Itching and its related factors in subtypes of eczema: a cross-sectional multicenter study in tertiary hospitals of China

Xin Wang1, Linfeng Li2, Xiaodong Shi3, Ping Zhou1 & Yiwei Shen1

Itching is a leading symptom of eczema or dermatitis and has a great impact on patients’ lives. Previous studies on itching have focused mostly on atopic dermatitis (AD). A cross-sectional multicenter study was conducted among outpatients with eczema from 39 tertiary hospitals in mainland China from July 1 to September 30, 2014. This work elaborates on itching in different types of eczema. Itching was very common (97%, 8499/8758) in outpatients with eczema. The severity of the itch increased with age and disease duration (P < 0.001). The top three subtypes of dermatitis with severe itching were atopic dermatitis (30.4%), widespread eczema (30.1%), and asteatotic eczema (27.9%). Widespread eczema refers to the involvement of more than three body parts, without clinical features of other specific types of eczema. The proportion of outpatients without itching was highest in hand eczema (6.8%). Positive correlations were observed between the severity of itching and the proportions of different diseases based on trend tests, including atopic dermatitis (P < 0.001), widespread eczema (P < 0.001), asteatotic eczema (P < 0.001), and autosensitization dermatitis (P < 0.001). Eczema outpatients with older age, longer disease duration, and, especially, a history of allergic diseases might be more prone to itching.

Pain and itching play critical roles in protecting organisms from sources of danger, such as extreme temperatures, reactive chemicals, and tissue injury. These sensations can result in neuronal modulation of the immune system or behavioral avoidance of future exposure to pathogens. Parasitic (e.g., Onchocerca volvulus) and fungal skin infections (e.g., Tinea pedis, Candida albicans) are characterized by intense itching1, which is a common symptom of eczema or dermatitis and has a great impact on patients2,3. Various substances that cause itching (pruritogens), such as cytokines and chemical messengers, are released from the affected area4,5. The prevalence of itching (once as reported to be approximately 10%) in the general population is not well documented6. A cross-sectional study of 2076 adults from a general internal medicine clinic has found that the prevalence of itching was 39.9% and increased with age (from 33.1% at age 19–39 years to 45.9% at age ≥ 80 years) in the United States7. A German population-based cross-sectional study found that the self-reported, 12-month, and lifetime prevalences of chronic pruritus (lasting ≥ 6 weeks) were 13.5%, 16%, and 22%, respectively8. In a Norwegian population-based cross-sectional study on self-reported skin morbidity, pruritus, the dominant symptom among adults, was experienced within the past week by 9% of women and 7.5% of men9.

Many studies on itching have been carried out in atopic dermatitis (AD), but very few have focused on other types of eczema. A recent study on AD has reported the frequency (85%), duration (41.5% with itching ≥ 18 h/d), and severity (6.5 of 10 on a numeric rating scale) of itching, as well as the frequency of AD-related sleep disturbance (55% with disturbance 5 days/week or more)10. Itching has significant adverse effects on patients’ quality of life, which can trigger depression1, anxiety, sleeplessness, and even suicidal thoughts, indicating more attention should be paid to this symptom. Itching and its related factors in eczema and dermatitis in China are unclear, so we performed a hospital-based multicenter cross-sectional epidemiologic survey in Chinese outpatients with AD.

1Department of Dermatology, Beijing Shijitan Hospital, Capital Medical University, 10 Tie Yi Road, Haidian District, Beijing, 100038, China. 2Department of Dermatology, Beijing Friendship Hospital, Capital Medical University, 95 Yong An Road, Xicheng District, Beijing, 100050, China. 3Market Research Department, China Telecom Corporation Limited Beijing Research Institute, Beijing, China. Correspondence and requests for materials should be addressed to L.L. (email: zoonli@sina.com)
Is there a history of generalized dry skin? Is there a history of infant eczema? Is there a history of flexural degree relatives) history of atopic diseases (asthma; allergic rhinitis; allergic conjunctivitis; atopic dermatitis)? were affected. Questions included: How old are you? What is your sex? How long have you suffered from this

Clinical characteristics of eczema outpatients with itching (N = 8758). The proportion of itching in each type of dermatitis is shown in Table 2. The top three subtypes of dermatitis with severe itching were atopic dermatitis (30.4%), widespread eczema (30.1%) and flexural dermatitis and infantile eczema. The purpose of the current study is to examine the association of itching with eczema and dermatitis in a department of dermatology in a Chinese population.

Results

Demographic characteristics (N = 8758). In this survey, 9688 outpatients were approached, and 295 refused to participate in this study (response rate 97%). In total, 9393 outpatients were screened, of whom 636 (6.7%) were excluded because of incomplete information. Finally, 8758 outpatients were recruited, and 97% of

Clinical characteristics (N = 8758). The clinical characteristics of eczema outpatients with itching are shown in Table 1. A positive correlation was observed between itching severity and suspected bacterial infection (P < 0.001, linear-by-linear association chi-square test). Similarly, a positive history of allergic disease, dry skin, flexion dermatitis and infantile eczema were more common as itching worsened (P < 0.001, linear-by-linear association chi-square test).

The mean disease duration of the outpatients with severe itching was 4.1 ± 5.85 years. A total of 8758 outpatients were divided into ten groups according to disease duration: the disease durations 9 years or less were combined in a single group. We divided that the proportion of severe itching in eczema outpatients increased significantly with disease duration (Spearman’s rank correlation test, P < 0.001, Fig. 2). As the number of involved body locations increased (range, 1–10), the proportion eczema outpatients with severe itching increased significantly (R = 0.988, P < 0.001, Spearman correlation) (Fig. 3). The top three involved sites with severe itching were the vulva (34.4%), chest (33.3%) and axilla (27.5%) (see Supplementary Fig. S1). The most common types of skin lesions with severe itching were pustular (32.4%), erosion (32.1%) and exudate (30.4%) (Fig. 4).

Pruritus proportion. The proportion of itching in each type of dermatitis is shown in Table 2. The top three subtypes of dermatitis with severe itching were atopic dermatitis (30.4%), widespread eczema (30.1%) and astecotic eczema (27.9%). Widespread eczema refers to the involvement of more than three body parts, without

| Itching Grade* | No (n = 259) | Mild (n = 2629) | Moderate (n = 4545) | Severe (n = 1325) | P |
|----------------|-------------|----------------|--------------------|------------------|---|
| Age (years) (mean ± SD)* | 32.2 ± 18.46 | 34.9 ± 17.67 | 35.3 ± 18.92 | 42.06 ± 18.70 | <0.001 |
| Sex (n, %) | | | | | 0.069 |
| Male | 127 (2.9) | 1326 (29.9) | 2263 (51.0) | 719 (16.2) | |
| Female | 132 (3.1) | 1303 (30.1) | 2282 (52.8) | 606 (14.0) | |
| Disease duration (years) (mean ± SD)* | 1.8 ± 2.37 | 2.3 ± 3.76 | 3.1 ± 5.53 | 4.1 ± 5.85 | <0.001 |
| Suspected bacterial infection (yes) (n, %)* | 31 (12.0) | 190 (7.2) | 441 (9.7) | 547 (41.3) | <0.001 |
| History of allergic disease (yes) (n, %)* | 24 (9.3) | 199 (7.6) | 717 (12.8) | 345 (26.0) | <0.001 |
| History of asthma (yes) (n, %) | 3 (1.2) | 40 (1.5) | 123 (2.7) | 61 (4.6) | <0.001 |
| History of allergic rhinitis (yes) (n, %) | 7 (2.7) | 60 (2.3) | 217 (4.8) | 117 (8.8) | <0.001 |
| History of allergic conjunctivitis (yes) (n, %) | 7 (2.7) | 46 (1.7) | 187 (4.1) | 78 (5.9) | <0.001 |
| History of atopic dermatitis (yes) (n, %) | 3 (1.2) | 22 (0.8) | 65 (1.4) | 25 (1.9) | 0.007 |
| History of dry skin (yes) (n, %)* | 49 (18.9) | 408 (15.5) | 957 (21.1) | 476 (35.9) | <0.001 |
| History of flexion dermatitis(yes) (n, %)* | 33 (12.7) | 207 (7.9) | 394 (8.7) | 244 (18.4) | <0.001 |
| History of infantile eczema(yes) (n, %)* | 16 (6.2) | 145 (5.5) | 484 (10.6) | 174 (13.1) | <0.001 |
clinical features of other specific types of eczema. The proportion of outpatients without itching was highest in hand eczema (6.8%).

Based on trend tests for itching rank in each type of dermatitis, a positive correlation was observed between the severity of itching and proportion of different diseases, including atopic dermatitis ($P < 0.001$), widespread eczema ($P < 0.001$), allergic contact dermatitis ($P = 0.021$), neurodermatitis ($P = 0.021$), nummular eczema ($P = 0.019$), asteatotic eczema ($P < 0.001$), and autosensitization dermatitis ($P < 0.001$).

Multivariable logistic regression analysis of itching and related factors ($N = 8758$). The 8758 outpatients were analyzed, and 8499 of them had itching. In the multivariate logistic regression analysis of itching and related factors, independent variables included age, sex, disease duration, suspected bacterial infection, and history of allergic disease, dry skin, infantile eczema, and flexion dermatitis. The results are listed in Supplementary Table S1.

Based on the multivariate logistic regression analysis, age (OR = 1.011, 95% CI: 1.004–1.018, $P = 0.003$), disease duration (OR = 1.096, 95% CI: 1.039–1.156, $P = 0.001$) and history of allergic disease (OR = 1.667, 95% CI: 1.063–2.616, $P = 0.026$) were positively associated with the risk of itching. A history of flexion dermatitis (OR = 0.496, 95% CI: 0.325–0.758, $P = 0.001$) was negatively associated with itching (but not sex, suspected bacterial infection, or a history of dry skin or infantile eczema).

Discussion
The probability of itching occurrence in eczema outpatients is related to many factors including age, disease duration, history of allergic disease and flexion dermatitis. Findings from the age and disease-duration subgroup analyses show that the severity of itching increases with age and disease duration. Age increases the risk of impaired skin barrier function, which can precipitate skin breakdown. Loss of function or structural stability in skin proceeds unavoidably as individuals age, resulting from intrinsic and extrinsic stimuli. This in turn contributes to a progressive loss of skin integrity. Intrinsic aging proceeds at a genetically determined pace, primarily
attributed to the accumulation of damage generated by cellular metabolism as well as biological aging. Extrinsic insults from the environment add to the dermatological signs of aging\(^1\). Aged skin is frequently characterized by xerosis and pruritus (itching). For patients with severe itching, scratching is almost inevitable. Scratching can aggravate dermatitis. This vicious feedback loop is called the itch-scratch cycle. Once the itch-scratch cycle is established, conscious effort is no longer sufficient to control scratching. The act of scratching becomes habitual, so that the disease progresses\(^1\). Lack of attention to this aspect almost always results in suboptimal treatment. Since the scratching occurs at the subconscious level or while asleep, the patient is powerless to break the cycle by him/herself\(^1\). Itching is more severe with the extension of the disease course, which is in line with our results.

In the present study, eczema outpatients with suspected bacterial infection are more prone to severe itching. Microbial infection caused by different types of pathogens often exhibit intense pain or itch. The molecular mechanism responsible for pathogenic infection-induced itching is not well understood. Itching may be directly triggered by pruriceptors or neurons, which are stimulated by pathogens or inflammatory factors released by mast cells\(^1\). A study of acute lesions of AD patients indicates that S. aureus can easily penetrate or invade the skin, mainly through scratching and feed off skin exudates\(^1\). That study also found that eczema outpatients with pustular, erosion or exudate were more susceptible to bacterial infection. That means eczema outpatients with erosion or exudate were more susceptible to bacterial infection, which correlated with the severity of itching. Elongation of sensory nerves in the epidermis under the stratum corneum due to drying and inflammation is also considered to be a cause of skin hyperesthesia\(^1\), which means these patients are more prone to itching. This suggests the importance of treating bacterial infection in pruritus patients.

A positive association has been identified between itching and history of allergic disease. History of allergic disease included asthma, allergic rhinitis, allergic conjunctivitis and atopic dermatitis (AD). Atopic dermatitis is an inflammatory skin disease characterized by intense pruritus and relapsed eczematous lesions\(^7\). It increases the risk for food allergy, asthma, allergic rhinitis, immune-mediated diseases, and mental disorders\(^1\). Specific defects in immune system can cause primary disturbances in immunologic disorders that induce IgE-mediated sensitization, epidermal barrier dysfunction, and subsequent local inflammation\(^9\). As the most important symptom of AD, pruritus has an abnormal interaction between immune cells and keratinocytes. Dysfunction of these cells activates...
TSLP and IL-13 is crucial to ameliorate pruritus in AD. We observed a negative association between itching and lesions. Based on trend tests for itching rank, positive correlations were observed between the severity of itch-widespread eczema (30.1%) and asthetotic eczema (27.9%), which was featured by dry skin or large areas of history of flexion dermatitis. However, the reason is unclear, which requires further exploration.

Compared to 6.9% when diagnosed by the dermatologists, these results suggested that UKWP criteria under-investigation, in which the prevalence of adult AD was estimated to be approximately 2.9% using the UKWP criteria, criteria (3.7%) vs. dermatologists’ diagnosis (8.0%). Intriguingly, similar findings were observed in a Japanese investigation, in which the prevalence of adult AD was estimated to be approximately 2.9% using the UKWP criteria, compared to 6.9% when diagnosed by the dermatologists. These results suggested that UKWP criteria under-estimate the true prevalence of adult AD. In 2016, Professor Zhang proposed three features as the criteria for adult/adolescent AD; of all 2662 patients, 60.3% satisfied the Chinese criteria, 48.2% satisfied the Hanifin and Rajka criteria, and 32.7% satisfied the Williams criteria. The Chinese criteria have higher sensitivity for adult/adolescent AD; of all 2662 patients, 60.3% satisfied the Chinese criteria, 48.2% satisfied the Hanifin and Rajka criteria, and 32.7% satisfied the Williams criteria. The Chinese criteria have higher sensitivity for adult/adolescent AD patients. Laboratory tests are necessary, but not all patients agree to do it. The UKWP criteria are suitable for epidemiological study, but some AD patients might be missed according to the Chinese criteria.

Our study showed that the top three subtypes of dermatitis with severe itching were atopic dermatitis (30.4%), widespread eczema (30.1%) and asthetotic eczema (27.9%), which was featured by dry skin or large areas of lesions. Based on trend tests for itching rank, positive correlations were observed between the severity of itching and the proportions of these three diseases (P < 0.001), as shown in Table 2. Dry skin is characterized by a disrupted barrier, resulting in lactation, lack of smoothness of the skin surface and development of pruritus. T-cells directly communicate with nerves to regulate neurogenic inflammation of pain and are involved in pruritus as well. Recent reports propose that T-cell signaling pathways are involved in dry skin pruritus. Zeta-chain-associated protein kinase 70 (ZAP70), as a T-cell receptor, may induce interleukin 2 (IL-2) secretion and promote nerve growth factor (NGF) secretion in skin. Another study showed that increased ZAP70 mediators that enhance the sprouting of nerve fibers and stimulate sensory nerve endings. To promote itch, TSLP derived from keratinocytes communicates directly with cutaneous sensory neurons. TSLP stimulates Th2 cells to produce cytokines, such as IL-13, to strengthen the growth of nerve fibers. Therefore, decreased expression of TSLP and IL-13 is crucial to ameliorate pruritus in AD. We observed a negative association between itching and history of flexion dermatitis. However, the reason is unclear, which requires further exploration.

### Table 2. The proportion of itching in each type of dermatitis (N = 8758).

| Classification                  | No. of patients (%) | Mild (%, n) | Moderate (%, n) | Severe (%, n) | P* |
|--------------------------------|---------------------|-------------|----------------|--------------|----|
| Unclassified eczema (3109/8758) | 2.3 (71)            | 30.6 (950)  | 52.5 (1633)    | 14.6 (455)   | 0.763 |
| Atopic dermatitis (682/8758)   | 0 (0)               | 17.4 (119)  | 52.2 (356)     | 30.4 (207)   | <0.001 |
| Irritant contact dermatitis (810/8758) | 4.8 (39)    | 34.9 (283)  | 48.9 (396)     | 11.4 (92)    | <0.001 |
| Widespread eczema (765/8758)  | 1.8 (14)            | 18.6 (142)  | 49.5 (379)     | 30.1 (230)   | <0.001 |
| Hand eczema (590/8758)        | 6.8 (40)            | 24.2 (143)  | 57.5 (339)     | 11.5 (68)    | 0.06  |
| Allergic contact dermatitis (513/8758) | 2.9 (15)        | 27.7 (142)  | 49.5 (254)     | 19.9 (102)   | 0.021 |
| Neurodermatitis (483/8758)    | 2.1 (10)            | 30.0 (145)  | 47.3 (228)     | 20.7 (100)   | 0.021 |
| Seborrhoeic dermatitis (447/8758) | 3.4 (15)        | 44.7 (200)  | 45.0 (201)     | 6.9 (31)     | <0.001 |
| Nummular eczema (400/8758)    | 1.8 (7)             | 25.8 (103)  | 55.8 (223)     | 16.8 (67)    | 0.019 |
| Asteototic eczema (301/8758)  | 5 (15)              | 22.9 (69)   | 44.2 (133)     | 27.9 (84)    | <0.001 |
| Photosensitive dermatitis (244/8758) | 2.9 (7)        | 24.6 (60)   | 57.0 (139)     | 15.6 (38)    | 0.187 |
| Autosensitization dermatitis (221/8758) | 1.4 (3)     | 25.8 (57)   | 45.7 (101)     | 27.1 (60)    | <0.001 |
| Dyshidrotic eczema (220/8758) | 2.3 (5)            | 29.5 (65)   | 51.4 (113)     | 16.8 (37)    | 0.465 |
| Stasis dermatitis (123/8758)  | 0.8 (1)             | 15.4 (19)   | 69.1 (85)      | 14.6 (18)    | 0.289 |

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5
Other major limitations of this study include the following. Because participants were recruited from multiple tertiary referral hospitals located in provincial capitals or central cities, most patients visiting these hospitals were in a better financial and medical-insurance status than the average. As a hospital-based study, a selective bias was inevitable due to a nonhomogeneous population and differential spatial distribution. In addition, no adequate treatment or follow-up were documented in our study. All these factors may have led to an unavoidable bias.

In summary, this study provides an informative profile of itching in Chinese outpatients. Eczema outpatients with older age, longer disease duration, and, especially, a history of allergic diseases might be more prone to itching. These results provide important evidence for the prevention and therapy of itching. High-quality cohorts or case-control studies are needed to verify the results of this survey.

Methods
Study design and subjects. This study was approved by Institutional Review Board (IRB) committee of Beijing Friendship Hospital, Capital Medical University. All experiments were performed in accordance with relevant guidelines and regulations. All participants provided oral informed consent. This prospective and cross-sectional study was conducted from July 1 to September 30, 2014. The information of outpatients diagnosed with eczema and dermatitis were collected from 39 tertiary hospitals in 15 provinces and municipalities in mainland China, including Guangdong, Chongqing, Hunan, Jiangxi, Henan, Zhejiang, Shanghai, Hubei, Jiangsu, Anhui, Shanxi, Beijing, Tianjin, Shandong, and Liaoning provinces, which covered most areas of China34 (see Supplementary Fig. S2). The inclusion criteria were outpatients diagnosed with eczema and dermatitis visiting the 39 tertiary hospitals from July 1 to September 30, 2014. The exclusion criteria included outpatients with serious mental illness or organic disease who could not cooperate with the investigation and outpatients who refused to provide oral informed consent.

Specific research content. All enrolled outpatients completed a specific survey on general demographic characteristics, disease duration, severity of itching, distribution of lesions, type of skin lesions and medical history. Itching was assessed and divided into four levels: (i) no itching; (ii) mild itching (neither the participant’s daily activities nor sleep was interrupted); (iii) moderate itching (daily activities were interrupted, but sleep was not affected); and (iv) severe itching (both the daily activities and sleep of participants were affected) (see Supplementary Fig. S3). History of allergic disease, dry skin, infantile eczema, and flexion dermatitis were also recorded. History of allergic disease included asthma, allergic rhinitis, allergic conjunctivitis and AD. Secondary bacterial infection was clinically suspected if superficial pustules, prudent exudation, or yellow crust was detected. Our previous study has shown such lesions correlated with laboratory results of bacterial culture. In eczema with clinical diagnosed bacterial infection, S. aureus was isolated in 92.9% of patients35.

Diagnostic criteria. All dermatologists involved in this study had abundant experience in clinical diagnosis and treatment of eczema and were trained in a standardized manner before the project. First, each subject was inspected by a dermatologist independently. Then, a questionnaire survey was conducted by dermatologists after a 10–15-minute dermatological physical examination and after the parents or guardians had filled out informed consent forms for pediatric outpatients.

Dermatitis and eczema were classified based on the International Classification of Diseases (ICD) – 10 (eczema ICD-10 codes: L30.902)36. The doctor diagnosed the disease strictly according to the definition of the disease from Andrews’ Diseases of the Skin: Clinical Dermatology tenth edition, simplified Chinese edition. Specific types of dermatitis, including atopic dermatitis (AD), irritant contact dermatitis (ICD), widespread eczema, hand eczema (HE), allergic contact dermatitis (ACD), neurodermatitis, seborheic dermatitis, nummular eczema, atopic eczema, photocontact dermatitis, autosensitization eczema, dyshidrotic eczema, and stasis dermatitis, were clinically diagnosed accordingly. The remaining, unspecified eczema was diagnosed as unclassified eczema (UE)37. According to the questionnaire and physicians’ evaluation, a comprehensive diagnosis of AD was made based on “UK Working Party criteria”38. Multiple diagnoses were possible, and no laboratory test was performed for diagnosis.

Statistical Analysis. All data were input into Statistical Package of Social Sciences software version 17.0 (IBM, NY) for statistical analysis. For continuous variables, mean ± standard deviation (SD) was used according to distribution. The normality of data was checked by the Kolmogorov-Smirnov test. Age conformed to a normal distribution, but disease duration was characterized by a skewed distribution. Statistical methods included the t-test, chi-square test, and correlation analysis. Differences in age and disease course between itching grade groups were evaluated by one-way ANOVA. Differences in sex, medical history, type of dermatitis and suspected bacterial infection between itching grade groups were analyzed by the chi-square tests. Missing data were excluded from the final analyses. All the analyses were two-tailed tests with the significance level of 0.05. Age, sex, disease duration, suspected bacterial infection, and history of allergic disease, dry skin, infantile eczema, and flexion dermatitis were included in logistic regression models for odds ratios (ORs) and 95% CI estimation.

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Author Contributions

Xin Wang and Lin-Feng Li performed the experiments and drafted the manuscript. Xiao-Dong Shi performed data analyses. Ping Zhou and Yi-wei Shen prepared Figures 1–6 and Tables 1–3. All authors reviewed the manuscript.

Additional Information

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