disease Clinical Research and Standardized Diagnosis and Treatment Project. To the best of our knowledge, this report represents the first large-scale, nationwide study examining the disease severity, risk factors, and comorbidities of AD in China. These data can guide the design of treatment strategies in clinic and facilitate active monitoring of changes and trends in clinical characteristics and patient management of AD, while also providing a baseline for future large-scale, controlled cohort studies.

Methods

Study design and populations

This nationwide, cross-sectional, epidemiological study included patients of all ages with AD who were clinically diagnosed using Williams Diagnostic Criteria^[17] in the respective departments of dermatology of participating hospitals in 30 of China's 34 provinces [Figure 1A, Supplementary Table 1, <http://links.lww.com/CM9/B924>]. This study involved a total of 205 hospitals, including 2 hospitals exclusively dedicated to pediatric healthcare. Patients who faced language or other barriers that prevented face-to-face interviews were excluded.

Ethics approval

All included patients provided written informed consent before participation. This research was registered in a publicly accessible database (<https://clinicaltrials.gov/>, ClinicalTrials.gov Identifier: NCT05316805, CORNERSTONE) and was approved by the Clinical Research

Ethics Committee of the Peking University First Hospital, ID: 2021/223.

Clinical examination and covariates

The medical history, comorbidities, and aggravating factors were selected *a priori*. In our study, patients' medical histories, comorbidities, and AD severity were evaluated concurrently, along with all the standardized measurement scales, by accredited physicians in the clinics. The general medical history included the patient's medical history, family medical history, and lifetime record of the incidence of allergies, hay fevers, and asthma. To determine AD severity, accredited dermatologists evaluated the Investigator's Global Assessment (IGA) and Eczema Area and Severity Index (EASI) scores of patients during their initial clinical visit. The IGA rating was used to describe the overall appearance of lesions at each visit, while the EASI score reflected the extent of affected areas and severity of AD. In this study, AD severity was classified based on IGA scores.^[18] Specifically, for this study, an IGA score of less than or equal to 2 was classified as mild, an IGA score of 3 was classified as moderate, and an IGA score of 4 was classified as severe. To determine comorbidities, we collected patient information on the prevalence of major comorbidities related to metabolism and common atopic comorbid diseases. Patients were also asked to identify aggravating factors of AD from a predetermined list provided by dermatologists. Additionally, several health-related scales, such as the weekly average Numeric Rating Scale Itch Intensity (NRSI), Atopic Dermatitis Control Tool (ADCT), Dermatology Life Quality Index (DLQI), Hospital Anxiety and Depression Scale (HADS), and Sleep Disturbance Scores (SDS), were determined at the same time to comprehensively assess pruritus intensity, AD disease control, quality of life, and mental health. Individual AD treatment plans from a comprehensive list of treatments including topical therapies, traditional

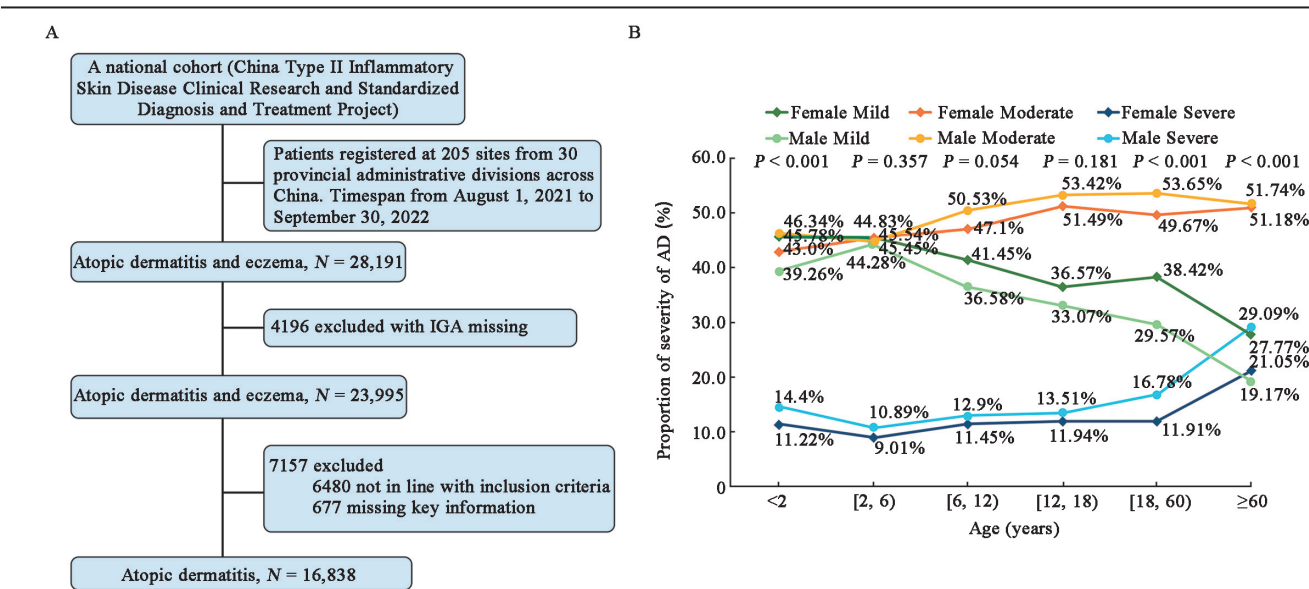


Figure 1: Data cleansing process in the cohort study and severity distribution of AD in China. (A) Flowchart of the selection process for eligible patients with AD included in the study. (B) Percentages of mild, moderate, and severe AD onset for male and female patients in all age groups. P values indicated differences in severity distribution by gender in each age group. AD: Atopic dermatitis; IGA: Investigator's Global Assessment.

systemic therapies, phototherapies, targeted therapies, anticonvulsants, and CNS depressants were also obtained from patients for analysis.

Statistical analysis

We have predetermined to perform age-stratified analyses on food-related aggravating factors using the following age groups: infants (<2 years), preschoolers (≥ 2 and <6 years), children (≥ 6 and <12 years), adolescents (≥ 12 and <18 years), adults (≥ 18 and <60 years), and older adults (≥ 60 years old).^[19] The percentage, mean (standard deviation [SD]), and median (interquartile range [IQR]) were used to describe the severity of AD and its characteristic population distribution. The Kruskal–Wallis rank test was conducted to examine differences in severity distributions of AD with comorbid diseases, as well as seasonal factors, food-related factors, environmental factors, and psychological factors. Considering the hierarchical or clustered structure of the data, where patients are naturally grouped within geographical units, a two-level mixed-ordered logistic regression model was employed. This modeling approach allowed for the evaluation of factors associated with disease aggravation while considering both regional-level variances and individual-level variances. Additionally, adjustments were made for potential confounding factors to ensure accurate estimates, and 95% confidence intervals (CIs) were calculated to provide a measure of precision. Furthermore, age-specific associations between food-related aggravating factors and the severity of AD were examined using mixed-effects ordered logistic regression. Statistical tests were two-tailed with $P < 0.05$, and data were analyzed by STATA 14.0 (StataCorp, College Station, TX, USA).

Results

Demographic and clinical characteristics

This study included a total of 16,838 AD patients (age 30.9 ± 24.1 years) enrolled from 205 hospitals across China from August 2021 to September 2022. The patients' demographic characteristics are summarized in Table 1. Among all included patients with AD, the stratification criteria resulted in a high percentage of moderate (49.51%) cases and smaller proportions of mild (35.72%) and severe (14.77%) cases. In terms of gender distribution, 9156 patients were men (54.91%), and 7519 patients were women (45.09%). A lower percentage of severe AD patients were females (12.14%) compared to males (16.91%). The majority of included patients belonged to the 18-year-old to 60-year-old age group and followed a distribution of: infants (<2 years): 5.13%; preschoolers (≥ 2 and <6 years): 12.74%; children (≥ 6 and <12 years): 12.90%; adolescents (≥ 12 and <18 years): 7.91%; adults (≥ 18 and <60 years): 44.84%; and older adults (≥ 60 years): 15.32%.^[19] In terms of severity, the proportion of patients with severe AD within each age group increased with age: from <10% in infants and preschoolers to 10–20% in children, adolescents, and adults, to 26.56% in older adults. The proportion of severe AD

was the highest in patients with AD onset at ≥ 60 years (26.73%). In terms of gender, the proportion of severe AD patients increased with the age of AD onset more drastically in males than females [Figure 1B].

The proportions of male and female patients were comparable among moderate AD cases. There were fewer mild AD patients with older age of onset in males than females. In the entire study population, fewer AD patients from rural areas were included. No significant difference was detected in AD severity distribution between urban and rural areas. The proportions of AD severity groups were similar across education levels. Overall, there was a higher proportion of patients with severe AD from northern China while there was a lower proportion of patients with severe AD from western China [Supplementary Table 2, <http://links.lww.com/CM9/B924>]. In the total population, patients with severe AD had higher EASI scores than patients with mild and moderate AD [Table 1].

Comorbidities with AD

In the total population, 9906 patients (60.95%) did not identify any comorbid diseases, 4717 patients (29.02%) identified as having one comorbid disease, while 1631 patients (10.03%) identified as having more than one comorbid disease. Among patients with at least one atopic comorbidity, allergic rhinitis had the highest prevalence, followed by food allergies, asthma, chronic urticaria, and drug allergies [Table 2]. Among severe AD patients, a significantly higher proportion of individuals had asthma and food allergies than other comorbidities. Patients with allergic rhinitis comprised a significantly higher proportion of moderate AD, and chronic urticaria was significantly higher among mild AD patients. Interestingly, there appears to be an association suggesting that chronic urticaria (odds ratio [OR], 0.74; 95% CI: 0.63–0.87, $P < 0.001$) may have a protective effect against moderate and severe AD, while food allergies (OR, 1.21; 95% CI: 1.06–1.37, $P = 0.003$) may potentially serve as a risk factor for AD. Among patients identified as having at least one non-atopic comorbidity related to metabolism, hypertension had the highest prevalence, followed by diabetes and coronary heart disease, respectively [Table 2]. Patients with hypertension, diabetes, or coronary heart disease were found in significantly higher proportions in the severe AD group than in the mild or moderate groups. Furthermore, hypertension (OR, 1.61, 95% CI: 1.35–1.93, $P < 0.001$) and diabetes (OR, 1.64, 95% CI: 1.27–2.12, $P < 0.001$) emerged as potential aggravating factors for AD.

Aggravating factors associated with AD

In this study, 14,783 patients (87.8%) did not report any aggravating factors, whereas 1953 patients (11.6%) reported one or more aggravating factors. Seasonal aggravating factors associated with spring, summer, or winter affected a significant proportion of severe AD patients. Fish and shellfish, lamb and beef, chili peppers, and alcohol were among the food-related aggravating factors. For environmental risk factors, sunlight, humidity,

Table 1: Demographics and clinical characteristics of patients with AD.*

Characteristics	Total	AD severity			z/ χ^2	P-value
		Mild	Moderate	Severe		
Number of participants, <i>n</i> (%)	16,838	6014 (35.72)	8337 (49.51)	2487 (14.77)		
Gender, <i>n</i> (%)						<0.001
Female	7519	3024 (40.22)	3582 (47.64)	913 (12.14)	-11.695 [†]	
Male	9156	2981 (32.56)	4627 (50.54)	1548 (16.91)		
Age groups, <i>n</i> (%)						<0.001
<2 years	863	421 (48.78)	363 (42.06)	79 (9.15)	563.052	
≥2 and <6 years	2145	1057 (49.28)	944 (44.01)	144 (6.71)		
≥6 and <12 years	2172	861 (39.64)	1048 (48.25)	263 (12.11)		
≥12 and <18 years	1332	444 (33.33)	659 (49.47)	229 (17.19)		
≥18 and <60 years	7551	2669 (35.35)	3832 (50.75)	1050 (13.91)		
≥60 years	2579	548 (21.25)	1346 (52.19)	685 (26.56)		
Marital status, <i>n</i> (%)						<0.001
Single	8995	3706 (41.20)	4236 (47.09)	1053 (11.71)	268.379	
Married	7530	2184 (29.00)	3961 (52.60)	1385 (18.39)		
Divorced	66	17 (25.76)	36 (54.55)	13 (19.70)		
Age at disease onset, <i>n</i> (%)						<0.001
<2 years	3307	1399 (42.30)	1481 (44.78)	427 (12.91)	363.644	
≥2 and <6 years	2139	957 (44.74)	969 (45.30)	213 (9.96)		
≥6 and <12 years	1550	601 (38.77)	760 (49.03)	189 (12.19)		
≥12 and <18 years	1186	409 (34.49)	625 (52.70)	152 (12.82)		
≥18 and <60 years	6522	2172 (33.30)	3407 (52.24)	943 (14.46)		
≥60 years	1904	406 (21.32)	989 (51.94)	509 (26.73)		
Habitual residence, <i>n</i> (%)						
Urban	14,753	5238 (35.50)	7366 (49.93)	2149 (14.57)	-0.303 [†]	0.762
Rural	1833	668 (36.44)	864 (47.14)	301 (16.42)		
Level of education, <i>n</i> (%)						<0.001
<Elementary school	6332	2623 (41.42)	2975 (46.98)	734 (11.59)	166.193	
Completed middle school	2590	811 (31.31)	1286 (49.65)	493 (19.03)		
Completed high school	2217	686 (30.94)	1112 (50.16)	419 (18.90)		
College diploma	2230	686 (30.76)	1225 (54.93)	319 (14.30)		
Bachelor's degree or higher	3221	1100 (34.15)	1635 (50.76)	486 (15.09)		
EASI score, median (IQR)	6.70 (2.90–15.00)	2.80 (1.30–5.60)	9.40 (4.65–18.05)	18.2 (9.60–28.30)	5333.090	<0.001

*There were missing data in each categorical variable in Table 1, but the missing proportions for each categorical variable were below 1.5%. [†]: Z test. AD: Atopic dermatitis; EASI score: Eczema Area and Severity Index Score; IQR: Interquartile range.

dryness, sweat, showering, skin friction, dust, and pollen were identified as contributing factors in severe AD, while stress, emotional problems, and sleep disorders were reported as psychological aggravating factors in these severe patients [Table 3].

AD severity was significantly associated with seasonal aggravating factors in patients who reported summer as a seasonal risk factor (OR, 1.23, 95% CI: 1.04–1.46, *P* = 0.014) [Table 3]. Among food-related aggravating factors, AD severity was significantly associated with fish and shellfish (OR, 1.74, 95% CI: 1.35–1.98, *P* < 0.001), lamb and beef (OR, 2.01, 95% CI: 1.59–2.56, *P* < 0.001), chili peppers (OR, 1.52, 95% CI: 1.19–1.95, *P* = 0.001), and alcohol (OR, 1.83, 95% CI: 1.36–2.48, *P* < 0.001) [Table 3]. More specifically, our findings revealed that milk and egg did not exhibit significant associations with AD severity across different age groups [Supplementary Figure 1, <http://links.lww.com/CM9/B924>]. However,

fish and shellfish demonstrated a significant association with AD severity in patients aged <2 years (OR, 1.50, 95% CI: 1.05–2.15, *P* = 0.026) and 18–59 years (OR, 2.02, 95% CI: 1.44–2.83, *P* < 0.001); lamb and beef showed a significant association with AD severity in patients aged <2 years (OR, 1.87, 95% CI: 1.19–2.96, *P* = 0.007) and 18–59 years (OR, 3.65, 95% CI: 2.42–5.50, *P* < 0.001); whereas chili peppers (OR, 2.03, 95% CI: 1.38–2.99, *P* < 0.001) and alcohol (OR, 2.24, 95% CI: 1.47–3.42, *P* < 0.001) exhibited significant associations with AD severity exclusively in patients aged 18–59 years [Supplementary Figure 1, <http://links.lww.com/CM9/B924>]. Furthermore, the environmental aggravating factors of sunlight (OR: 1.79, 95% CI: 1.42–2.25, *P* < 0.001), humidity (OR, 1.61, 95% CI: 1.23–2.11, *P* = 0.001), sweat (OR, 1.27, 95% CI: 1.08–1.48, *P* = 0.004), showering (OR, 1.63, 95% CI: 1.26–2.11, *P* < 0.001), skin friction (OR, 1.84, 95% CI: 1.37–2.46, *P* < 0.001), dust (OR, 1.55, 95% CI: 1.24–1.92, *P* < 0.001),

Table 2: Comorbidities associated with severity of AD examined in mixed-effects ordered logistic regression.

						Mixed-effect ordered logistic regression*		
						Level one		Level two
AD severity								
Comorbidities	Total	Mild	Moderate	Severe	P-value	OR	P-value	Variance
		(n = 5826)	(n = 8106)	(n = 2322)		(95% CI)		(95% CI)
Atopic comorbidity, n (%)								
Asthma	745	272 (4.67)	338 (4.17)	135 (5.81)	0.434	1.09 (0.94–1.26)	0.262	0.08 (0.03–0.23)
Allergic conjunctivitis	363	136 (2.33)	162 (2.00)	65 (2.80)	0.735	1.16 (0.95–1.43)	0.153	0.07 (0.03–0.22)
Chronic urticaria	639	288 (4.94)	288 (3.55)	63 (2.71)	<0.001	0.74 (0.63–0.87)	<0.001	0.07 (0.02–0.21)
Food allergy	1057	387 (6.64)	495 (6.11)	175 (7.54)	0.611	1.21 (1.06–1.37)	0.003	0.08 (0.03–0.22)
Drug allergy	303	104 (1.79)	145 (1.79)	54 (2.33)	0.231	1.18 (0.94–1.48)	0.149	0.08 (0.03–0.22)
Contact dermatitis	89	29 (0.50)	40 (0.49)	20 (0.86)	0.148	1.41 (0.93–2.13)	0.110	0.07 (0.03–0.22)
Allergic rhinitis	4358	1642 (28.18)	2044 (25.22)	672 (28.94)	0.067	1.02 (0.95–1.10)	0.556	0.08 (0.03–0.23)
Comorbidities related to metabolism, n (%)								
Hypertension	547	113 (1.94)	274 (3.38)	160 (6.89)	<0.001	1.61 (1.35–1.93)	<0.001	0.08 (0.03–0.22)
Diabetes	247	50 (0.86)	126 (1.55)	71 (3.06)	<0.001	1.64 (1.27–2.12)	<0.001	0.08 (0.03–0.22)
Coronary heart disease	137	22 (0.38)	77 (0.95)	38 (1.64)	<0.001	1.66 (1.19–2.32)	0.003	0.08 (0.03–0.22)

*Dependent variable: severity of AD (mild, moderate, severe), the association between each atopic comorbidity/comorbidities related to metabolism and severity of AD was examined separately by mixed-effect two-level (level one: individual; level two: region) ordered logistic regression after adjusting for gender, marital status, age on disease set, educational level and inducing or aggravating factors. An likelihood ratio test comparing the model with the one-level model favored the random-intercept model with $P < 0.05$ for all the analyses. For atopic comorbidity analysis, each model has an effective sample size of 16,070. For comorbidities related to metabolism analysis, each model has an effective sample size of 15,571. AD: Atopic dermatitis; CI: Confidence interval; OR: Odds ratio.

Table 3: Aggravating factors associated with the severity of AD examined in mixed-effects ordered logistic regression.

						Mixed-ordered logistic regression*		
						Level one		Level two
		AD severity						
Factors	Total	Mild (<i>n</i> = 6104)	Moderate (<i>n</i> = 8377)	Severe (<i>n</i> = 2487)	<i>P</i> -value	OR (95% CI)	<i>P</i> -value	Variance (95% CI)
Seasonal factors, <i>n</i> (%)								
Spring	250	100 (1.66)	102 (1.22)	48 (1.93)	0.800	0.97 (0.75–1.25)	0.794	0.08 (0.03–0.23)
Summer	615	211 (3.51)	280 (3.36)	124 (4.99)	0.025	1.23 (1.04–1.46)	0.014	0.08 (0.03–0.23)
Autumn	315	125 (2.08)	143 (1.72)	47 (1.89)	0.264	0.88 (0.70–1.10)	0.269	0.08 (0.03–0.23)
Winter	564	222 (3.69)	249 (2.99)	93 (3.74)	0.360	0.93 (0.78–1.11)	0.410	0.08 (0.03–0.23)
Food-related factors, <i>n</i> (%)								
Milk	156	70 (1.16)	61 (0.73)	25 (1.01)	0.095	0.87 (0.63–1.20)	0.392	0.08 (0.03–0.23)
Egg	186	74 (1.23)	81 (0.97)	31 (1.25)	0.557	1.12 (0.83–1.51)	0.473	0.08 (0.03–0.23)
Fish and shellfish	471	130 (2.16)	240 (2.88)	101 (4.06)	<0.001	1.64 (1.35–1.98)	<0.001	0.08 (0.03–0.23)
Lamb and beef	285	69 (1.15)	145 (1.74)	71 (2.85)	<0.001	2.01 (1.59–2.56)	<0.001	0.08 (0.03–0.23)
Chili peppers	269	78 (1.30)	130 (1.56)	61 (2.45)	<0.001	1.52 (1.19–1.95)	0.001	0.08 (0.03–0.23)
Alcohol	173	38 (0.63)	91 (1.09)	44 (1.77)	<0.001	1.83 (1.36–2.48)	<0.001	0.08 (0.03–0.23)
Environmental factors, <i>n</i> (%)								
Sunlight	315	88 (1.46)	147 (1.76)	80 (3.22)	<0.001	1.79 (1.42–2.25)	<0.001	0.08 (0.03–0.23)
Humidity	225	72 (1.20)	93 (1.12)	60 (2.41)	0.002	1.61 (1.23–2.11)	0.001	0.08 (0.03–0.23)
Dryness	561	206 (3.43)	234 (2.81)	121 (4.87)	0.108	1.20 (1.00–1.43)	0.050	0.08 (0.03–0.23)
Sweat	710	251 (4.17)	312 (3.74)	147 (5.91)	0.033	1.27 (1.08–1.48)	0.004	0.08 (0.03–0.23)
Shower	240	66 (1.10)	121 (1.45)	53 (2.13)	<0.001	1.63 (1.26–2.11)	<0.001	0.08 (0.03–0.23)
Rub	189	51 (0.85)	89 (1.07)	49 (1.97)	<0.001	1.84 (1.37–2.46)	<0.001	0.08 (0.03–0.23)
Dust	364	118 (1.96)	163 (1.96)	83 (3.34)	0.003	1.55 (1.24–1.92)	<0.001	0.08 (0.03–0.23)
Pollen	148	34 (0.57)	74 (0.89)	40 (1.61)	<0.001	2.15 (1.54–3.00)	<0.001	0.08 (0.03–0.30)
Psychological factors, <i>n</i> (%)								
Stress	344	89 (1.48)	158 (1.90)	97 (3.90)	<0.001	1.99 (1.59–2.50)	<0.001	0.08 (0.03–0.23)
Emotional problem	332	94 (1.56)	151 (1.81)	87 (3.50)	<0.001	1.80 (1.44–2.26)	<0.001	0.08 (0.03–0.23)
Sleep disorder	288	70 (1.16)	140 (1.68)	78 (3.14)	<0.001	1.89 (1.49–2.41)	<0.001	0.08 (0.03–0.23)

*Dependent variable: severity of AD (mild, moderate, severe), the association between complicated factor and severity of AD was examined separately by mixed-effect two-level (level one: individual; level two: region) ordered logistic regression after adjusting for gender, marital status, age on disease set, educational level, and comorbidity. An likelihood ratio test comparing the model with the one-level model favored the random-intercept model with $P < 0.05$ for all the analyses. Each model has an effective sample size of 15,571. AD: Atopic dermatitis; CI: Confidence interval; OR: Odds ratio.

and pollen (OR, 2.15, 95% CI: 1.54–3.00, $P < 0.001$) were also significantly associated with AD severity [Table 3]. Stress (OR, 1.99, 95% CI: 1.59–2.50, $P < 0.001$), emotional problems (OR, 1.80, 95% CI: 1.44–2.26, $P < 0.001$), and sleep disorders (OR, 1.89, 95% CI: 1.49–2.41, $P < 0.001$) were all psychological aggravating factors significantly linked to AD severity [Table 3].

Health-related measurements associated with AD severity

Patient-reported health-related measurements, including weekly average NRSI, DLQI, HADS, ADCT, and SDS, all increased in scores with the severity of AD [Supplementary Table 3, <http://links.lww.com/CM9/B924>]. The mean weekly NRSI, SDS, DLQI, and ADCT scores were significantly higher in severe AD patients than in moderate and mild AD patients. Moreover, an assessment of SDS distribution revealed that a higher percentage of mild AD patients (28.39%, 1561/5498) reported no sleep disturbance per week, as compared to moderate (10.66%, 833/7809) and severe (5.50%, 127/2307) AD patients

[Supplementary Figure 2, <http://links.lww.com/CM9/B924>]. In contrast, a higher proportion of severe AD patients (46.47%, 1072/2307) reported 7 days of sleep disturbance per week than mild (15.13%, 832/5498) or moderate (22.04%, 1721/7809) AD patients [Supplementary Figure 2, <http://links.lww.com/CM9/B924>].

Treatment plans and AD

The top six therapies for AD patients included topical glucocorticoids (32.26%), oral antihistamines (28.66%), moisturizers (19.58%), topical calcineurin inhibitors (TCI) (5.99%), glycyrrhizin (5.82%), and dupilumab (5.80%) [Table 4 and Supplementary Figure 3, <http://links.lww.com/CM9/B924>]. In addition, commonly recommended therapies in international guidelines including TCI (5.99%), dupilumab (5.80%), systemic glucocorticoids (4.05%), cyclosporine (0.82%), methotrexate (0.54%), and NB-UVB (0.76%) had relatively low usage rates in this study population [Table 4].

Table 4: Therapeutic distribution of Chinese patients with AD at enrollment.*

Variables	Total	AD severity			χ^2	P-value
		Mild	Moderate	Severe		
Topical therapy, n (%)	n = 16,148	n = 5743	n = 8098	n = 2307		
Moisturizer	3162 (19.58)	1089 (18.96)	1454 (17.96)	619 (26.83)	92.006	<0.001
Glucocorticoids	5210 (32.26)	1629 (28.36)	2527 (31.21)	1054 (45.69)	234.304	<0.001
Calcineurin inhibitors	968 (5.99)	298 (5.19)	442 (5.46)	228 (9.88)	72.648	<0.001
Antibiotic ointments	484 (3.00)	148 (2.58)	223 (2.75)	113 (4.90)	33.810	<0.001
NSAIDs	76 (0.47)	26 (0.45)	34 (0.42)	16 (0.69)	2.932	0.231
Crisaborole ointment	94 (0.58)	32 (0.56)	41 (0.51)	21 (0.91)	5.159	0.076
Others	879 (5.44)	311 (5.42)	417 (5.15)	151 (6.55)	6.811	0.033
Oral therapy, n (%)	n = 15,813	n = 5594	n = 7962	n = 2257		
Antihistamines	4532 (28.66)	1278 (22.85)	2273 (28.55)	981 (43.46)	334.486	<0.001
Antibiotics	149 (0.94)	41 (0.73)	67 (0.84)	41 (1.82)	21.977	<0.001
Systemic steroids	641 (4.05)	174 (3.11)	275 (3.45)	192 (8.51)	135.240	<0.001
Cyclosporine	130 (0.82)	35 (0.63)	55 (0.69)	40 (1.77)	29.322	<0.001
Methotrexate	86 (0.54)	15 (0.27)	51 (0.64)	20 (0.89)	14.126	0.001
Tripterygium glycosides	198 (1.25)	36 (0.64)	97 (1.22)	65 (2.88)	65.198	<0.001
Glycyrrhizin	921 (5.82)	274 (4.90)	440 (5.53)	207 (9.17)	56.138	<0.001
Thalidomide	124 (0.78)	21 (0.38)	69 (0.87)	34 (1.51)	27.842	<0.001
Phototherapy, n (%)	n = 15,728	n = 5572	n = 7926	n = 2230		
NB-UVB	120 (0.76)	24 (0.43)	59 (0.74)	37 (1.66)	31.817	<0.001
UVA	7 (0.04)	2 (0.04)	3 (0.04)	2 (0.09)	1.195	0.550
PUVA	5 (0.03)	1 (0.02)	4 (0.05)	0 (0)	1.915	0.384
Targeted therapy, n (%)	n = 15,758	n = 5574	n = 7940	n = 2244		
Dupilumab	914 (5.80)	280 (5.02)	468 (5.89)	166 (7.40)	16.764	<0.001
Omalizumab	10 (0.06)	6 (0.11)	3 (0.04)	1 (0.04)	2.668	0.263
JAK inhibitors	24 (0.15)	4 (0.07)	14 (0.18)	6 (0.27)	4.633	0.099
Anticonvulsant and CNS depressants, n (%)	n = 15,694	n = 5567	n = 7904	n = 2223		
Gabapentin	47 (0.30)	11 (0.20)	19 (0.24)	17 (0.76)	18.976	<0.001
Pregabalin	28 (0.18)	10 (0.18)	11 (0.14)	7 (0.31)	3.009	0.222
Antidepressants	40 (0.25)	29 (0.52)	8 (0.10)	3 (0.13)	24.099	<0.001
Opioids	1 (0.01)	0 (0)	0 (0)	1 (0.04)	6.060	0.048

*There were missing data in each categorical variable. CNS: Central nerve system. JAK: Janus kinase; NB-UVB: Narrow band ultraviolet B; NSAIDs: Non-steroidal anti-inflammatory drugs; PUVA: Psoralen and ultraviolet A; UVA: Ultraviolet A.

Discussion

This study provides an overview of the demographics, disease characteristics, comorbidities, and aggravating factors associated with AD across various age groups and severity levels in China. In line with POEM scores, a study conducted in the United States found a higher prevalence of mild AD among adult patients compared to moderate cases.^[20] Conversely, the current Chinese population showed a greater proportion of adult patients with moderate AD and fewer cases of mild or severe AD. This difference may arise from variations in the scoring systems utilized to define severity groups across the studies. In addition, results in the current study suggest that AD is poorly managed in Chinese individuals of all age groups. Notably, we observed variations in the distribution of AD severity groups across different geographic regions. For instance, severe AD was generally higher in northern provinces than in western and central provinces, although severe AD was prevalent in economically developed southern regions. These results suggested several possible aggravating factors, such as low temperatures and arid climate conditions in northern China, which could negatively affect skin and have been reported to exacerbate pruritus.^[21] Alternatively, the regional flora in southern China, including subtropical grasses or endemic pollen, are well-known environmental allergens^[22] that have been associated with more severe AD.^[23]

Early onset AD patients often develop atopic comorbidities such as allergic rhinitis, asthma, food allergies, and allergic conjunctivitis.^[24] Our findings indicate that infants with greater AD severity at baseline exhibited a higher likelihood of developing allergic rhinitis and food allergies as compared to other comorbidities. However, no such relationship with atopic comorbidities has yet been established in adult-onset AD. The current data support that allergic rhinitis is the most prevalent comorbidity with AD, while food allergies, asthma, and allergic conjunctivitis also occur in substantial but markedly smaller proportions of AD patients. Importantly, the occurrence of asthma and food allergies decreased across the multi-age group, further linking these main comorbidities with early onset AD.

Hypertension had the highest prevalence in AD patients with at least one non-atopic comorbidity related to metabolism, followed by diabetes and coronary heart disease. This finding was in agreement with other studies that found higher odds of diabetes, high blood pressure, and heart disease in both adult and pediatric AD patients.^[25,26] Hypertension is also a significant risk factor of AD, and was most common in severe AD patients in our study, aligning well with work by Abdallah and Vestergaard^[27] that linked moderate-to-severe AD with hypertension. Thus, careful attention should be paid to non-atopic comorbidities in AD-specific interventions.

In our study, stress, emotional problems, and sleep disorders were reported in a significantly higher proportion of severe AD patients compared to mild or moderate. Adolescent men with AD with high stress were previously shown to have a 46% higher risk of developing severe AD

than patients with no stress.^[28] Sleep disorders are also strongly associated with AD and have been reported in 47–80% of children and 33–87.1% of adults with AD.^[29] The American Academy of Dermatology (AAD) recently published guidelines advising clinicians to assess and treat AD patients with unaddressed mental health issues on a case-by-case basis.^[30] Consequently, further investigation is warranted to better understand the relationship between psychological comorbidities and AD.

Furthermore, the management of AD has obstacles and unmet needs possibly unique to China. Several guidelines recommend the use of moisturizers, topical glucocorticoids, TCI, and topical antimicrobials as topical anti-inflammatory treatments.^[31–33] For severe AD, systemic immunomodulating medications such as cyclosporine, azathioprine, methotrexate, or mycophenolate mofetil, and phototherapy are recommended.^[31–34] By contrast, antihistamines have been shown to be ineffective in reducing pruritus, while systemic steroids may have severe adverse effects.^[35,36] Biological agents and Janus kinase (JAK) inhibitors were recently recommended to treat severe AD.^[37–40] However, the assessment of treatment plans in this study suggested that Chinese AD patients do not receive sufficient therapeutic intervention. For instance, emollient moisturizers can alleviate AD symptoms,^[41,42] yet only 19.58% of AD patients reported using topical moisturizers in this study. By contrast, 43.46% of patients use antihistamines, while 8.51% use systemic steroids, as primary treatments, neither of which aligns with most guidelines. Furthermore, relatively few patients in our cohort reported using systemic immunomodulatory medications and targeted therapies. We hypothesize that the reason for undertreatment may be a poor understanding of guidelines among doctors. Some patients also relied on Chinese medicine, such as tripterygium or glycyrrhizin, which lack any evidence of efficacy in treating AD. This pattern of undertreatment may explain the high proportion of severe AD patients in this study, which could be addressed by increasing the use of systemic immunomodulating therapies, targeted therapies, and awareness of these medications.

The cross-sectional design of this study limits our ability to determine temporal relationships between aggravating factors and the severity of AD. In addition, according to the study protocol, all eligible AD patients' data from the 205 affiliated hospitals were intended to be uploaded to the data collection platform. However, due to inherent limitations of the data collection platform, we were unable to determine the precise number of units that declined or were unable to participate in the study. Moreover, further research is necessary to investigate the influence of interactions between heritability and environmental factors on AD severity.

In conclusion, this study is a pioneering report detailing the severity distribution and demographic characteristics of AD patients across all ages in China. The effective long-term management of AD and AD-related comorbidities continues to pose challenges, necessitating further research on aggravating factors and an improved understanding of the underlying mechanisms.

Acknowledgments

We thank patients from the Cornerstone cohort for their cooperation. We appreciate computer technicians Wenwei Zhu and Guofeng Sun for database technical help.

Funding

This work was supported by the PKU-Baidu Fund (No. 2020BD012) and National Natural Science Foundation of China (No. 81903213).

Conflicts of interest

None.

Data availability statement

The authors confirm that the data supporting the findings of this study are available within the article and its supplementary materials, <http://links.lww.com/CM9/B924>.

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How to cite this article: Zhao JH, Zhang ZX, Chen HG, Dou X, Zhao ZT, Liu LL, Wang Y, Li H. Associations of demographics, aggravating factors, comorbidities, and treatments with atopic dermatitis severity in China: A national cross-sectional study. *Chin Med J* 2024;XXX:1–9. doi: 10.1097/CM9.0000000000003042