ORIGINAL ARTICLE

Lifetime prevalence of recurrent aphthous stomatitis and its related factors in Northern Iranian population: The PERSIAN Guilan Cohort Study

Abbas Darjani[1] · Farahnaz Joukar[2] · Mohammareza Naghipour[3] · Mehrnaz Asgharnezhad[3] ·
Fariborz Mansour-Ghanaei[2,3]

Abstract

Objectives Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral inflammatory ulcerative lesions. The aim of this large population base study was estimated lifetime prevalence of RAS and its related factors among the Northern Iranian population.

Materials and methods This study was conducted on 10,520 participants aged 35–70 years based on the PERSIAN Guilan Cohort Study (PGCS). Prevalence proportions and multivariate logistic regression models were constructed for lifetime RAS prevalence using the SPSS software. Data on potential correlates of RAS including demographic profiles, lifestyle habits, and self-reported past medical histories were obtained.

Results The lifetime prevalence of RAS was 8.3%. Multivariate logistic models showed that urbanization (adjusted odds ratio (AOR) = 1.2) and having a history of systemic disease, including rheumatic disease (AOR = 2.1), genital aphthous disease (AOR = 11.7), depression (AOR = 1.3), chronic headaches (AOR = 1.8), diabetes mellitus (AOR = 1.6), and epilepsy (AOR = 2), were independent predictors of RAS. In addition, smokers (AOR = 0.5) and individuals older than 50 years of age (AOR = 0.8) were less likely to have a history of RAS. The lifetime prevalence of RAS among the Northern Iranian population was relatively low.

Conclusions It seems that predisposing factors, such as younger age, urbanization, and systemic disease, including rheumatic disease, genital aphthous disease, depression, chronic headaches, diabetes mellitus, epilepsy, and not smoking, could contribute to RAS prevalence.

Keywords Prevalence · Stomatitis · Aphthous · Related factor

Clinical relevance Patients with underlying diseases, including rheumatic disease, depression, chronic headaches, diabetes mellitus, and epilepsy should pay special attention to oral health to prevent RAS. The practitioner should pay attention to the management of the underlying disease of RAS patients.

This manuscript has not been published in whole or in part and is not under consideration elsewhere.

✉ Fariborz Mansour-Ghanaei
fmansourghanaei@gmail.com; ghanaie@yahoo.com

Abbas Darjani
darjani@gums.ac.ir

Farahnaz Joukar
farajov@gmail.com

Mohammareza Naghipour
naghi@gums.ac.ir

Mehrnaz Asgharnezhad
asgharnezhad98@yahoo.com

[1] Department of Dermatology, School of Medicine Guilan University of Medical Sciences, Rasht, Iran

[2] GI Cancer Screening and Prevention Research center and Caspian Digestive Diseases Research Center, Guilan University of Medical Sciences, Rasht, Iran

[3] Gastrointestinal and Liver Diseases Research Center, Guilan University of Medical Sciences , Razi Hospital, Sardar-Jangle Ave., Rasht 41448-95655, Iran

Introduction

Recurrent aphthous stomatitis (RAS) is one of the most prevalent oral inflammatory ulcerative lesions [1] characterized by well-circumscribed, yellow-white appearance painful ulcerations covered by a fibrin clot with an epithelial defect on the non-keratinized or movable oral mucosae [2]. RAS can cause severe pain that can affect the function of eating, swallowing, and speaking and prompt patients to seek evaluation and treatment from health care providers [3]. Approximately 2–66% of the worldwide general population is affected by RAS [1]. This wide range of prevalence is due to the variety of research populations, locations and settings, and diagnostic criteria used [4]. The prevalence of RAS in the central Iranian population was estimated to be 20–26% that was rather high [5].

While the pathogenesis of RAS is uncertain, despite its high clinical prevalence, there are numerous potential predisposing factors with an extensive differential of possible underlying diseases [4]. Genetic factors, local trauma, hematinic deficiencies (such as vitamin B_{12}, folic acid, iron), nutritional deficiencies [6], psychological stress [7], bacterial and viral infections (such as *Streptococcus mitis*, *Helicobacter pylori*, and Epstein-Barr virus), and immune or endocrine disturbances have all been implicated as etiological factors of RAS [8]. The side effects of drugs, such as angiotensin-converting enzyme inhibitors and nonsteroidal anti-inflammatory drugs, have been implicated as triggers for RAS [9]. RAS lesions can be the mucosal manifestations of a variety of disorders such as Behçet disease [10], systemic lupus erythematosus [11], and periodic fever, aphthous stomatitis, pharyngitis, and adenitis (PFAPA) syndrome [12], which should be considered in patient evaluation and management. However, oftentimes, no distinct underlying disorder will be found [13]. Some studies have demonstrated a higher prevalence of RAS among non-smokers, women, white races, younger persons, and high-socioeconomic-status individuals [8, 14].

Although the potential bio-psycho-social factors associated with RAS have also been suggested in previous studies, precise role and effect value of these related factors in the prediction of RAS remain equivocal. Therefore, the aim of this large population base study was estimating the lifetime prevalence of RAS and its related factors among the Northern Iranian population. This study was based on data from the PERSIAN Guilan Cohort Study (PGCS), a prospective, population-based cohort study in Guilan, Iran.

Materials and methods

Study design and participants

The PERSIAN Guilan Cohort Study (PGCS) data sets were used in this community based cross-sectional study [15]. This study was conducted from October 8, 2014, to January 20, 2017, as part of the Prospective Epidemiological Research Studies in Iran (PERSIAN) [16]. PGCS was a multistage probability sample of the Northern Iranian population, in which 10,520 individuals from 35 to 70 years of age were interviewed. A detailed discussion of the study methods has been described elsewhere [17]. The participation rate was 83.2% [15]. The research protocol was approved by the institutional ethical committee and all participants were informed in detail about the study and consent was obtained prior to the enrollment in the studies [15].

Data collection

Data were collected by trained interviewers during a face-to-face interview and a physical examination [15]. Diagnostic criteria for RAS were in accordance with the criteria by the World Health Organization's Guide to the epidemiology and diagnosis of oral mucosal diseases and conditions [18]. A well-demarcated yellow-white painful ulcer with the peripheral erythematous halo was defined as RAS [18]. To determine the lifetime prevalence of RAS, lesion descriptions were provided to participants and they were asked if they ever had recurrent aphthous (canker sores) inside their mouths and responses were based on recall. In addition to the RAS history, demographic profile (including age, gender, educational level, and habitat), lifestyle habits (including smoking status, non-smoker versus current smoker), alcohol consumption (none or currently use), and body mass index (BMI) and self-reported past medical histories were obtained. Also, information about self-report oral hygiene behavior, including flossing, tooth brushing, and use of mouthwash or denture, were collected.

Statistical analysis

Statistical package for the social science (SPSS) version 17.0 (SPSS Inc., Chicago, IL, USA) was used for all data analysis. RAS lifetime prevalence according to characteristics of the study population was compared with chi-square test and Fisher's exact test. Univariate and multivariate logistic regression models were performed to determine independent correlated factors (independent variables) of the RAS lifetime prevalence (dependent variables) and unadjusted and adjusted odds ratios and 95% CI were calculated. All variables with a p value less than or equal to 0.2 in univariate analysis were fitted to a multivariate logistic regression model.

Result

This study was performed on 10,520 individuals 35–70 years of age, representing the Northern Iranian population.

Table 1 shows the lifetime RAS prevalence for levels of characteristics of the study population that may be associated

with RAS. Overall, the lifetime prevalence of RAS was 8.3%, with no significant differences among levels of education. On initial analysis, RAS lifetime prevalence was significantly more common among females (9.8%), urban population (9.6%), younger than 50 years of age (9%), and unemployed (9.1%) (all p value < 0.05) (Table 1).

Geographical location using Garmin GPSMAP 78s of participants that were with and without recurrent aphthous stomatitis (RAS) is shown in Fig. 1.

The lifetime prevalence of RAS increased significantly in subjects with a history of rheumatic disease (including 6 cases of Behcet's disease) (17.5%), chronic lung disease (11.7%), thyroid disease (10.3%), genital aphthous disease (52.3%), depression (11.8%), chronic headaches (15%), diabetes mellitus (8.7%), and epilepsy (16.9%), than those with no history (7.7–8.2%) (all p value < 0.05). Past medical history of hypertension was not significantly associated with RAS lifetime prevalence (Table 1). The lifetime prevalence of RAS was significantly less common among subjects with a history of smoking (5%) and alcohol consumption (5.3%) (all p value < 0.001) (Table 1). Table 2 demonstrates the results of univariate and multivariate logistic regression to explore the independent correlates of lifetime prevalence of RAS. The multivariate analyses revealed that subjects older than 50 years of age had lower odds of RAS than those in the younger group (adjusted OR = 0.8, p value = 0.02). Urban dwellers (adjusted OR = 1.2, p value = 0.001) had greater odds of having a positive lifetime history of RAS than rural dwellers (Table 2).

Individuals who reported having a rheumatic disease (adjusted OR = 2.1), genital aphthous disease (adjusted OR = 11.7), depression (adjusted OR = 1.3), chronic headaches (adjusted OR = 1.8), diabetes mellitus (adjusted OR = 1.6), and epilepsy (adjusted OR = 2) in the past medical history had higher odds of RAS than those without a positive history (all p value < 0.05) (Table 2). Compared with non-smokers, individuals who had a history of smoking (adjusted OR = 0.5, p value = 0.001) had half times lower odds of RAS (Table 2). No independent association was found between RAS and gender, occupation, educational level, alcohol consumption, BMI, history of hypertension, chronic lung disease, and thyroid disease (Table 2).

Table 3 shows the frequency of oral hygiene behaviors, including flossing (16.4%), tooth brushing (94%), and use of mouthwash (4%), was significantly more common among individuals who had a history of RAS than those without a positive history (all p value < 0.05). Having dentures was not significantly different between the two groups (Table 3).

Discussion

The current study investigated the lifetime prevalence of RAS and its related factors among the Northern Iranian population. In this study, we demonstrate that RAS was not very prevalent (8.3%) in this population and indicates that the prevalence of RAS was lower in the Northern population compared with that in the central (25.2%) Iran [19]. Although this difference may be due to the differences in participants' characteristics, including genetic factors, medical condition, socioeconomic status, and lifestyle in this particular region, differences in the studies' method, including selection of the study population and the definition of the disease, can be another reason for this difference. Compared with other studies across the world, there has been significant variation in the RAS prevalence in various regions around the world [20]. The estimated prevalence rates of RAS vary from 2 to 50% in the general population [21]. In the current study, we found that the 51–70-year-old participants were less likely to have a history of RAS (adjusted odds ratio = 0.8). Studies have shown the peak age of RAS onset is usually the second and third decades and the prevalence reduced as the age increased [13]. However, logically, the lifetime prevalence should be increased with age. Since RAS is more common in young people [22], the probable cause of our finding is a recall bias over time with the elderly.

Our results revealed that participants from urban areas were more likely to have a history of RAS (adjusted OR = 1.2) than rural dwellers. Since the studies suggest that stress is associated with RAS [21] and urban dwellers are more exposed to stress [23], it may confound the relationship. The current study demonstrated that nonsmoker individuals had significantly higher odds of RAS than subjects who had a history of smoking. This is in line with several previous studies that have revealed a protective effect of smoking on aphthous stomatitis [14].

The underlying mechanism was probably the protective layer of keratin over the oral mucosa, which was formed by the high concentration of nicotine. A cross-sectional study reported that the protective effect of nicotine on RAS was dose-dependent and there was no change in already existing aphthous with smoking [24].

In the current study, we analyzed the association of systemic diseases with RAS and a significantly higher frequency of the RAS was revealed in subjects with a history of rheumatic disease, in line with previous studies [8]. Behcet's disease is one of the most common rheumatic diseases associated with RAS [4, 25]. In 80% of Behcet's cases, aphthous stomatitis is the presenting sign [25].

Diabetes mellitus was another common systemic disorder that had been associated with an increased risk of RAS in our study population. A potential role of diabetes mellitus in the development of RAS was suggested in some studies [26]. The recent hypothesis was that RAS might be a manifestation of metabolic abnormalities, especially insulin resistance and hyperglycemia [27].

Table 1 Recurrent aphthous stomatitis (RAS) lifetime prevalence according to characteristics of the study population

Variables	Recurrent aphthous stomatitis (RAS) lifetime prevalence		p value*
	Number	%	
Total participants (n = 10,520)	820	8.3	
Demographic factors			
Gender			
Male (n = 4887, 46.5%)	318	6.5	< 0.001
Female (n = 5633, 53.5%)	552	9.8	
Age			
≤ 50 (n = 5233, 49.7%)	473	9	
> 50 (n = 5287, 50.3%)	397	7.5	0.005
Occupation			
Employed (n = 5739, 54.6%)	433	7.5	0.002
Unemployed (n = 4781, 45.4%)	437	9.1	
Educational level			
High school or less (n = 8028, 76.3%)	673	8.4	
Diploma or more (n = 2492, 23.7%)	197	7.9	0.4
Habitat			
Urban (n = 4613, 43.8%)	444	9.6	
Rural (n = 5907, 56.2%)	426	7.2	< 0.001
Past medical history (self-report)			
History of diabetes mellitus			
Yes (n = 1705, 16.2%)	148	8.7	
No (n = 8815, 83.8%)	555	6.3	0.001
History of hypertension			
Yes (n = 2425, 23.1%)	185	7.6	
No (n = 8095, 76.9%)	685	8.5	0.2
History of rheumatic disease			
Yes (n = 309, 2.9%)	54	17.5	
No (n = 10,211, 97.1%)	816	8	< 0.001
History of chronic lung disease			
Yes (n = 386, 3.7%)	45	11.7	
No (n = 10,134, 96.3%)	825	8.1	0.01
History of thyroid disease			
Yes (n = 1020, 9.7%)	105	10.3	
No (n = 9500, 90.3%)	765	8.1	0.01
History of genital aphthous disease			
Yes (n = 130, 1.2%)	68	52.3	
No (n = 10,390, 98.8%)	802	7.7	< 0.001
History of depression			
Yes (n = 549, 5.2%)	65	11.8	
No (n = 9971, 94.8%)	805	8.1	0.002
History of chronic headaches			
Yes (n = 1111, 10.6%)	167	15	
No (n = 9409, 89.4%)	703	7.5	< 0.001
History of epilepsy			
Yes (n = 77, 0.7%)	13	16.9	
No (n = 10,443, 99.3%)	857	8.2	0.01
Life style			
History of smoking			
Yes (n = 2591, 24.6%)	130	5	
No (n = 7929, 75.4%)	740	9.3	< 0.001
History of alcohol consumption			
Yes (n = 1515, 14.4%)	80	5.3	
No (n = 9003, 85.6%)	790	8.8	< 0.001
BMI (kg/m^2)			
< 25 (n = 2883, 27.4%)	233	8.1	
≥ 25 (n = 7637, 72.6%)	637	8.3	0.6

Data are expressed as number (percentages)

*Statistical significance based on the chi-square or Fisher's exact test

BMI, body mass index; *RAS*, recurrent aphthous stomatitis

Fig. 1 Geographical location of men and women with and without recurrent aphthous stomatitis (RAS)
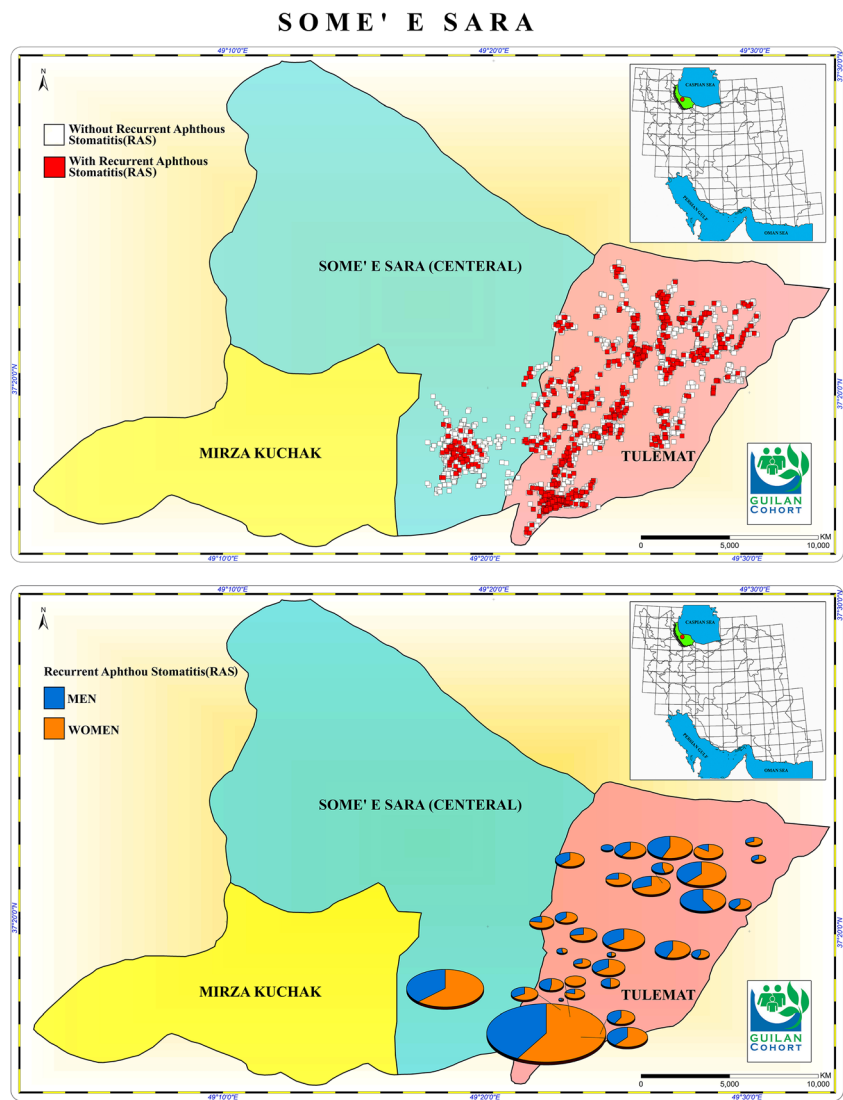
Our results demonstrated that genital aphthous strongly associated with RAS (adjusted odds ratio = 11.7). This finding is probably due to the similarity of the physio-pathological mechanism [28].

Another systemic disorder that was associated with an increased risk of RAS in our study was depression and this association was in agreement with other studies [29, 30]. A recent population-based study reported that a higher prevalence of depression symptoms was associated with a higher prevalence of RAS. This relationship was persistent even after adjusting for age, gender, and level of stress [31].

Another finding of the current study was an independent association between epilepsy and RAS. Hitherto, there have been no reports on the direct correlation between epilepsy and RAS, although some studies on RAS induced by anti-epileptic drugs including valproate have been reported [32].

Our findings revealed that individuals with a history of chronic headache were more likely to have a history of RAS. Although there have been no reports on the direct association between headache and RAS yet, studies suggested that stress and headache are closely related [33]. Stress can be a contributing factor to the headache onset and progression to chronic conditions and exacerbate headache episodes [33, 34]. On the other hand, stress has been proposed as a triggering factor of RAS [29, 35]. Therefore, it seems that the mediating role of stress is a possible cause of this finding.

In our study, the prevalence of oral hygiene behaviors, including flossing, tooth brushing, and use of mouthwash, especially were higher in participants with a history of RAS than in those without RAS history. These findings may be due to preventive behavior in individuals who experience aphthous [36, 37].

Table 2 Univariate and multivariate logistic regression analysis of variables associated with lifetime recurrent aphthous stomatitis (RAS) prevalence

Variables	Recurrent aphthous stomatitis (RAS) lifetime prevalence					
	Unadjusted			Adjusted*		
	OR	(95% CI)	*p* value	OR	(95% CI)	*p* value
Demographic factors						
Gender						
Male (ref)						
Female	1.5	1.3–1.8	< 0.001	1.05	0.8–1.3	0.6
Age						
≤ 50 (ref)						
> 50	0.8	0.7–0.9	0.004	0.8	0.7–0.9	0.02
Occupation						
Employed (ref)						
Unemployed	1.2	1.07–1.4	0.003	0.9	0.7–1.1	0.6
Educational level						
High school or less (ref)						
Diploma or more	0.9	0.7–1.1	0.4	-	-	-
Habitat						
Rural (ref)						
Urban	1.3	1.2–1.5	< 0.001	1.2	1.1–1.4	0.001
Past medical history						
History of diabetes mellitus						
No (ref)						
Yes	1.4	1.3–2	0.001	1.6	1.3–2	< 0.001
History of hypertension						
No (ref)						
Yes	0.8	0.7–1.1	0.1	-	-	-
History of rheumatic disease						
No (ref)						
Yes	2.4	1.8–3.2	< 0.001	2.1	1.5–3.01	< 0.001
History of chronic lung disease						
No (ref)						
Yes	1.4	1.1–2	0.01	1.3	0.9–1.8	0.08
History of thyroid disease						
No (ref)						
Yes	1.3	1.1–1.6	0.01	1.1	0.9–1.4	0.2
History of genital aphthous disease						
No (ref)						
Yes	13.1	9.2–18.6	< 0.001	11.7	8.1–16.9	< 0.001
History of depression						
No (ref)						
Yes	1.5	1.1–2	0.002	1.3	1.01–1.7	0.04
History of chronic headaches						
No (ref)						
Yes	2.1	1.8–2.6	< 0.001	1.8	1.5–2.2	< 0.001
History of epilepsy						
No (ref)						
Yes	2.2	1.2–4.1	0.007	2	1.1–3.8	0.02
Life style						
History of smoking						
No (ref)						
Yes	0.5	0.4–0.6	< 0.001	0.5	0.4–0.7	< 0.001
History of alcohol consumption						
No (ref)						
Yes	0.5	0.4–0.7	< 0.001	0.8	0.6–1.01	0.1
BMI (kg/m^2)						
< 25 (n = 2883, 27.4%)						
≥ 25 (n = 7637, 72.6%)	1	0.8–1.2	0.6	-	-	-

*Adjusted odds ratio: Adjusted for all variables that were significant in univariate analyses

CI, confidence interval; *BMI*, body mass index; *RAS*, recurrent aphthous stomatitis

While the current study conducted on a large population base data, they are not without limitations. It is cross-sectional and may be used to explore associations, not causation. While large sample sizes create multivariate analysis possible, low

Table 3 Oral hygiene behaviors in recurrent aphthous stomatitis (RAS) cases compare with no RAS

	RAS number (%)	No RAS number (%)	p value*
Flossing (n = 1481, 14.1%)	143 (16.4%)	1338 (13.9%)	0.04
Tooth brushing (n = 9707, 92.3%)	818 (94%)	8889 (92.1%)	0.04
Use mouthwash (n = 286, 2.7%)	35 (4%)	251 (2.6%)	0.01
Has dentures (n = 2436, 23.2%)	185 (21.3%)	2251 (23.3%)	0.1

Data are expressed as number (percentages)

*Statistical significance based on the chi-square or Fisher's exact test

RAS, recurrent aphthous stomatitis

prevalence of RAS leads to small cell size and statistical power decreases with an increasing number of variables. Also, the lifetime RAS prevalence should be interpreted with caution based a subject's recall.

The lifetime prevalence of RAS among the Northern Iranian population was 8.1%, which is relatively low as compared with that of other Iranian populations. The predictive factors that are independently correlated with lifetime prevalence of RAS were younger age, urbanization, and systemic disease, including rheumatic disease, genital aphthous disease, depression, chronic headaches, diabetes mellitus, and epilepsy. Smoking is associated with a lower prevalence of RAS in this population.

Compliance with ethical standards

References

1. Edgar NR, Saleh D, Miller RA (2017) Recurrent aphthous stomatitis: a review. J Clin Aesthet Dermatol 10(3):26–36

2. Chiang C-P, Yu-Fong Chang J, Wang YP, Wu YH, Wu YC, Sun A (2019) Recurrent aphthous stomatitis–etiology, serum autoantibodies, anemia, hematinic deficiencies, and management. J Formos Med Assoc 118(9):1279–1289

3. Wiriyakijja P, Fedele S, Porter S, Mercadante V, Ni Riordain R (2017) Patient-reported outcome measures in recurrent aphthous stomatitis: a critical assessment of quality properties. Oral Dis 23(8):1168–1179. https://doi.org/10.1111/odi.12726

4. Cui RZ, Bruce AJ, Rogers RS III (2016) Recurrent aphthous stomatitis. Clin Dermatol 34(4):475–481. https://doi.org/10.1016/j.clindermatol.2016.02.020

5. Najafi F, Rezaei S, Hajizadeh M et al (2020) Decomposing socioeconomic inequality in dental caries in Iran: cross-sectional results from the PERSIAN cohort study. ArchPublic Health 78(1):1–11. https://doi.org/10.1186/s13690-020-00457-4

6. Du Q, Ni S, Fu Y, Liu S (2018) Analysis of dietary related factors of recurrent aphthous stomatitis among college students. Evid Based Complement Alternat Med 2018:1–7. https://doi.org/10.1155/2018/2907812

7. Ajmal M, Ibrahim L, Mohammed N, Al-Qarni H (2018) Prevalence and psychological stress in recurrent aphthous stomatitis among female dental students in Saudi Arabia. Clujul Medical 91(2):216–221. https://doi.org/10.15386/cjmed-840

8. Ślebioda Z, Dorocka-Bobkowska B (2019) Systemic and environmental risk factors for recurrent aphthous stomatitis in a Polish cohort of patients. Advances in Dermatology and Allergology/Post py Dermatologii i Alergologii 36(2):196–201. https://doi.org/10.5114/ada.2018.74638

9. Kaur M, Sahota JK (2018) Recurrent apthous stomatitis-a review. J Adv Med Dent Scie Res 6(4):9–12. https://doi.org/10.21276/jamdsr

10. Hall A (2019) Aphthous ulcers and Behçet's disease. In: Atlas of Male Genital Dermatology. Springer: 141–143. https://doi.org/10.1007/978-3-319-99750-6

11. Plewa MC, Chatterjee K (2018) Aphthous stomatitis. In: StatPearls [Internet]. StatPearls Publishing

12. Manthiram K, Nesbitt E, Morgan T, Edwards KM (2016) Family history in periodic fever, aphthous stomatitis, pharyngitis, adenitis (PFAPA) syndrome. Pediatrics 138(3):e20154572. https://doi.org/10.1542/peds.2015-4572

13. Zain RB (1999) Classification, epidemiology and aetiology of oral recurrent aphthous ulceration/stomatitis. Annal Dent Univ Malaya 6:34–37

14. Kalpana R (2016) Relation between smoking and recurrent aphthous stomatitis. OralMaxillofac Pathol J 7(2):761–762. https://doi.org/10.5005/jp-journals-10037-1087

15. Mansour-Ghanaei F, Joukar F, Naghipour MR et al (2019) Cohort Profile: The PERSIAN Guilan Cohort Study (PGCS). Arch Iran Med 22(1):39–45

16. Eghtesad S, Mohammadi Z, Shayanrad A, Faramarzi E, Joukar F, Hamzeh B, Farjam M, Zare Sakhvidi MJ, Miri-Monjar M,

Moosazadeh M, Hakimi H, Rahimi Kazerooni S, Cheraghian B, Ahmadi A, Nejatizadeh A, Mohebbi I, Pourfarzi F, Roozafzai F, Motamed-Gorji N, Montazeri SA, Masoudi S, Amin-Esmaeili M, Danaie N, Mirhafez SR, Hashemi H, Poustchi H, Malekzadeh R (2017) The PERSIAN cohort: providing the evidence needed for healthcare reform. Arch Iran Med 20(11):291–295

17. Poustchi H, Eghtesad S, Kamangar F, Etemadi A, Keshtkar AA, Hekmatdoost A, Mohammadi Z, Mahmoudi Z, Shayanrad A, Roozafzai F, Sheikh M, Jalaeikhoo A, Somi MH, Mansour-Ghanaei F, Najafi F, Bahramali E, Mehrparvar A, Ansari-Moghaddam A, Enayati AA, Esmaeili Nadimi A, Rezaianzadeh A, Saki N, Alipour F, Kelishadi R, Rahimi-Movaghar A, Aminisani N, Boffetta P, Malekzadeh R (2018) Prospective epidemiological research studies in Iran (the PERSIAN Cohort Study): rationale, objectives, and design. Am J Epidemiol 187(4):647–655. https://doi.org/10.1093/aje/kwx314

18. Kramer I, Pindborg JJ, Bezroukov V, Infirri JS (1980) Guide to epidemiology and diagnosis of oral mucosal diseases and conditions. World Health Organization. Community dentistry and oral epidemiology 8(1):1–26. https://doi.org/10.1111/j.1600-0528.1980.tb01249.x

19. Ghanaei FM ,Joukar F, Rabiei M, Daneshzadeh A, Kord Valeshabad A (2013) Prevalence of oral mucosal lesions in an adult Iranian population. Iran Red Crescent Med J 15(7):600–604. https://doi.org/10.5812/ircmj.4608

20. Al-Johani K (2019) Prevalence of recurrent aphthous stomatitis among dental students: a cross sectional study. J Contemp Dent Pract 20(8):893–895. https://doi.org/10.5005/jp-journals-10024-2630

21. Gheni Taher M (2018) Prevalence of recurrent aphthous ulceration in the Diyala population. Diyala J Med 15(2):112–118. https://doi.org/10.26505/DJM

22. Shiva A, Charati JY, Elkaei A, Zamanzadeh M (2019) Prevalence of recurrent Aphthous stomatitis in university students and its relation with anxiety. J Mazandaran Univ Med Sci 29(180):108–112

23. Böbel TS, Hackl SB, Langgartner D, Jarczok MN, Rohleder N, Rook GA, Lowry CA, Gündel H, Waller C, Reber SO (2018) Less immune activation following social stress in rural vs. urban participants raised with regular or no animal contact, respectively. Proc Natl Acad Sci 115(20):5259–5264. https://doi.org/10.1073/pnas.1719866115

24. Sawair FA (2010) Does smoking really protect from recurrent aphthous stomatitis? Ther Clin Risk Manag 6:573-577. https://doi.org/10.2147/TCRM.S15145

25. Bulur I, Onder M (2017) Behçet disease: new aspects. Clin Dermatol 35(5):421–434. https://doi.org/10.1016/j.clindermatol.2017.06.004

26. Ramanathan A, Deepak T, Manjunath M, Krishna S, AG A, Arun A, Lakhani H (2017) A comparative study of oral health status between type 2 diabetics and non diabetic subjects.J Glob Diabetes Clin Metab 2(2):2–5

27. Rohani B (2019) Oral manifestations in patients with diabetes mellitus. World J Diabetes 10(9):485–489. https://doi.org/10.4239/wjd.v10.i9.485

28. Mohammed D (2019) Oro-genital aphthous stomatitis: A case of mistaken herpes simplex virus type 2.The Pharma Innovation Journal 8(6):41–43

29. Dhopte A, Naidu G, Singh-Makkad R, Nagi R, Bagde H, Jain S (2018) Psychometric analysis of stress, anxiety and depression in patients with recurrent aphthous stomatitis-a cross-sectional survey based study. J Clin Exp Dent 10(11):1109–1114

30. Karaer IC, Urhan A, Reyhani I (2020) Stress and recurrent aphthous stomatitis. Medicine Science 9(1):170–174

31. Hariyani N, Bramantoro T, Nair R, Singh A, Sengupta K (2020) Depression symptoms and recurrent aphthous stomatitis—evidence from a population-based study in Indonesia. Oral Dis 26(5):948–954. https://doi.org/10.1111/odi.13303

32. Ryan M, Baumann RJ, Miller CS, Baker C (2002) Valproate-associated stomatitis. J Child Neurol 17(3):225–227. https://doi.org/10.1177/088307380201700315

33. Srivastav R, Chaurasia P, Bhardwaj A, Hyanki D (2019) Comparative study of effect of stress on headache in medical and non-medical students. Int J Physiol 7(3):145–149. https://doi.org/10.5958/2320-608X.2019.00103.3

34. Bung S, Saile H, Laessle R (2017) Depression, stress symptoms, and cortisol awakening response in female adolescents with chronic headache. Adolescent Psychiatry 7(2):105–111

35. Khare P, Sharva V, Handa H, Amit K, Jain M (2017) Association of recurrent aphthous stomatitis and psychological stress in school going teenagers of Bhopal city, Central India: a descriptive study. Indian Journal of Multidisciplinary Dentistry 7(2):82–86. https://doi.org/10.4103/ijmd.ijmd-23-17

36. AL-Omiri MK, Karasneh J, Alhijawi MM, M.A Zwiri A, Scully C, Lynch E, (2015) Recurrent aphthous stomatitis (RAS): a preliminary within-subject study of quality of life, oral health impacts and personality profiles. J Oral Pathol Med 44(4):278–283. https://doi.org/10.1111/jop.12232

37. Mehdipour M, Zenooz AT, Sohrabi A, Gholizadeh N, Bahramian A, Jamali Z (2016) A comparison of the effect of triamcinolone ointment and mouthwash with or without zinc on the healing process of aphthous stomatitis lesions. Journal of dental research, dental clinics, dental prospects 10(2):87–91. https://doi.org/10.15171/joddd.2016.014