



# Clinical Features and Risk Factors for Nasal Rosacea: A Hospital-Based Retrospective Study

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## ABSTRACT

**Introduction:** At present, some studies have reported that nasal rosacea may be an independent disease, but phenotypic characteristics and risk factors for nasal rosacea remain unknown. This study aimed to clarify the clinical features and explore the risk factors for nasal rosacea.

**Methods:** A hospital-based retrospective study was conducted, including 1615 rosacea patients and 1501 healthy individuals. The patients were

divided into three groups based on the involved areas of the lesions (non-nasal, intermediate and nasal rosacea group). Their demographic data and clinical features were obtained from patients' medical records, and risk factors of nasal rosacea were analyzed.

**Results:** There were 927 (57.4%), 647 (40.1%) and 41 (2.5%) cases in the non-nasal, intermediate and nasal rosacea groups, respectively. Of 41 patients with nasal rosacea, all (100.0%) had fixed erythema and 17 cases (41.5%) had phymatous changes. Compared with control group, male gender (adjusted odds ratio [aOR] = 2.39, 95% confidence interval [CI] = 1.14, 4.99), obesity (aOR = 3.19, 95% CI 1.86, 11.79) and alcohol use (aOR = 1.58, 95% CI 1.22, 5.40) were risk factors for nasal rosacea, but these three factors were not risk factors for non-nasal rosacea and intermediate rosacea groups. Among patients with nasal lesions (compared with patients without nasal phymatous changes), family history of rosacea was a risk factor (aOR = 2.12, 95% CI 1.01, 4.46) for nasal phymatous changes and Fitzpatrick IV skin type was a protective factor (aOR = 0.49, 95% CI 0.28, 0.86).

**Conclusion:** Nasal rosacea has relatively specific clinical features and independent risk factors, suggesting that it may be a special type of rosacea.

**Keywords:** Phenotype; Phymatous change; Nasal rosacea; Rosacea; Risk factor

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### Key Summary Points

Nasal rosacea refers to rosacea with nasal lesions, which has been thought to be an independent disease, but phenotypic characteristics and risk factors for nasal rosacea remain unknown

We clarified the clinical features and explored the risk factors for nasal rosacea, expecting nasal rosacea would be different from extra-nasal rosacea

After data collection and risk factor analysis, we were surprised to find that nasal rosacea has relatively specific clinical features and independent risk factors

On the basis of our study's results, we consider that nasal rosacea may be a special type of rosacea and need more attention

## INTRODUCTION

Rosacea is a common chronic inflammatory skin condition involving mainly the convexities of the central face, including the cheeks, nose, chin and central forehead [1]. Rosacea is conventionally classified into four major subtypes: erythematotelangiectatic rosacea (ETR), papulopustular rosacea (PPR), phymatous rosacea (PhR) and ocular rosacea [2]. Currently, new classification favors a patient-tailored phenotype rather than classification based in subtypes; phenotypes in this case include flushing, fixed erythema, papules and pustules, telangiectasia, phymatous changes, burning and tingling, etc. [3–7]. To date, many risk factors for rosacea, such as family history, types of photosensitivity, alcohol consumption and others, have been reported [8–14].

In terms of primary areas, cheeks and nose are the most commonly affected areas [15]. It has been clinically observed that some patients

tend to have nasal-confined lesions. Only one early-phase study with a small sample size has reported that localized nasal rosacea frequently presented with the ETR and PhR subtypes, which were different from those exhibited by extra-nasal rosacea, and hypothesized that nasal rosacea might be an independent condition [16]. However, this study did not provide a description of the phenotypic characteristics of rosacea. Moreover, our previous study also demonstrated that lesions in different facial areas in patients with rosacea showed significant differences in clinical features, and this was through a simply parallel comparison of rosacea in different facial areas [17]. Nevertheless, these two studies neither focused on risk factors of nasal rosacea nor paid attention to the progress and related factors of nasal phymatous changes.

Based on the current stage of research, many issues still need to be resolved. Some of these unanswered questions include: What are the phenotypic characteristics of nasal rosacea? Are these characteristics distinct from those of rosacea in other facial areas? What are the unique factors of nasal rosacea? Could nasal rosacea really be considered a special type of rosacea?

The current study was mainly designed to describe the phenotypic characteristics of nasal rosacea in detail and analyze the possible risk factors as well as provide clinical data on nasal rosacea to promote precise treatment and patient education and lay the foundations for further research into the mechanisms of this special type of rosacea.

## METHODS

### Study Design and Participants

This study was a hospital-based cross-sectional study, including 1615 patients and 1501 healthy individuals. All 1615 patients were diagnosed with rosacea according to the criterion of the aligned 2019 ROSacea Consensus (ROSCO) and 2017 National Rosacea Society phenotype recommendations [4, 6]. These patients were admitted to the Xiangya Hospital from July 2017 to March 2019 and enrolled in the study

consecutively. Exclusion criteria comprised symptoms and diseases interfering with the evaluation, including erosion, steroid use, severe bacterial or fungal infection, other skin disorders, pediatric diseases, pregnancy and history of systematic diseases, whereas patients with acne were not excluded. Moreover, the patients needed to be newly diagnosed patients and not to have been treated recently. Therefore, patients who had used topical drugs within 2 weeks, used tetracycline oral drugs or photoelectric therapy within 1 month or used isotretinoin within 6 months, at either our hospital or another institution, were excluded from the study. Healthy individuals were included as healthy control group, who were physical examination personnel without history of skin diseases or other systematic diseases in the physical examination center at the same period. The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. The detailed protocol of this study was approved by the Institutional Review Board of Xiangya hospital, Central South University (Ethical Application Ref: 201611608). Informed written consents were obtained from every participant.

### Data Collection

Demographic and clinical data were gathered from patients' medical records, including age, sex, body mass index (BMI), marital status, occupation, years of education, personal monthly income, skin type, Fitzpatrick skin type (Fitzpatrick III—sometimes burn, usually tan; Fitzpatrick IV—never burn, always tan), smoking status and alcohol use. Among these variables, age was recorded in four categories: < 24 years old, 25–34 years old, 35–44 years old and > 44 years old; body mass index, which was calculated as weight in kilograms divided by height in meters squared, was classified into three categories: underweight ( $\text{BMI} < 18.5 \text{ kg/m}^2$ ), normal ( $18.5 \text{ kg/m}^2 \leq \text{BMI} < 24 \text{ kg/m}^2$ )

and overweight or obese ( $\text{BMI} \geq 24 \text{ kg/m}^2$ ); years of education was recorded in two categories: < 12 years or 12 years; > 12 years. Personal monthly income was recorded in three levels: high, middle and low income. Occupation was recorded in two categories: physical and non-physical labor. The clinical phenotypic features collected included flushing, persistent erythema, telangiectasia, papules/pustules, phymatous changes and ocular manifestations, according to the global scale provided by the 2017 ROSCO panel [6]. Moreover, patients' clinical data on whether acne and dermatographia existed were collected from patients via dermatologists' observation and inquiry. Among them, the record of dermatographia required dermatologists to perform a skin scratch test. (The physician uses a device such as a broken cotton swab to draw a line slowly on the flexion of the patient's forearm. If there is redness, edema, swelling or exudation at the scratched skin, and it does not disappear for > 20 min, it can be judged positive). In this study, patients were classified into three groups: (1) nasal rosacea group (rosacea lesions limited to the nose); (2) intermediate rosacea group (rosacea lesions with both nasal and extra-nasal areas); (3) non-nasal rosacea group (rosacea lesions without nasal involvement).

### Statistical Analysis

Patient clinico-demographic characteristics were compared among all groups using the Pearson chi-square test for categorical variables and Kruskal-Wallis test for ranked variables. All categorical variables and ranked variables were represented by values and proportions. Multivariate logistic regression analysis was performed, and odds ratios (OR) and 95% confidence intervals (CI) were calculated. The adjusted OR (aOR) was also calculated in the regression model. All reported *P*-values are two sided with  $\alpha = 0.05$ . All statistical analyses were performed using SPSS version 25.0 (SPSS Inc., Chicago, IL, USA).

## RESULTS

### Demographic Characteristics

The cohort study consisted of 1615 patients with rosacea and 1501 healthy individuals. Of these patients, 927 (57.4%) had rosacea without nasal involvement (non-nasal rosacea group), 647 (40.1%) had rosacea with nasal lesions (intermediate rosacea group), and 41 (2.5%) had rosacea with nose-confined lesions (nasal rosacea group). Generally, there were significant differences between the control and total rosacea groups related to all characteristics studied, except for smoking status ( $P = 0.155$ ), age ( $P < 0.001$ ), gender ( $P < 0.001$ ), BMI ( $P = 0.004$ ), marital status ( $P < 0.001$ ), occupation ( $P < 0.001$ ), number of years of education ( $P < 0.001$ ), personal monthly income ( $P = 0.033$ ), Fitzpatrick skin type ( $P < 0.001$ ) and alcohol consumption ( $P = 0.01$ ). The proportion of men in the nasal rosacea group was higher than that in the intermediate rosacea (39.0% vs. 13.1%,  $P < 0.001$ ) and the non-nasal rosacea groups (39.0% vs. 5.7%,  $P < 0.001$ ); all other characteristics were similar in each patient group (Table 1).

### Clinical Features of the Nasal Rosacea Group

Since the diagnosis and classification of rosacea have evolved from the subtype to the phenotype approach, unlike previous studies, our study analyzed clinical features based on patient phenotypes rather than conventional subtypes. Of 41 patients in the nasal rosacea group, all (100.0%) had erythema (Fig. 1a), 17 (41.5%) had phymatous changes (Fig. 1b), 12 (29.3%) had flushing, 11 (26.8%) had papules and pustules, 6 (14.6%) had burning and tingling sensations, 4 (9.8%) had telangiectasia, and 1 (2.4%) had rosacea combined with ocular manifestations. In addition, the phymatous changes seen in the 17 patients were all accompanied by erythema (Fig. 1b). The majority of patients developed nasal hyperplasia within 3–5 years, and a few patients could develop it within 10–20 years, reflecting the

progression from onset to the phymatous changes (Fig. 2).

### Risk Factor Analysis

#### *Risk Factors for Distinct Groups of Rosacea*

Compared with the control group, male gender (aOR = 0.47, 95% CI 0.35, 0.63) and Fitzpatrick skin type IV (aOR = 0.58; 95% CI 0.48, 0.71) were found to be protective factors for the total rosacea group. The result of comparing the control group with the non-nasal group was consistent with that of the total rosacea group (male gender: aOR = 0.27, 95% CI 0.18, 0.41; Fitzpatrick skin type: IV aOR = 0.60, 95% CI 0.48, 0.75). However, only skin type IV had protective effects on patients in the intermediate rosacea group (aOR = 0.58; 95% CI 0.45, 0.75), and male gender was no longer a protective factor (aOR = 0.74, 95% CI 0.52, 1.07). Different from other groups, when comparing the control group with the nasal rosacea group, male gender (aOR = 2.39; 95% CI 1.14, 4.99), being overweight or obese (aOR = 3.19; 95% CI 1.86, 11.7) and consumption of alcohol (aOR = 1.58; 95% CI 1.22, 5.40) were risk factors for the nasal rosacea group, and skin type IV was not found to be associated with nasal rosacea (aOR = 0.79, 95% CI 0.38, 1.67) (Table 2).

#### *Risk Factors Associated with Nasal Phymatous Changes*

A total of 647 cases of intermediate rosacea and 41 cases of nasal rosacea were mixed, meaning both were characterized by patients with nasal lesions. Among 688 observed patients, there were 86 (12.5%) patients with nasal phymatous changes and 602 (87.5%) without these changes. Compared with patients without phymatous changes, Fitzpatrick skin type IV was a protective factor for nasal phymatous changes (aOR = 0.49; 95% CI 0.28, 0.86;  $P = 0.011$  for trend), and family history of rosacea was a risk factor for developing nasal phymatous changes (aOR = 2.12; 95% CI 1.01, 4.46;  $P = 0.049$  for trend). In contrast to risk factors for nasal rosacea, there were no differences between the nasal phymatous and control groups (patients without phymatous changes) with aspects to

**Table 1** Distributions of selected characteristics related to total rosacea, non-nasal rosacea, intermediate rosacea, nasal rosacea and controls

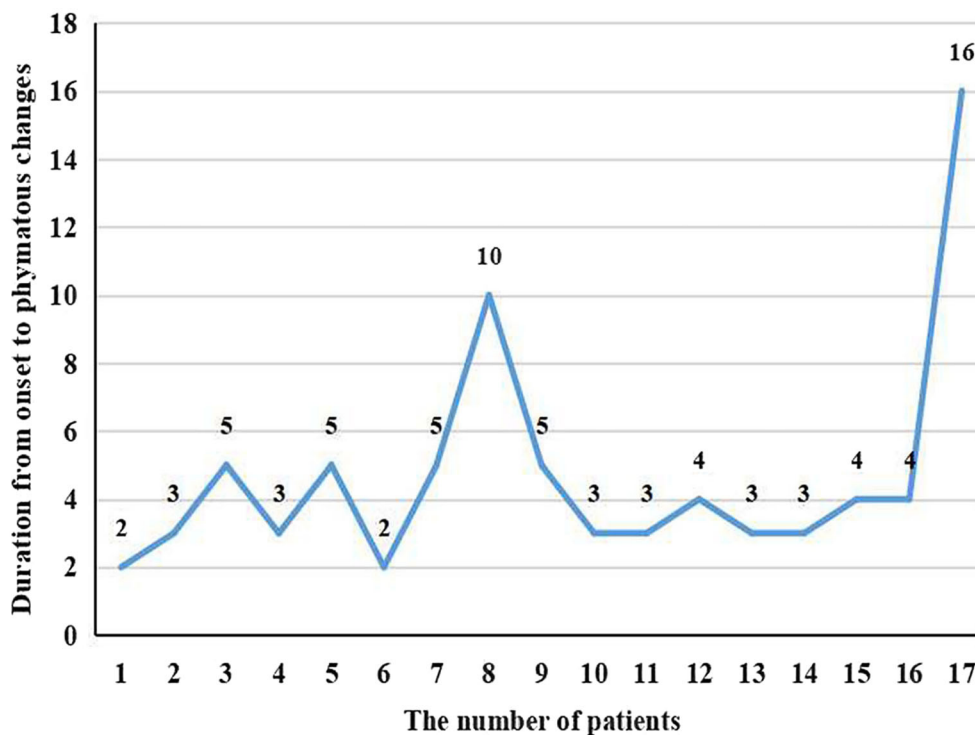
Characteristics	Controls		Total rosacea		<i>P</i>	Non-nasal rosacea		Intermediate rosacea		Nasal rosacea		<i>P</i>
	<i>N</i> =	%	<i>N</i> =	%		<i>N</i> =	%	<i>N</i> =	%	<i>N</i> =	%	
	<b>1501</b>		<b>1615</b>			<b>927</b>		<b>647</b>		<b>41</b>		
Age (years)					< 0.001							0.492
< 25	385	25.6	539	33.4		302	32.6	219	33.8	18	43.9	
25–34	784	52.2	433	26.8		255	27.5	170	26.3	8	19.5	
35–44	205	13.7	343	21.2		203	21.9	135	20.9	5	12.2	
> 44	127	8.5	300	18.6		167	18.0	123	19.0	10	24.4	
Gender					< 0.001							< 0.001
Male	279	18.6	154	9.5		53	5.7	85	13.1	16	39.0	
Female	1222	81.4	1461	90.5		874	94.3	562	86.9	25	61.0	
BMI					0.004							0.584
Underweight	288	19.2	312	19.3		178	19.2	127	19.6	7	17.1	
Normal	1067	71.1	1085	67.2		633	68.3	426	65.8	26	63.4	
Overweight or obese	146	9.7	218	13.5		116	12.5	94	14.5	8	19.5	
Marital status					< 0.001							0.497
Unmarried	820	54.6	416	25.8		247	26.6	157	24.3	12	29.3	
Married	681	45.4	1199	74.2		680	73.4	490	75.7	29	70.7	
Occupation					< 0.001							0.741
Physical labor	718	47.8	689	42.7		388	41.9	282	43.6	19	46.3	
Non-physical labor	783	52.2	926	57.3		539	58.1	365	56.4	22	53.7	
Years of education					< 0.001							0.121
≤ 12 years	296	19.7	937	58.0		539	58.1	368	56.9	30	73.2	
> 12 years	1205	80.3	678	42.0		388	41.9	279	43.1	11	26.8	
Personal monthly income					0.033							0.195
High income	414	27.6	499	30.9		296	31.9	191	29.5	12	29.3	
Middle income	635	42.3	690	42.7		400	43.1	268	41.4	22	53.7	
Low income	452	30.1	426	26.4		231	24.9	188	29.1	7	17.1	
Fitzpatrick skin type					< 0.001							0.230
III type	999	66.6	1110	68.7		627	67.6	458	70.8	25	61.0	
IV type	502	33.4	505	31.3		300	32.4	189	29.2	16	39.0	
Smoking					0.155							0.589

**Table 1** continued

Characteristics	Controls		Total rosacea		<i>P</i>	Non-nasal rosacea		Intermediate rosacea		Nasal rosacea		<i>P</i>
	<i>N</i> =	%	<i>N</i> =	%		<i>N</i> =	%	<i>N</i> =	%	<i>N</i> =	%	
	<b>1501</b>		<b>1615</b>			<b>927</b>		<b>647</b>		<b>41</b>		
No	88	5.9	115	7.1		60	6.5	52	8.0	3	7.3	
Yes	1413	94.1	1500	92.9		867	93.5	595	92.0	38	92.7	
Alcohol use					0.01							0.493
No	208	13.9	128	7.9		72	7.8	51	7.9	5	12.2	
Yes	1293	86.1	1487	92.1		855	92.2	596	92.1	36	87.8	



**Fig. 1** **A** Male, 54 years old, erythema was found only on the nose. **B** Male, 55 years old, erythema and phymatous changes were found with papules and pustules on the nose



**Fig. 2** Most patients developed nasal hyperplasia within 3–5 years, and for a few patients this was as long as 10–20 years

**Table 2** Odds ratios of non-nasal, intermediate and nasal rosacea compared with controls

Characteristics	Total rosacea OR <sub>adj</sub> (95% CI)	Non-nasal rosacea OR <sub>adj</sub> (95% CI)	Intermediate rosacea OR <sub>adj</sub> (95% CI)	Nasal rosacea OR <sub>adj</sub> (95% CI)
Gender				
Female	1.00	1.00	1.00	1.00
Male	<b>0.47 (0.35, 0.63)</b>	<b>0.27 (0.18, 0.41)</b>	0.74 (0.52, 1.07)	<b>2.39 (1.14, 4.99)</b>
BMI				
Underweight	1.00	1.00	1.00	1.00
Normal	0.88 (0.68, 1.12)	0.86 (0.65, 1.15)	0.77 (0.57, 1.06)	1.19 (0.40, 3.16)
Overweight or obese	1.34 (0.92, 1.93)	1.37 (0.90, 2.09)	1.39 (0.89, 1.77)	<b>3.19 (1.86, 11.79)</b>
Fitzpatrick skin type				
III type	1.00	1.00	1.00	1.00
IV type	<b>0.58 (0.48, 0.71)</b>	<b>0.60 (0.48, 0.75)</b>	<b>0.58 (0.45, 0.75)</b>	0.79 (0.38, 1.67)
Smoking				
No	1.00	1.00	1.00	1.00
Yes	1.12 (0.69, 1.80)	1.56 (0.91, 2.68)	0.97 (0.54, 1.74)	0.23 (0.03, 2.11)
Alcohol use				
No	1.00	1.00	1.00	1.00
Yes	1.31 (0.82, 2.09)	1.40 (0.83, 2.33)	1.06 (0.58, 1.93)	<b>1.58 (1.22, 5.40)</b>

OR<sub>adj</sub> Adjusted by age, marital status, occupation, education and income vs. control group

The symbol [bold] represents the data has statistical significance

male gender (aOR = 1.42, 95% CI 0.73, 2.80), obesity (aOR = 1.53, 95% CI 0.64, 3.65) and alcohol consumption (aOR = 1.30, 95% CI 0.41, 4.12) (Table 3).

## DISCUSSION

Previous studies have evaluated the clinical features of nasal rosacea and progression between distinct subtypes [15–18], and only few studies have described the clinical features of nasal rosacea based on patients’ phenotypic characteristics. Furthermore, no research has systematically analyzed the demographic characteristics and risk factors of nasal rosacea.

In our study, we applied a phenotypic approach to patients and demonstrated the clinical features of 41 patients with nasal rosacea. We found that all of them had fixed

erythema and nearly half of them had nasal phymatous changes, while flushing and papulopustular conditions were phenotypes not commonly observed. Meanwhile, we found that the incidence rate of phymatous changes on the cheeks was markedly lower than that on the nose (only approximately 4.6%; data not shown). This difference might arise from the divergent distribution of differentially functional fibroblast subpopulations in these two facial areas; detailed explanation in this regard requires further relevant studies [19]. Moreover, we observed that only a few patients had self-reported symptoms, such as burning and tingling sensations. Conversely, in our previous study, self-reported symptoms on the cheeks were more common [17]. Thus, taken together, we can conclude that the clinical features of nasal rosacea are indeed different from those of rosacea in other facial areas.

**Table 3** Factors associated with phymatous change among patients with nasal lesions

Related factors	Observed population <i>N</i> = 688	Nasal phymatous		OR <sub>adj</sub> (95% CI)	<i>P</i>
		<i>N</i> = 86	%		
Gender					0.306
Female	587	70	11.9	1.00	
Male	101	16	15.8	1.42 (0.73, 2.80)	
BMI					0.548
Underweight	134	14	10.4	1.00	
Normal	452	58	12.8	1.38 (0.71, 2.70)	
Overweight or obese	102	14	13.7	1.53 (0.64, 3.65)	
Fitzpatrick skin type					<b>0.011</b>
III type	483	67	13.9	1.00	
IV type	205	19	9.3	0.49 (0.28, 0.86)	
Smoking					0.548
No	633	80	12.6	1.00	
Yes	55	6	10.9	0.68 (0.19, 2.45)	
Alcohol use					0.656
No	635	79	12.4	1.00	
Yes	53	7	13.2	1.30 (0.41, 4.12)	
Family history of rosacea					<b>0.049</b>
No	638	75	11.8	1.00	
Yes	50	11	22.0	2.12 (1.01, 4.46)	
Acne					0.553
No	463	60	13.0	1.00	
Yes	225	26	11.6	0.88 (0.51, 1.49)	
Dermagraphia					0.214
No	497	58	11.7	1.00	
Yes	190	28	14.7	1.37 (0.82, 2.28)	
Aczema					0.605
No	616	75	12.2	1.00	
Yes	71	11	15.5	1.21 (0.59, 2.50)	

OR<sub>adj</sub> Adjusted by age, duration, marital status, occupation, education and income

The symbol [bold] represents the data has statistical significance



Since nasal rosacea has relatively specific clinical features and its pathogenesis is unclear, we investigated risk factors for nasal rosacea, hoping to provide some clinical clues regarding its etiology. We have concluded that male gender and Fitzpatrick IV skin type are protective factors for all rosacea and non-nasal rosacea groups; furthermore, Fitzpatrick skin type IV remains a protective factor for the intermediate rosacea group, further confirming the result of our previous studies [20, 21]. Conversely, Fitzpatrick skin type IV was no longer found to be a protective factor for nasal rosacea, and male gender, being overweight or obese, and consumption of alcohol were found to be risk factors instead. Our results provide new risk factors for nasal rosacea. Current findings show that hormones could affect rosacea via angiectasis and inflammatory cell infiltration, and men usually secrete more potent androgens than women after attainment of puberty [22, 23]. As for obese individuals, adipose tissue can also synthesize androgen, promoting hyperandrogenism in these individuals; moreover, these individuals may have more sebaceous glands on their noses [13, 24]. More importantly, there are more androgen receptors on the nose than cheeks [25]. These aforementioned findings might be the reasons why males and obese individuals are more prone to developing nasal rosacea, but detailed mechanistic studies are required in this regard. Alcohol consumption can stimulate vasodilation and aggravate persistent erythema, thus playing a role in the chronic vascular inflammation necessary to cause erythema on the nose [26, 27]. Therefore, based on the risk factors mentioned herein, patients should be actively encouraged to avoid alcohol consumption and maintain a healthy weight to prevent nasal rosacea. According to our findings, nasal rosacea has specific clinical features and risk factors; thus, we hold the view that nasal rosacea might be considered a special type of rosacea, and future investigations on its pathogenic mechanisms are required.

In terms of nasal phymatous changes, our study found that Fitzpatrick skin type IV had a protective effect, while family history of rosacea was a risk factor. There are some conflicting reports on risk factors for phymatous changes

on the nose (rhinophyma) [9, 10, 28, 29]. A previous study showed no association between alcohol consumption and rhinophyma, while a recent case-control study revealed a highly significant association between the two [10, 29]. In our study, alcohol consumption showed no association with nasal phymatous changes. Alcohol consumption in China is lower than in Western countries, especially among women. Furthermore, the types of alcohol also vary among different countries and should be taken into account. Moreover, consistent with a previous study [10], family history of rosacea was found to be a risk factor for nasal phymatous changes, probably because some specific genes contribute to nasal phymatous changes. Further studies on related genetic mechanisms are required. Additionally, we observed that all nasal phymatous changes occurred because of fixed erythema. Therefore, in clinical practice, more attention should be paid to the family histories of patients with rosacea and nasal fixed erythema; if family history of disease is noted, these patients should be treated promptly to avoid serious damage in the future, such as nasal hypertrophy.

### Limitations

However, our study had several limitations. First, the clinical data we used were from our hospital, which covers only the South Central Chinese population. Therefore, it cannot be representative of the national population. Second, potential recall bias may exist during clinical data collection. Third, this was a retrospective study and thus could suggest only correlation rather than causation. Therefore, the above-mentioned findings still require further prospective and comprehensive investigation in a larger population.

### CONCLUSION

In conclusion, we clarified the demographic and clinical features of patients with nasal rosacea and investigated the potential risk factors for nasal rosacea. We found that nasal rosacea has specific clinical features and

independent risk factors, supporting the hypothesis that it may be a special type of rosacea. Even though the results of this study require further elucidation, they may provide comprehensive clinical data on nasal rosacea to enable further research and provide practical recommendations to prevent risk factors in patients.

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**Authorship.** All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

**Author Contributions.** Study conception and design were performed by Ben Wang and Ji Li. Material preparation, data collection and analysis were performed by Hong-fu Xie Zhi-xiang Zhao, Fang-fen Liu, Yan Tang, Ying-xue Huang, Dan Jian and Wei Shi. The first draft of the manuscript was written by Ai-ke Wu and Fang-fen Liu, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

**Disclosures.** Ai-ke Wu, Fang-fen Liu, Hong-fu Xie, Zhi-xiang Zhao, Yan Tang, Ying-xue Huang, Dan Jian, Wei Shi, Ben Wang and Ji Li have nothing to disclose.

**Compliance with Ethics Guidelines.** The detailed protocol of this study was approved by

the Institutional Review Board of Xiangya Hospital, Central South University (Ethical Application Ref: 201611608). The study was performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Written informed consents have been obtained from every participant.

**Data Availability.** All data generated or analyzed during this study are included in this published article.

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