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Analysis of factors influencing patch test reactions: Results from a large- population-based study in Chinese

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Abstract

Background: Patch test, as a helpful tool in clinic diagnosis and safety assessment of cosmetics, is affected by many factors.

Objectives: To investigate the influencing factors of patch test reactions in a highly standardized large-scale dataset of Chinese.

Methods: Patch test data (n = 151,280) from safety assessments of cosmetic products were obtained following internationally standardized patch testing protocols during 2004–2017 in China.

Results: The frequency of patch test reactions was 1.45% (2,191/151,280), with majority of the reactions being "score 1" reactions (also known as doubtful reactions, n = 2,075) and a small number being "score 2" reactions (weak reactions, n = 116). Patch test reactions were 67% more frequent in winter ($p < 0.001$), associated with temperatures ($p < 0.001$), rather than relative humidity (P:0.29). The frequency of reactions was higher in men than in women (p:0.001), especially in winter. The risk to develop reactions clearly increased with age in women ($p < 0.001$), but not in men (p:0.14). In women, the frequency of reactions in the old group (≥50 years old) was 30% more than the young group (<30 years old).

Conclusions: The frequency of patch test reactions to cosmetic products was 1.45% in our large-scale study. The influencing factors of patch test include season, sex, and age, which should be considered when conducting and interpreting patch testing.

KEYWORDS
influencing factors, patch test to cosmetics, skin reactions

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1 | INTRODUCTION

Patch test is a helpful tool in many fields. Apart from its use to confirm suspected contact dermatitis, the patch test procedure can also be used in the safety assessment of cosmetic products. According to the published literatures, patch test results are influenced by diverse factors, including age, sex, season, and meteorological factors.[1-5] All these factors potentially compromise the performance of patch test, which leads to the inherent inaccuracy of the patch test method. Large-scale studies to systematically examine the influencing factors of patch test reactions based on the highly standardized datasets, however, are scarce.

According to current regulations in China,[6] a single 24 h patch test as the safety assessment is required for certain categories of pre-marketing cosmetic products (including sunscreens, skin whitening products, and deodorants). It can evaluate the potential of skin reactions of a given cosmetic product. Shanghai Skin Disease Hospital is one of the sites qualified to perform the evaluation tests in China and therefore has accumulated a large highly standardized patch test dataset with pre-marketing cosmetic products during 2004–2017. To better understand the influencing factors which might potentially affect the outcome of such patch test method, we here analyzed 151 280 safety assessment patch test data from the large-scale population-based dataset in Chinese. The results can be considered in both the design of patch test studies and the interpretation of patch test readings.

2 | MATERIALS AND METHODS

2.1 | Study sample

Our dataset included 151 280 patch test results, which were generated by patch testing a total of 16 478 pre-marketing cosmetics in 4029 healthy volunteers, during 2004 and 2017 in Shanghai Skin Disease Hospital. The age range of the volunteers was 18 to 64 years, with 2895 women [71.85%] and 1134 men [28.15%]. Individuals during pregnancy and lactation or who had been diagnosed with any type of immunodeficiency disorders, inflammatory skin diseases, autoimmune diseases, insulin-dependent diabetes mellitus, as well as self-reported sensitive skin condition, had been excluded from patch testing. We also excluded individuals that were being treated for asthma or any other chronic respiratory disease, or had undergone bilateral mastectomy and bilateral axillary lymph node resection, or had used antihistamine medication within the week, immunosuppressive drugs within the month, anti-inflammatory drugs within the last 2 months, or had been under treatment for any cancer within the last 6 months prior to patch testing, or were participating in any other clinical testing. Individuals with damaged skin in or around the test sites were also not included in the study. All participants voluntarily joined and signed written informed consent before the study, which had been approved by the local ethics committee at Shanghai Skin Disease Hospital, China.

2.2 | Patch testing

The single occlusive patch tests (Figure S1) as the safety assessment were carried out according to a standard protocol of the Chinese Cosmetic Regulation [2015].[6,7] According to the regulation, test materials were among the defined categories of pre-marketing cosmetics (including sunscreens, skin whitening products, and deodorants). For all tests, the patch test materials were pre-marketing cosmetics. The detailed classified information of cosmetics can be seen in Table S1. The patch tests were performed on the upper back of the volunteers which on average simultaneous testing of up to 37 patches. Each volunteer came for four visits (Figure S1). Patch tests were applied on the back skin at Day 0 (D0). After 24 h of occlusion, the patches were removed and the first reading was performed 30 min later (Day 1, D1). The second reading was conducted 24 h later at Day 2 (D2) and the third reading 48 h after removing the patches, that is, at Day 3 (D3). For patch testing, 8-mm Finn chambers (SmartPractice, Phoenix) were used. The reading of the patch test reaction was performed according to the ICDRG (International Contact Dermatitis Research Group) criteria.[8,9] In our study, scores 0 mean no reaction, and scores 1–4 were defined as a reaction (Figure S1). Scores 1 to 4 correspond to doubtful (?+), weak (+), strong (++), and extreme (+++) reactions in ICDRG criteria, respectively.

2.3 | Measure of climatic factors

The Shanghai Baoshan Metrology Station provided the climatic data for the period from 2005 to 2017, including average temperature (°C) and relative humidity (%) in daily resolution. In order to assess the associations of climatic factors with the patch test reaction, the average of climatic factors during a 4-day period of patch testing (from the day application (D0) to the day of the last reading (D3)) was considered.

2.4 | Statistical analysis

The associations of age with patch test reactions were analyzed by logistic regression and expressed as odds ratio (95% CI). To determine the independently influencing factors and to avoid the influence of confounding factors, multivariable logistic regression was performed to calculate the adjusted statistics. The variance inflation factor was used to identify possible multicollinearity, and no high multicollinearity was found (<10 for all). Significance levels were adjusted with Bonferroni correction for the multiple comparisons. All statistical calculations were performed using R software (version 3.5.1).

3 | RESULTS

A total of 151,280 patch tests obtained from 4,029 healthy volunteers were included in the analysis. The overall reaction rate of patch test was 1.45% (2,191/151,280). The reactions were usually mild in the study, with 2075 (94.71%) reactions being scored as score 1 (also known as

TABLE 1 Influencing Factors of Skin Reactions

Factors	Case/Total (%)	Crude OR	Crude P	Adjusted OR[a]	Adjusted P[a]
Age	-	1 [1–1.01]	0.06	1 [1–1.01]	0.45
in men	-	1 [0.99–1]	0.30	1 [0.99–1]	0.14
in women	-	1.01 [1.01–1.02]	<.001	1.01 [1.01–1.02]	<0.001
Sex					
Men	716/44800 (1.6%)	1 [ref]	-	1 [ref]	-
Women	1475/106480 (1.39%)	0.86 [0.79–0.95]	0.002	0.86 [0.79–0.95]	0.001
Season[b]					
Winter	658/31001 (2.12%)	1 [ref]	-	1 [ref]	-
Spring	455/39745 (1.14%)	0.53 [0.47–0.6]	<0.001	0.54 [0.48–0.61]	<0.001
Summer	664/46174 (1.44%)	0.67 [0.6–0.75]	<0.001	0.68 [0.61–0.76]	<0.001
Autumn	414/34360 (1.2%)	0.56 [0.5–0.64]	<0.001	0.56 [0.5–0.64]	<0.001
Climatic factors[c]					
Temperature, °C	-	0.98 [0.98–0.99]	<0.001	0.98 [0.98–0.99]	<0.001
Relative humidity, %		1 [1–1]	0.34	1 [1–1]	0.29

Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; ref, reference

[a]Adjusted statistic was calculated by multivariable logistic regression to adjust for age, sex, and season. Significant P values are bolded (<0.05).

[b]Season: winter: January-February-March; spring: April-May-June; summer: July-August-September; Autumn: October-November-December.

[c]The logistic regression model for climatic factors was skin reaction to cosmetics ~temperature + humidity (+ age +sex in adjusted model).

doubtful reactions according to the ICDRG criteria) and 116 (5.29%) reactions being score 2 (weak reactions). We conducted logistic regression analysis to assess the relevance of meteorological factors, age, and sex as potential influencing factors for patch test reactions.

3.1 | Meteorological actors

The risk to develop a patch test reaction to a tested product was significantly lower in spring (adjusted odds ratio [aOR]: 0.54, 95% CI: 0.48–0.61, $p < 0.001$), summer (aOR: 0.68, 95% CI: 0.61–0.76, $p < 0.001$), and autumn (aOR: 0.56, 95% CI: 0.50–0.64, $p < 0.001$), as compared with winter (Table 1). Patch test reactions were 1.67 times more frequent in winter as compared with the other seasons (winter: 2.12% vs. non-winter: 1.27%, $p < 0.001$). This finding remained the same in both women and men (Table 2). After stratified by reaction scores, the score 1 reactions showed the similar results, while score 2 reactions in winter were only significantly higher than in spring (*p*: 0.001, Table 3). We further investigated which climatic factors were independently associated with patch test reactions. We found that patch test reactions were more frequent if testing was performed when outside temperatures were low (°C, aOR: 0.98, 95% CI: 0.98–0.99, $p < 0.001$, Table 1). We did not observe a significant association between patch test reactions and outside relative humidity (%, $p < 0.05$).

3.2 | Sex

Interestingly, there was a statistically significant sex difference in the frequency of patch test reactions (*p*: 0.001; Table 1). The frequency of patch test reactions was slightly higher in men compared with women (1.6% *versus* 1.39%). Of note, the significant sex difference only held true in individuals with the age group of 18–50 years old (Table S2), but showed no difference in individuals with the age group over 50 years old. After stratification by seasons, we found that these results only held true in winter (2.45% *versus* 1.98%, *p*:.007, Table 4), when men were 24% more likely to develop a reaction than women. However, such sex effect was not observed in other seasons ($p>0.05$).

3.3 | Age

There was a significant association between age and patch test reactions (*p*:0.045, Table 1). A stratified analysis revealed that in women, the risk of developing patch test reactions significantly increased with age (aOR: 1.01, 95% CI: 1.01–1.02, $p < 0.001$). In women, the frequency of reactions in the old group (≥50 years old, 1.5%) was 30% more than the young group (<30 years old, 1.15%, Table S2). In contrast, this association could not be detected in men ($p > 0.05$, Figure 1).

4 | DISCUSSION

This is the first study, to our knowledge, to examine influencing factors of patch test reactions in an unprecedentedly, highly standardized, large-scale patch test dataset. Traditionally, research on influencing factors of the patch test method is usually based on patients with dermatitis. In our dataset, a major advantage of using the general healthy population is to avoid the bias from the patient's atopic constitution on the patch test results, and the influencing factors thus can be estimated more accurately.

TABLE 2 Associations between season and patch test reactions stratified by sex

	Case/Total (%)	Crude OR	Crude P	Adjusted OR[a]	Adjusted p[a]
in women					
Winter[b]	422/21354 (1.98%)	1 [ref]	-	1 [ref]	-
Spring	316/27979 (1.13%)	0.57 [0.49–0.66]	<0.001	0.57 [0.49–0.66]	<0.001
Summer	459/32610 (1.41%)	0.71 [0.62–0.81]	<0.001	0.72 [0.63–0.82]	<0.001
Autumn	278/24537 (1.13%)	0.57 [0.49–0.66]	<0.001	0.57 [0.49–0.66]	<0.001
in men					
Winter[b]	236/9647 (2.45%)	1 [ref]	-	1 [ref]	-
Spring	139/11766 (1.18%)	0.48 [0.39–0.59]	<0.001	0.47 [0.38–0.58]	<0.001
Summer	205/13564 (1.51%)	0.61 [0.51–0.74]	<0.001	0.61 [0.5–0.73]	<0.001
Autumn	136/9823 (1.38%)	0.56 [0.45–0.69]	<0.001	0.56 [0.45–0.69]	<0.001

Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; ref, reference;

[a]Adjusted statistic was calculated by multivariable logistic regression to adjust for age. Significant *p* values are bolded (<0.05/2).

[b]Season: winter: January-February-March; spring: April-May-June; summer: July-August-September; Autumn: October-November-December.

TABLE 3 Associations between season and patch test reactions stratified by reaction scores

	Case/Total (%)	Crude OR	Crude P	Adjusted OR[a]	Adjusted p[a]
in score=1					
Winter[b]	624/30967 (2.02%)	1 [ref]	-	1 [ref]	-
Spring	438/39728 (1.1%)	0.54 [0.48–0.61]	<0.001	0.55 [0.48–0.62]	<0.001
Summer	623/46133 (1.35%)	0.67 [0.6–0.74]	<0.001	0.67 [0.6–0.75]	<0.001
Autumn	390/34336 (1.14%)	0.56 [0.49–0.63]	<0.001	0.56 [0.49–0.64]	<0.001
in score=2					
Winter[b]	34/30377 (0.11%)	1 [ref]	-	1 [ref]	-
Spring	17/39307 (0.04%)	0.39 [0.21–0.68]	0.001	0.38 [0.21–0.67]	0.001
Summer	41/45551 (0.09%)	0.8 [0.51–1.27]	0.35	0.78 [0.5–1.24]	0.29
Autumn	24/33970 (0.07%)	0.63 [0.37–1.06]	0.08	0.62 [0.37–1.05]	0.08

Abbreviations: OR, odds ratio; 95% CI: 95% confidence interval; ref, reference

[a]Adjusted statistic was calculated by multivariable logistic regression to adjust for age and sex. Significant *p* values are bolded (<0.05/2).

[b]Season: winter: January-February-March; spring: April-May-June; summer: July-August-September; Autumn: October-November-December.

In our study, the frequency of patch test reactions was 1.45% in the general population. Comparisons with other studies are hampered by the fact that different test protocols might have been employed. It is worth noting that the reactions are usually mild in the study (scores 1–2). A possible explanation for this is that healthy individual without an atopic constitution is less prone to allergic reaction than patients with dermatitis. Another possible explanation is that the patch test ingredients in our study were cosmetic products, which are developed to please skin.

We found that patch test reactions were more frequent in winter as compared with other seasons. Such result is in line with several previous studies which have shown that during winter the number of positive patch test reactions to allergens is increasing.[2,10,11] It is also evident in diagnostic patch testing.[12] This likely reflects the fact that the skin barrier is compromised during winter, with a decrease in stratum corneum (SC) lipids and extensibility, and an increase in skin permeability,[13-15] making the skin more prone to irritation and penetration of potential contact allergens in winter. We further identified that cold weather was independently associated with patch test reactions, consistent with findings in previous studies.[3-5] Experiments in mice also shown that low temperature delays barrier recovery and inhibits the production of lamellar bodies,[16] which leads to skin barrier dysfunction, allowing more allergen to penetrate the epidermis. We did not observe the association between dry weather and patch test reactions, which may be explained by the comfortable humidity in Shanghai and does not change significantly throughout the year (relative humidity, mean: 70%, sd: 12%). Our results suggest that patch testing readings are stable when humidity is within a medium range. Consistent with the literature,[5] this research found that score 1 reactions are more seasonally dependent than score 2 reactions, which was hardly affected by weather conditions (it also may be caused by the insufficient statistical power of score 2 reactions). Thus, the weather condition is a factor that should

TABLE 4 Associations between sex and patch test reactions stratified by season

Season	Sex	Case/Total (rate, %)	p^a
winter	women	422/21354(1.98%)	0.007
	men	236/9647(2.45%)	
spring	women	316/27979(1.13%)	0.49
	men	139/11766(1.18%)	
summer	women	459/32610(1.41%)	0.37
	men	205/13564(1.51%)	
Autumn	women	278/24537(1.13%)	0.04
	men	136/9823(1.38%)	

[a]The *p* value was calculated by multivariable logistic regression to adjust for age. Significant *p* values are bolded (<0.05/4).

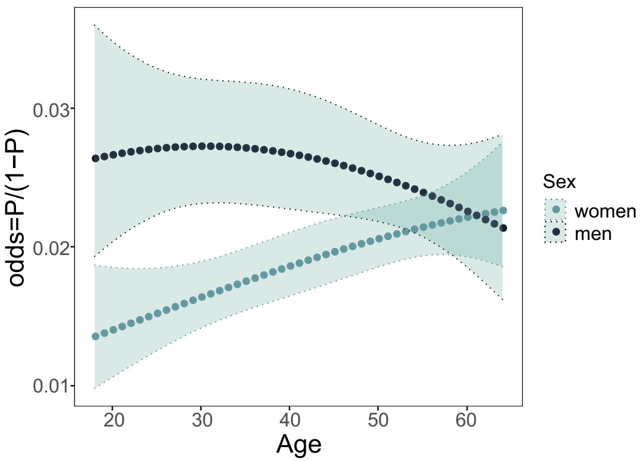

FIGURE 1 Odds for Patch Test Reactions to Cosmetics According to Age. The y-axis indicates the odds of patch test reactions. The blue points represent men; the dark points represent women; the ribbons represent 95% confidence interval. The logistic regression model was patch test reactions ~age + age^2 + sex + season

be considered during patch testing, but will not have substantial effect on the positive reaction.

We found the frequency of patch test reactions was slightly higher in men compared with women in winter. These results are different from the popular perception that women are more likely to have skin reactions to cosmetics. This is mainly because, in real-world settings, women use more cosmetic products than men,[17,18] naturally increasing the volume of skin reactions in women. Besides, men are more prone to develop the impaired barrier caused by the excess amount of sebum and a lack of appropriate skincare regimen due to tacky feeling.[19] An increase of fatty acids in the sebum can inhibit SC barrier function by altering the intercellular lipid structure.[20]

In our study, the risk of patch test reactions increased with age in women. The results are in line with previous studies which showed that the positive reaction rate of patch test with cosmetic ingredients increased with age[21,22] and is consistent with the assumption that repetitive cutaneous exposure is necessary for the development of a delayed type of hypersensitivity reaction to a contact allergen.

The present study identified that patch test reactions were associated with season, age, and sex. We hope these findings can provide new considerations for the patch test practice. For example, patch testing with cosmetics possibly leads to false-positive reactions in winter and should thus retested in summer or under warm conditions. Both men and women should be recruited for the testing and have a balanceable proportion. If possible, future studies with further tests for positive reactions could provide deeper insight into the specific antigens.

Our patch test protocol was slightly different from the patch test protocol used in the diagnosis of contact allergy. Patches usually remained occluded for 48 h, and readings are being done 0.5–72 h after removing the patches during the diagnosis of contact allergy. In our study, we occluded patches for only 24 h and performed readings at 0.5–48 h after removing the patches. However, it made little effect on the patch test results as the concordant reaction between 24 h exposure and 48 h exposure was high (74~93%)[23]; and most reactions will not change after 48 h.[24] In line with this, we found the influencing factors of our safety assessment patch test protocols are similar to the factors of diagnostic patch tests. We cannot eliminate the possibility of biased frequency estimation because (1) all cosmetics were newly developed products and had not yet been in contact with the general population; (2) test subjects in this study were recruited on a voluntary enrollment basis, which is not an entirely random sampling from the general population. Such non-random bias should, however, not impact the relationship between patch test reactions and season, age, and sex.

5 | CONCLUSION

Overall, we provide solid evidence based on patch test results in a highly standardized large-scale study in healthy population that patch test reactions, with a general frequency of 1.45%, were associated with season, sex, and age. These influencing factors (e.g., season, sex, and age) should be considered in both the design of patch test studies and the interpretation of patch test readings.

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CONFLICT OF INTEREST

All the listed authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Ying Zou and Sijia Wang conceived and planned the study, interpreted the data, and revised the manuscript. Bingjie Li analyzed the data and drafted the manuscript. Ying Cheng and Yimei Tan take responsibility for data collection and data interpretation. Fudi Wang, Weiyi Hu, and Xuemin Wang have involved in the data collection and data interpretation. Wei Liu and Jean Krutmann interpreted the data and revised the manuscript.

DATA AVAILABILITY STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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