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Recurrent aphthous stomatitis (RAS) and its related factors among the Azar cohort population

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Abstract

Introduction Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral inflammatory ulcerative lesions, characterized by painful ulcers that develop on non-keratinized oral mucosa, significantly affecting the quality of life. This study aimed to evaluate the prevalence of RAS and its associated risk factors within the Azar cohort population.

Methods This cross-sectional study utilized data from the Azar cohort, which has been ongoing since 2014 in Shabestar City, East Azarbaijan, Iran, involving 15,006 adults aged 35 to 70 years. To assess the prevalence of RAS, participants were provided with a description of these lesions and asked whether they had ever experienced RAS in the oral cavity. Data collection was based on self-reports and examinations conducted by the physicians involved in the Azar cohort. Participants with RAS were classified into the RAS group, while the remaining participants were categorized into the non-RAS group. We assessed the association between RAS and various factors using binary logistic regression.

Results In the study population, there were 3,503 individuals in the RAS group and 11,503 individuals in the non-RAS group. The prevalence of RAS in the Azar cohort was 23.34%. Individuals over 50 years of age ($p < 0.001$), those with a poor ($p < 0.001$) or very poor ($p = 0.02$) socio-economic status, a low educational level ($p = 0.01$), smokers ($p < 0.001$) and individuals with a history of smoking who have since quit ($p = 0.01$) were significantly less affected by RAS. Conversely, individuals with genital aphthous lesions ($p < 0.001$), depression ($p < 0.001$), rheumatoid disease ($p = 0.01$), and food allergies ($p < 0.001$) were significantly more affected by RAS.

Conclusions Factors such as being under 50 years of age, possessing a high socioeconomic status, having a higher level of education, experiencing genital aphthous disease, suffering from depression, having rheumatoid disease, and having food allergies may be associated with a higher prevalence of RAS.

Keywords "Stomatitis, Aphthous"; "arthritis, Rheumatoid"; social class, Smoking

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Introduction

Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral mucosal diseases, characterized by recurrent painful ulcers. The prevalence of RAS in the general population ranges from 5 to 66%, with an average of 20 [1, 2]. RAS significantly impacts the quality of life of patients due to associated pain and frequent recurrences. This condition increases saliva production and interferes with essential activities such as eating, drinking, and speaking. Because the underlying cause of RAS remains unknown, there is no definitive treatment available; patients typically receive only palliative care [3]. RAS can result from systemic diseases and trauma. However, recent studies have identified a variety of potential etiologies including vitamin deficiencies, disturbances in oral microbiota, hematological factors, stress, genetic polymorphisms, and imbalances between oxidants and antioxidants, among others [4, 5].

If epithelial necrosis extends beyond the basement membrane, nerve endings become exposed, leading to severe pain that adversely affects the patient's diet, communication, and overall quality of life [6]. As individuals age, the recurrence rate of this condition decreases [7]. In comparison to males, females are more frequently affected [8]. Generally, individuals with higher socioeconomic status are at a greater risk of developing the disease [9]. The incidence of RAS is lower in smokers than in non-smokers, which is associated with the duration and intensity of smoking [7]. A study involving 10,520 participants aged 37 to 70 years, based on the Gilan Cohort Study, reported a prevalence of RAS at 8.3% [10].

Although several established factors are associated with RAS, its etiology remains unclear. Nutrient deficiencies-such as those of vitamin B12, vitamin D, iron, zinc, and selenium-disorders of microbial flora, trauma, poor lifestyle habits, medications, allergies, psychological factors, anemia, immune diseases (including Behçet's disease, periodic fever, pharyngitis, and adenitis syndrome, and Crohn's disease), genetic susceptibility, and other factors have all been implicated in the development of RAS [11–14]. However, the pathogenesis is complex and involves multiple contributing factors. Immune dysregulation associated with various triggers may facilitate the development of RAS. Recent large-scale bioinformatics analyses have confirmed the roles of the immune system and inflammatory processes in this condition. In patients with anemia, RAS can be attributed to nutrient deficiencies, particularly those of iron, vitamin B12, or folic acid [12].

To our knowledge, no large sample sized study has been conducted on the relationship between the RAS and various variables in northwest Iran. Given the substantial sample size (15,006 individuals) and the availability of diverse data within the Azar cohort, the aim of this study is to investigate the prevalence of RAS and its associated factors within the Azar cohort population.

Materials and methods

This cross-sectional study utilized data obtained from baseline phase of the Azar cohort study, which is part of the Prospective Epidemiological Research Studies (PERSIAN cohort) for Iranian adults [15, 16]. In 2014, the Azar cohort started in Shabestar city in East Azerbaijan province, Iran. In the Azar cohort study, 15,006 adults, aged 35 to 70 years participated. The data collected through the Persian cohort's questionnaires [15]. The objectives of the Azar cohort, the sampling method, the variables, and the collection tools and methods have been detailed in previous papers [16]. Trained interviewers collected data through face-to-face interviews and physical examinations. The diagnostic criteria for RAS followed the World Health Organization's Guide to the epidemiology and diagnosis of oral mucosal diseases and conditions. RAS was defined as a well-demarcated yellow-white painful ulcer with the peripheral erythematous halo [17]. To determine the lifetime prevalence of RAS, descriptions of the lesions were provided to participants, who were then asked whether they had ever experienced recurrent canker sores inside their mouths. The participants' responses were based on their recall of past occurrences [10].

In this cross-sectional study, the data pertaining to RAS and various associated variables were extracted from the information collected during the initial phase of the Azar cohort study. Participants identified as having RAS were classified into RAS group, while the remaining participants were categorized into non-RAS group.

In addition, demographic characteristics including age, gender, education level, socioeconomic status, and place of residence, were extracted. Lifestyle factors, including smoking status, alcohol consumption, and frequency of tooth brushing, were assessed in this study. Additionally, data were collected on the history of genital aphthous stomatitis, and various chronic diseases, including hypertension, diabetes, depression, rheumatoid disease, chronic headaches, thyroid disorders, anemia, multiple sclerosis, and epilepsy were also recorded. The study further examined the use of specific supplements, including folic acid, iron, vitamin D (in tablet and injection), zinc, and multivitamins. Othe variables, such as body mass index (BMI), food allergies, the Decayed, Missing, and Filled Teeth (DMFT) index and it's components were also extracted.

The educational level is categorized into three groups: under diploma, diploma, and university degree. The socio-economic status variable is divided into five categories: very poor, poor, average, good, and very good. The smoking variable includes three subgroups: smokers,

ex-smokers, and non-smokers. BMI is classified into five categories: <18.5, 18.5–24.9, 25-29.9, and ≥ 30 (kg/m2). In the Azar cohort, the oral examination was conducted in accordance with the World Health Organization (WHO) Oral Health Surveys: Basic Methods by a single examiner-a general practitioner trained by an experienced dentist. The DMFT index was accurately recorded using a headlight, intraoral mirror, and explorer [18].

Table 1 Demographic features of RAS group and non-RAS group

Variables	Categories	RAS[1] group: 3503	non-RAS group = 11,503	*p*-value
		N (%)		
Gender	Male	1378 (39.3)	5334 (46.4)	< 0.001
	Female	2125 (60.7)	6169 (53.6)	
Age (years)	≤ 50	2129 (60.8)	5714 (49.07)	< 0.001
	> 50	1374 (39.2)	5789 (50.3)	
Wealth Scale Index	Very Poor	680 (19.4)	2800 (24.3)	< 0.001
	Poor	541 (15.4)	1990 (17.3)	
	Moderate	715 (20.4)	2341 (20.4)	
	Good	823 (23.5)	2302 (20.0)	
	Very Good	744 (21.2)	2070 (18.0)	
Educational level	Under diploma	1737 (49.6)	6631 (57.6)	< 0.001
	Diploma	1379 (39.4)	3936 (34.2)	
	University	387 (11.0)	936 (8.1)	
Place of residence	Urban	2457 (70.1)	7974 (69.3)	0.37
	Rural	1046 (29.9)	3529 (30.7)	
Tooth brushing frequency (per day)	≥ 1	1264 (36.1)	3251 (28.3)	< 0.001
	< 1	2239 (63.9)	8252 (71.7)	
Smoking	Never	2912 (83.1)	8489 (73.8)	< 0.001
	Ex-smoker	238 (6.8)	1008 (8.8)	
	Smoker	353 (10.1)	2006 (17.4)	
Alcohol consumption	Yes	47 (1.3)	236 (2.1)	0.007
	No	3456 (98.7)	11,267 (97.9)	

1 Recurrent aphthous stomatitis

In the Azar cohort, the participants completed a written informed consent form and were free to withdraw from the study at any time and for any reason. This cross-sectional study received approval from the Ethics Committee of Tabriz University of Medical Sciences in Tabriz, Iran (IR.TBZMED.REC.1401.132).

Statistical analysis

A comparison of the frequency of variables among groups was conducted using the chi-square test. The comparison of mean DMFT and M component was performed using t-test. The Mann-Whitney U test, median and interquartile range were used for D and F components. Initially, binary logestic regression was carried out to assess the relationship between RAS and the various variables. Variables with a *p*-value of less than 0.2 were selected for multiple logestic regression analysis. A *p*-value of less than 0.05 was considered statistically significant. All statistical tests were performed using SPSS version 18.

Results

This study was conducted using data collected during the baseline phase of the Azar cohort to investigate the relationship between RAS and various variables. The entire population of the Azar cohort, consisting of 15,006 adults aged 35 to 70, was divided into two groups: 3,503 individuals in the RAS group and 11,503 individuals in the non-RAS group. The prevalence of RAS in the Azar cohort population was 23.34%. Demographic features and prevalence of studied variables in the RAS group and non-RAS group were reported in Tables 1 and 2. Individuals in the RAS group had a lower mean DMFT, D and M index than those in the non-RAS group. (Table 3).

Findings of logestic regression analysis

Being over 50 years of age, having a lower socioeconomic status, possessing a lower level of education and brushing at least once a day were identified as protective factors for RAS. Smokers, as well as individuals with a history of smoking and alcohol consumers, were also significantly less likely to experience RAS. In contrast, females and people with genital aphthous ulcers were more likely to experience RAS. Furthermore, patients with high blood pressure and diabetes were significantly less likely to suffer from RAS. RAS showed a significant association with depression, rheumatoid disease, chronic headaches, chronic lung disease, thyroid disorders, and food allergies. Moreover, individuals with a lower DMFT index were more likely to experience RAS. There was no significant association between RAS and anemia, multiple sclerosis, or epilepsy when compared to the non-RAS group. Conversely, individuals who consumed folic acid, iron

Table 2 Prevalence of studied variables in RAS group and non-RAS group

Variables		RAS[1] group: 3503	non-RAS group:11,503	*p*-value
		N%		
Genital Aphthous		114 (3.3)	13 (0.1)	< 0.001
Hypertension		623 (17.8)	2416 (21.0)	< 0.001
Diabetes		346 (9.9)	1400 (12.2)	< 0.001
Depression		743 (21.2)	1819 (15.8)	< 0.001
Rheumatic Disease		151 (4.3)	363 (3.2)	0.1
Chronic Headaches		481 (13.7)	1412 (12.3)	0.02
Chronic Lung Disease		144 (4.1)	394 (3.4)	0.06
Thyroid Disease		343 (9.8)	967 (8.4)	0.01
Anemia		202(5.8)	604(5.3)	0.23
Multiple sclerosis		7(0.2)	14(0.1)	0.30
Epilepsy		31(0.9)	98(0.9)	0.84
Folic acid supplement		69(2.0)	157(1.4)	0.01
Iron supplement		166(4.7)	382(3.3)	< 0.001
Vitamin D (tab) supplement		55(1.6)	141(1.2)	0.12
Vitamin D (inj) supplement		38(1.1)	77(0.7)	0.20
Zinc supplement		121(3.5)	306(2.7)	0.01
Multi-vitamine supplement		30(0.9)	82(0.7)	0.37
Food Allergy		480 (13.7)	1180 (10.3)	< 0.001
Body mass index **(kg/m^2)**	< 18.5	20 (0.6)	73 (0.6)	0.13
	18.5–24.9	717 (20.5)	2400 (20.9)	
	25-29.9	1492 (42.7)	4656 (40.5)	
	30≥	1268 (36.3)	4370 (38.0)	

[1] Recurrent aphthous stomatitis

Table 3 Comparison of the mean DMFT and its components in the studied groups

variabe	RAS[1] group	non-RAS group	
	Mean ± SD[2]		*p*-value
DMFT[3]	19.73 ± 8.79	21.74 ± 8.94	< 0.001[8]
D[4]	1.98 ± 3.11 (Median = 0.00;IQR[7] = 3)	2.28 ± 3.79 (Median = 0.00;IQR = 3)	0.94[9]
M[5]	14.75 ± 10.94	17.40 ± 11.30	< 0.001[8]
F[6]	3.00 ± 4.06 (Median = 1;IQR = 6)	2.06 ± 3.54 (Median = 0.00;IQR = 3)	< 0.001[9]

[1]Recurrent aphthous stomatitis; [2]standard deviation; [3]Decayed, missing and filled teeth; [4]Decayed teeth; [5]Missing teeth; [6]Filled teeth; [7]Inter quartile range;[8]T-test; [9]Mann-Whitneynull U test

supplements, vitamin D tablets, vitamin D injections, and zinc supplements experienced significantly more RAS.

Variables that had a *p*-value less than 0.2 in logestic regression analysis were included in multiple logestic regression analyses. People over 50 years old (OR = 0.78, $p < 0.001$), people with poor socioeconomic level (OR = 0.85, $p = 0.02$) and very poor (OR = 0.74, $p < 0.001$), and people with undergraduate education (OR = 0.83, $p = 0.01$) were significantly less likely to suffer from RAS. People who smoke (OR = 0.55, $p < 0.001$) or have a history of smoking but have quit now (OR = 0.79, $p = 0.01$) are also significantly less affected by RAS. A history of genital aphthous is significantly associated with more RAS (OR = 28.93, $p < 0.001$). In this study, depression (OR = 1.36, $p < 0.001$), rheumatoid disease (OR = 1.30, $p = 0.01$), and food allergy (OR = 1.24, $p < 0.001$) were reported to have a significant relationship with more incidence of RAS. With the increase of DMFT, the occurrence of RAS decreased significantly (OR = 0.99, $p < 0.001$). The results are shown in Table 4.

Discussion

In the present study, the prevalence of RAS was found to be 23.34%. Comparatively, a previous study reported a lifetime prevalence of RAS at 8.3% [10]. In research conducted by Davatchi et al. [19], the prevalence of RAS in a general population in Iran was observed to be 25.2%. Additionally, a study by Sina et al. [20], conducted in Tabriz over a two-year period, reported the prevalence of minor RAS to be 0.3%. These discrepancies may be attributed to variations in the populations studied, variations in study design, sample size, data collection methods, diagnostic criteria used, and different environmental factors.

In this study, the frequency of RAS was higher among females that is in line with a study conducted in Turkey reported that females were 1.53 times more likely to develope RAS [21]. In contrast, other studies have found no significant differences in prevalence or RAS according to gender [22]. Based on the variant findings, it seems that gender cannot be considered a risk factor for the occurrence of RAS.

In the study of Mazzoleni et al. [13] in 2020, a significant relationship was reported between older age and a lower prevalence of RAS. In Darjani et al. [10] study, it was also reported that people over 50 years of age had less history of RAS. Both of these findings align with the results of the present study. The possible explanations may partially lie in age-related changes in both the innate and adaptive components of the immune system. In elderly individuals, neutrophils exhibit reduced chemotactic and phagocytic capacities. Additionally, changes in immune cell populations are accompanied by altered cytokine production and responsiveness, diminished proliferative responses, defects in signal transduction, and reduced antigen recognition. The relatively low prevalence of autoimmune diseases among elderly patients may be attributed to an age-related increase in peripheral regulatory T cells, a process potentially linked to RAS.

In this study, individuals with poor economic status exhibited significantly fewer cases of RAS. A possible explanation is the relationship between early immune system development and nutrition and living conditions during the first year of life. Children from families with higher socioeconomic status are exposed to fewer pollutants and germs, which promotes the development of

Table 4 The relationship between the studied variables and the RAS in univariate and multiple regression

Variables	Categories	Unadjusted			Adjusted		
		OR[1]	95% CI[2]	*p*-value	OR	95% CI	*p*-value
Gender	Female	1.33	1.23–1.44	< 0.001	1.05	0.94–1.16	0.39
	Male	Ref					
Age (years)	≥ 50	0.63	0.59–0.69	< 0.001	0.78	0.71–0.86	< 0.001
	< 50	Ref					
Wealth Scale Index	Very Poor	0.68	0.60–0.76	< 0.001	0.74	0.65–0.84	< 0.001
	Poor	0.76	0.76–0.86	< 0.001	0.85	0.74–0.97	0.02
	Moderate	0.85	0.75–0.96	0.007	0.89	0.79–1.01	0.08
	Good	0.99	0.89–1.12	0.93	0.95	0.84–1.07	0.42
	Very Good	Ref					
Educational level	Under diploma	0.63	0.56–0.72	< 0.001	0.83	0.71–0.96	0.01
	Diploma	0.85	0.74–0.97	0.02	0.95	0.83–1.10	0.50
	University	Ref					
Place of residence	Rural	0.96	0.89–1.05	0.36	-	-	-
	Urban	Ref					
Tooth brushing frequency (per day)	≥ 1	0.70	0.64–0.76	< 0.001	1.02	0.93–1.13	0.66
	< 1	Ref					
Smoking	Never	Ref					
	Ex-smoker	0.69	0.59–0.80	< 0.001	0.79	0.67–0.93	0.01
	Smoker	0.51	0.45–0.58	< 0.001	0.55	0.47–0.63	< 0.001
Alcohol Consumption	Yes	0.65	0.47–0.89	0.007	0.89	0.64–1.25	0.50
	No	Ref					
Genital Aphthous	Yes	29.73	16.73–52.84	< 0.001	28.93	16.18–51.72	< 0.001
	No	Ref					
Hypertension	Yes	0.81	0.74–0.90	< 0.001	0.91	0.82–1.02	0.10
	No	Ref					
Diabetes	Yes	0.79	0.70–0.90	< 0.001	0.90	0.79–1.03	0.11
	No	Ref					
Depression	Yes	1.43	1.30–1.58	< 0.001	1.36	1.22–1.51	< 0.001
	No	Ref					
Rheumatic Disease	Yes	1.38	1.14–1.68	0.001	1.30	1.06–1.59	0.01
	No	Ref					
Chronic Headaches	Yes	1.14	1.02–1.27	0.02	0.94	0.84–1.06	0.34
	No	Ref					
Chronic Lung Disease	Yes	1.21	1.00-1.47	0.06	1.21	0.99–1.48	0.67
	No	Ref					
Thyroid Disease	Yes	1.18	1.04–1.35	0.01	1.00	0.87–1.15	0.98
	No	Ref					
Anemia	Yes	1.11	0.94–1.30	0.23	-	-	-
	No	Ref					
Multiple sclerosis	Yes	1.64	0.66–4.07	0.28	-	-	-
	No	Ref					
Epilepsy	Yes	1.04	0.69–1.56	0.85	-	-	-
	No	Ref					
Folic acid supplement	Yes	1.45	1.09–1.93	0.01	1.02	0.75–1.39	0.89
	No	Ref					
Iron supplement	Yes	1.45	1.20–1.75	< 0.001	1.14	0.94–1.39	0.19
	No	Ref					
Vitamin D (Tablet) supplement	Yes	1.29	0.94–1.76	0.12	1.06	0.77–1.48	0.71
	No	Ref					
Vitamin D (injection) supplement	Yes	1.63	1.10–2.41	0.02	0.32	0.88–1.98	0.18
	No	Ref					

Table 4 (continued)

Variables	Categories	Unadjusted			Adjusted		
		OR[1]	95% CI[2]	*p*-value	OR	95% CI	*p*-value
Zinc supplement	Yes	1.31	1.06–1.62	0.01	1.18	0.94–1.48	0.15
	No	Ref					
Multi-vitamine supplement	Yes	1.20	0.79–1.83	0.39	-	-	-
	No	Ref					
Food Allergy	Yes	1.39	1.24–1.55	< 0.001	1.24	1.10–1.40	< 0.001
	No	Ref					
Body mass index **(kg/m^2)**	< 18.5	0.92	0.56–1.51	0.74	1.16	0.70–1.94	0.57
	25-29.9	1.07	0.97–1.19	0.18	1.00	0.90–1.11	0.95
	30≥	0.97	0.88–1.08	0.58	0.88	0.79–0.99	0.03
	18.5–24.9	Ref					
DMFT[3]	-	0.98	0.97–0.98	< 0.001	0.99	0.98–0.99	< 0.001

[1]Odds ratio; [2]Confidence interval; 3Decayed, missing and filled teeth

more T helper 2 (Th2) cells rather than Th1 cells. This shift in immune balance may increase susceptibility to immune-related conditions, including RAS and allergies. Supporting this, Souza et al. [23] reported a higher prevalence of RAS among individuals with higher socioeconomic status. This report is consistent with the findings of the present study. In the study of Mazzoleni et al. [13], it was reported that people with lower income are more likely to suffer from RAS. This report is inconsistent with the findings of the present study.

In the present study, smokers or quitters were significantly less likely to have RAS. Although the mechanism of the effect of smoking on RAS is not completely clear, the effect of smoking on the diversity of the microbial population of saliva is probably the cause of the relationship between smoking and RAS. Also, nicotine metabolites probably decrease the level of pro-inflammatory cytokines and increase anti-inflammatory cytokines. Another possible cause is the protective layer of keratin on the oral mucosa, which is caused by the high concentration of nicotine. In the study of Mazzoleni et al. [13], a significant relationship between smoking and a lower prevalence of RAS was reported. This report was consistent with the findings of the present study. In a 2019 study by Ślebioda et al. [11], no association was found between smoking and the prevalence of RAS. In another study by Souza et al. [23], as well as in Darjani et al. [10] study, the protective effect of smoking on the pest was reported. These reports were consistent with the findings of the present study. Sawair reported that the intensity and long duration of smoking had a protective effect on RAS, but if there were lesions, smoking had no relationship with the severity of RAS [24]. In a study conducted by Manoj et al. [25], a significant relationship was seen between smoking and the prevalence of RAS. This report is inconsistent with the findings of the present study.

According Hariyani et al. [26], depression was associated with a higher prevalence of RAS. It was also reported in Darjani etal.'s study that depression is one of the predisposing factors for RAS [10]. These reports are in line with the results of the present study. Parafunctional habits have been suggested as potential triggers for RAS in individuals with depression and stress, however, there is not enough evidence in this regard [27]. The alterations in the immune system among patients with mental health conditions, such as depression, may contribute to the development of RAS [28]. Given the unclear relationship between depression and RAS, further research is needed.

The results of this research showed that a history of food allergy has a significant relationship with RAS. Ślebioda et al. [11] reported that allergy was common in patients with RAS. This confirms the immunologic nature of RAS; as salivary IgE and eosinophil cationic protein have been reported to be higher in patients with RAS [29].

The results of the present study showed that a history of rheumatoid disease has a significant relationship with more RAS. Behcet's disease is one of the most common rheumatic diseases associated with RAS [30]. The findings of this study demonstrated a significant relationship between a history of genital aphthous ulcers and a higher frequency of RAS. Similarly, Darjani et al. [10] reported that genital aphthous ulcers are one of the predisposing factors for RAS.

In the present study, with the increase of DMFT, the occurrence of RAS decreased significantly. In the study of Bajoria et al. [31], most of the people with RAS (72.8%) had a greater DMFT index, which is in contrast with the results of the present study. In the study of Tecco et al. [32], a significant relationship was observed between the presence of decayed teeth and minor RAS. In total, the risk of minor RAS in children with decayed teeth was 3.15 times higher than in other children. And the risk of minor RAS was 3.30 times higher for children with DMFT index greater than zero.

In the present study, the relationship between anemia and RAS was not significant. But in the study of Ślebioda et al. [11], anemia was reported as one of the predisposing factors for RAS. Sumathi et al. [33] reported that serum ferritin levels were significantly lower in individuals with RAS. Some studies have reported that the levels of folate, ferritin and vitamin B12 are significantly lower in people with RAS [12, 33]. Deficiencies in iron, vitamin B12, and folic acid can lead to atrophy of the oral epithelium. This atrophy may help clarify the increased susceptibility to RAS in individuals with these deficiencies [34].

In the study of Ślebioda et al. [11], hypertension was reported as one of the predisposing factors for RAS. But in the present study, the relationship between hypertension and RAS was not significant. The relationship between hypertension and RAS can be explained by the effects of antihypertensive medications. In the study conducted by Ślebioda et al., the most severe progression of RAS was observed in patients using β-blockers [11]. This discrepancy in findings may be attributed to the varying types of antihypertensive medications used by the participants.

In the studies conducted by Manoj et al. [25] and Darjani et al. [10]., a significant relationship was found between diabetes and the risk of RAS. However, in the present study, no significant relationship was found between diabetes and RAS. It is proposed that RAS might be a manifestation of metabolic abnormalities [10]. However more studies are needed to confirm this.

In this study, no significant relationship was observed between RAS and chronic headaches. However, Darjani et al. [10] showed that individuals with chronic headache were more likely to have experienced RAS. Mediating role of stress has been proposed for this relationship, however there is not enough evidence [10].

The role of obesity in the development of RAS has not been adequately explored. The present study showed no significant relationship between BMI and RAS. Oluwadaisi et al. [14] demonstrated an increased BMI in individuals with RAS. This association has been attributed to cytokine dysregulation associated with obesity. Further studies are needed to elucidate the relationship between obesity and RAS.

Strengths and limitations

One of the strengths of this study is that it represents an investigation into the prevalence of RAS and its associated factors in the population of northwestern Iran, utilizing a large sample size. Given the substantial sample size and the cultural and genetic homogeneity of the local population, the findings can be generalized to the residents of this region. However, a notable limitation of the study is the lack of categorization of RAS into its subtypes: minor, major, and herpetiform. Moreover, the present study was conducted on a particular cohort and it's in one group of population, which is a shortcoming of the study. Therefore, the results may not be directly relevant to other populations around the world. Another limitation is that the causality can not be assessed in the cross-sectional study.

Conclusion

In the present study, RAS was significantly less frequent among individuals over 50 years old, those with poor and very poor socio-economic level, individuals with lower educational attainment and smokers. Conversely, a significant association was observed between RAS and a history of genital aphthous ulcers, depression, rheumatoid disease, and food allergies. It is recommended to conduct a prospective study to further investigate the relationship between RAS and its associated factors, with a focus on distinguishing between the minor, major, and herpetiform subtypes.

Abbreviations

DMFT	Decayed, Missing, and Filled Teeth in the permanent dentition
PERSIAN	Prospective Epidemiological Research Studies in Iran
BMI	Body Mass Index
OR	Odds Ratio

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Author contributions

NSh, and EF contributed to the conceptualization of the study, performing the statistical analyses and interpreting data; EF contributed to the data collection. KK, NSh, SY, ZM, and EF contributed in writing and revising the manuscript. All authors read and approved the final version of the manuscript; and agreed to be responsible for all aspects of the study including the accuracy of the work done.

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Data availability

The datasets used and/or analyzed during the current study are available in the repository of the Azar cohort center and will be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study has been performed following the Declaration of Helsinki and has been approved by the Ethics Committee of Tabriz University of Medical Sciences (IR.TBZMED.REC.1401.132). We confirm that all methods were performed by the relevant guidelines and regulations. At the time of enrollment, written informed consent to participate in the study was obtained from participants (or their legal guardians in the case of illiterate participants). The steps of the study were explained to the participants, and people who

filled out the informed consent were included. They were free to leave the study at any time, and for any reason.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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