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Depression Symptoms and recurrent aphthous stomatitis – evidence from a population-based study in Indonesia

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Running title: Depression and RAS

Key words: recurrent aphthous stomatitis, depression, Indonesia, population-based study

ABSTRACT

Objectives: This study aims to report the prevalence and distribution of recurrent aphthous stomatitis (RAS) among Indonesian adults and to test the relationship between symptom of depression and RAS.

Methods: Data from the 2007 Indonesia Family Life Survey (IFLS 2007) was analysed to assess the association between symptom of depression and RAS. The prevalence of RAS in the previous month was self-reported. Symptom of depression was measured using the 10-item Center for Epidemiologic Studies Depression (CES-D) scale. The distribution of RAS according to age, sex, and level of stress was also presented in the bivariate analysis. Multivariable logistic regression models were fitted to test associations between symptom of depression and RAS, controlling for age, sex and the stress level.

Results: The previous month prevalence of RAS in Indonesian population was 12%. The adjusted odds ratios (ORs) from the logistic regression models indicate that, for each unit increase in the CES-D depression score (range: 0-30), there was a 9% increase in the odds of having RAS (OR: 1.09, 95%CI: 1.08-1.10). Being older and being male was related with lower prevalence of RAS.

Conclusions: A higher score of depression was related to a higher prevalence of RAS. This association was persistent even after controlling for age, sex and the level of stress.

Key words: recurrent aphthous stomatitis, depression, Indonesia, population-based study

INTRODUCTION

Recurrent aphthous stomatitis (RAS) is the most common ulcerative disease in the oral mucosa. It appears as a single or multiple recurrent painful shallow ulcers, usually round in shape, with well-defined erythematous haloes and yellow or grey pseudomembranous floors (Preeti et al., 2011). RAS has a characteristic prodromal burning sensation that lasts from 2 to 48 hours before an ulcer appears. It could occur in healthy individuals and is typically located on the buccal or labial mucosa or the tongue, and rarely on the gingiva or the heavily keratinised palatal mucosa. On average, 20% of the global population is affected by RAS (Akintoye & Greenberg, 2014). RAS is usually treated using topical and systemic therapies (Akintoye & Greenberg, 2014). The goals of RAS therapy are to improve the function and

quality of life of patients by decreasing pain and ulcer size, promoting healing, and decreasing the frequency of recurrence (Akintoye & Greenberg, 2014).

The prevalence of RAS varies from 0.5% (Zain, 2000) to 67% (Pratibha et al., 2012) depending on the ethnic and socioeconomic groups studied (Akintoye & Greenberg, 2014) as well as the prevalence measure used (i.e., point, period or lifetime prevalence) (Zain, 2000). The lifetime and previous month prevalence of RAS among Indonesians have been reported to be 68% (among dental students, n=66) (Suling et al., 2013) and 48% (among prisoners, n=56) (Junhar et al., 2015), respectively. However, the prevalence or incidence in a large, nationally representative sample in Indonesia that can be generalised to the Indonesian population has not yet been reported.

Several factors have been proposed as possible causative agents for RAS. These include genetic factors; local factors such as trauma; nutritional factors such as vitamin B-complex or folate deficiency; hematologic and immunologic factors; food allergies; drugs and psychosocial problems such as stress, anxiety and depression (Akintoye & Greenberg, 2014; Gavic et al., 2014; Natah et al., 2004). However, a definitive aetiology of RAS is yet to be clearly established. The association between depression and RAS has been examined in a handful of studies (Al-Omiri et al., 2012; Alshahrani & Baccaglini, 2014; Gavic et al., 2014; Suresh et al., 2015). Depression has been found to be associated with pain intensity and symptoms reinforcement of RAS in some of these studies (Alshahrani & Baccaglini, 2014; Gavic et al., 2014). Pathways to explain the pathophysiological relationship between depression and RAS have also been proposed. One hypothesised pathway is that stress or depression may induce parafunctional habits such as tongue, lip or cheek biting, and thus, cause trauma to the oral soft tissues, and this trauma may predispose to RAS (Camila de Barros et al., 2009). Other suggested pathways include changes in the immune system of patients with mental health conditions, leading to RAS (Chiappelli & Cajulis, 2004). However, there is limited evidence from population-based epidemiological studies, and majority of the existing studies examining the association between depression and RAS have been conducted on small samples and have consequently lacked adequate statistical power to address the hypothesis.

Therefore, there are gaps in knowledge about the prevalence of RAS in the Indonesian population and limited evidence on the association between RAS and depression. To address these gaps in evidence, this large, population-based study (with individual-level data) aimed to report the prevalence and distribution of RAS in the Indonesian population and examine

the associations between symptom of depression and RAS. It was hypothesised that symptom of depression is associated with RAS prevalence.

METHODS

Data and variables

Data were obtained from the 2007 Indonesia Family Life Survey (IFLS). The IFLS is an on-going longitudinal multi-purpose survey that was started in collaboration with the RAND Corporation (USA) in 1993, with follow-up data collection taking place in 1997, 2000, 2007 and 2014. The IFLS collects data from more than 30,000 individuals living in 13 of the 27 provinces in the country. The survey is representative of about 83% of the entire Indonesian population. The sampling is stratified by province. In addition, households to be interviewed are randomly selected within the provinces to include both rural and urban areas. Additional details of the survey can be found elsewhere (Frankenberg & Karoly, 1995; Strauss et al., 2009).

All variables including the outcome (RAS), the exposure of interest (depression) and the covariates were gathered from the IFLS 2007 questionnaire. The 2007 wave was used as it was the first time that a validated mental health instrument was used to measure depression (Tampubolon & Hanandita, 2014). The presence or absence of RAS was self-reported by the respondents based on their experience of the disease in the past four weeks. The question about RAS was asked in Indonesian language using a term for RAS that is commonly used by lay persons (sariawan). Symptom of depression was measured using the 10-item Center for Epidemiologic Studies Depression (CES-D) scale (Andresen et al., 1994). This scale was developed to measure depressive symptoms in the general population (Radloff, 1977). Its validity in various Asian settings, including in Indonesia, has been demonstrated previously (Mackinnon et al., 1998). Each respondent was asked to report how often in the past week they had experienced the 10 depressive symptoms listed on the CES-D scale. The responses were recorded using a four-category rating scale that ranged from 0 to 3 (0 = rarely or none of the time or 0-1 day in a week; 1 = some or little of the time or 1-2 days in a week; 2 = moderately or much of the time or 3-4 days in a week; 3 = most or almost all the time or 5-7 days in a week). After reverse-coding the positively phrased items, we calculated the scores as the sum of these responses (theoretical range 0-30, where 0 represents people with no depression and 1-30, ascending levels of depression) (Tampubolon & Hanandita, 2014). Analysis using the continuous score was used here because cut-offs have not been validated for the Indonesian sample (Tampubolon & Hanandita, 2014). However, the CES-D

commonly has a positive or right-skewed distribution (Radloff, 1977); thus, groups with higher means also tend to have higher variances. Therefore, additionally, three categories were created to assess the effect of various cut-offs on the relationship between symptom of depression and RAS. Earlier studies in other populations have used 10 as a cut-off (Andresen et al., 1994); nevertheless, uncertainty regarding the appropriate cut-offs in this population lead to the creation of 3 categories in this study. Thus, the CES-D score was categorised into low (CES-D score, 0-5), intermediate (CES-D score, 6-10) and high (CES-D score, >10) symptom of depression.

The covariates included all possible confounding factors available in the data set, namely, age, sex and level of stress. Previous studies have shown these factors to be associated with RAS (Natah et al., 2004; Zain, 2000; Abdullah, 2013; Axéll & Henricsson, 1985; Akintoye & Greenberg, 2014). Thus age, sex and level of stress were chosen as the covariates. In this research, age was treated as a continuous covariate. Sex was entered as a dummy variable (male and female). The level of stress was self-reported on a global item measuring stress by the respondents as having no stress, low stress or high stress during work or study life.

Statistical analyses

The statistical analyses were performed in SAS-callable (Research Triangle Institute, North Carolina). Descriptive characteristics of the study participants were estimated. Bivariate analyses were performed using chi-squared test for the categorical covariates (gender and stress) and logistic regression for the continuous exposure and covariates (symptom of depression and age, respectively). Finally, multivariable logistic regressions were used to estimate the odds ratios (OR) of experiencing RAS and their 95% confidence intervals (95%CI). The statistical significance of the associations was evaluated at $P < 0.05$.

Ethical approval

Ethical approval for IFLS 2007 was obtained from the University of Gadjah Mada Research Ethics Committee (Indonesia) and the Institutional review board of the RAND corporation. This particular study involved only a secondary analysis, thus, no new ethic clearance was required.

RESULTS

A total of 29,029 participants were included in this study. Table 1 shows the characteristics of the study participants, 52.4% of whom were female. The mean age of the participants was 36.9 years (SD=15.6; range, 15–97 years). The mean depression symptoms (CES-D) score was 4.09 (95%CI=4.05–4.13; range, 0–30). When the CES-D score was categorised, 21.5% and 5.5% of the population were found to have intermediate and high symptom of depression, respectively. Among the respondents with high depression symptoms (CES-D score >10), the score varied from 11 to 30, with the mean score being 14.2. Only 5.98% (95%CI=5.65–6.31) of the study participants reported a high level of stress.

The previous month prevalence of RAS was 11.95% (95%CI=11.58–12.33). The unadjusted associations between RAS and symptom of depression (exposure of interest) and those between RAS and the covariates (age, sex and level of stress) are presented in Table 2. Both symptom of depression and the covariates were associated with RAS. Higher score and level of depression symptoms were related to higher prevalence of RAS. People with higher levels of stress also presented a higher prevalence of RAS compared with those having no stress. Older individuals and males had lower prevalence of RAS.

Table 3 shows the results of the multivariable analyses of the associations between symptom of depression (measured continuously using the CES-D) and RAS. Associations between depression symptoms and RAS were present even after adjustment for the covariates. After controlling for age, gender and stress, a one unit increase in the CES-D depression score was associated with a 9% increase in the odds of having RAS (OR [95%CI] = 1.09 [1.08–1.10]).

Table 4 shows the results from the multivariable logistic regression models for the associations between the depression categories (categorised ordinally) and RAS. In the unadjusted analyses, individuals in the intermediate and high depression symptoms categories had higher odds of having RAS (OR [95%CI] = 1.56 [1.43–1.69] and 2.98 [2.64–3.36], respectively) than those with low depression symptoms. After adjusting with all the covariates, these odds were marginally higher: OR [CI] = 1.59 [1.44–1.76] and 3.01 [2.58–3.50] for people with intermediate and high CES-D score, respectively.

DISCUSSION

The findings of this study show that the previous month prevalence of RAS among the general Indonesian population is 12%. The prevalence of RAS is lower in males, older individuals and individuals without stress. The result also reveals that more depressive symptoms were associated with higher odds of having RAS, and it persisted even after

adjustment for the covariates (age, sex and stress). The analyses showed a dose-response relationship between depression scores and RAS.

Age, sex and level of stress were chosen as covariates in this study as they have been shown to be associated with RAS (Natah et al., 2004; Zain, 2000; Abdullah, 2013; Axéll & Henricsson, 1985; Akintoye & Greenberg, 2014). Research has shown that women (Abdullah, 2013; Axéll & Henricsson, 1985) have a higher risk of RAS than men. RAS among women could be triggered by hormonal imbalance, such as that caused by their menstruation cycle (Maheswaran et al., 2015). A study also reported that such hormonal imbalance may be related to occasional stress or depression (Mohamadirizi & Kordi, 2013). Furthermore, people with different age and gender could have different coping mechanisms for handling problems that lead to the occurrence of depression. In addition, stress has been known as possible causative agent of RAS (Akintoye & Greenberg, 2014). Stress has also been related to depression as research has shown that stress usually occurs prior to the onset of a depression (Mazure, 1998). Another study reported that participants exposed to high-stress jobs had a twofold risk of depression compared to those having low job demands with no stress involved (Melchior et al., 2007). However, it is also known that depression could occur without stress being a causal antecedent (Beck & Alford, 2009). In this analysis, we checked the associations between depression and RAS, adjusted for age, sex and the level of stress, and did not measure the mediation effect of depression in the association between stress and RAS.

RAS is the most common oral ulcerative condition. Its measurements around the world could be reported through point, period or lifetime prevalence. The current study shows that the previous month prevalence of RAS among Indonesians older than 15 years of age was slightly less than 12%. This prevalence was lower than the previous month prevalence of RAS reported among dental students in India, which was almost 22% (Pratibha et al., 2012). This difference could be due to the differences in the sampling strategy, where the current study looked at a representative sample, and Prathiba et al. assessed a convenience sample of students. Dental students could be more aware of RAS, therefore report it more frequently. Another possible cause of this difference could be the level of stress. Research showed that university students, especially dental and medical students, experience considerable amount of stress (Tosevski, 2010; Elani et al, 2014). Considering that stress has an association with depression and RAS (Akintoye & Greenberg, 2014; Melchior et al., 2007), it is reasonable to adjust stress in this analysis.

RAS has been reported to be more common among women, among persons in the second and third decade of life, and among students (Abdullah, 2013; Axéll & Henricsson, 1985). Men had lower odds of having RAS than women in this study. This finding is consistent with the results of other studies (Abdullah, 2013; Axéll & Henricsson, 1985). Hormonal changes during the menstruation cycle was posited as a probable mechanism for increased incidence of RAS among women (Maheswaran et al., 2015). However, a study by Rao and colleagues had discordant findings with regard to increased odds of RAS in women (Rao et al., 2015). As regards age, previous epidemiological studies on RAS prevalence showed a general trend that RAS prevalence is lower among the first decade of life, reaching a peak in the second and third decades of life, before decreasing (Zain, 2000). As our sample consists of people aged 15–97 years, the finding of a decrease in RAS prevalence with increasing age is consistent with other studies.

The current findings that more depressive symptoms were associated with higher odds of having RAS are similar to those seen in previous research undertaken in different populations (Gavic et al., 2014; Ship, Brightman, & Laster, 1967). Gavic et al. (2014) showed that in patients with RAS, depression was positively correlated with the pain intensity and symptoms reinforcement of RAS. Ship et al. (1967) showed that dental and medical students with RAS had higher scores of depression compared with hospital patients with no history of RAS. Other studies however, have failed to reveal any association between depression and RAS (Ferguson, Carter, & Boyle, 1984; Picek et al., 2012).

It is known that minor physical injuries to the oral mucosa amongst those susceptible to RAS can frequently trigger RAS lesions (McCartan et al., 1996). Trauma could predispose to RAS by inducing edema and early cellular inflammation associated with an increased viscosity of the oral submucosal extracellular matrix (Stone, 1991; Akintoye & Greenberg, 2014). Thus, a previous hypothesis proposed that stress or depression may induce parafunctional habits such as tongue, lip or cheek biting, and thus causes trauma to oral soft tissues, and this trauma may predispose to ulceration (Camila de Barros et al., 2009). However, a study revealed insufficient evidence on the association between levels of parafunctional habits and severity of RAS, and concluded that mental stress may act as a triggering or modifiable risk factor rather than an etiological factor for aphthous stomatitis (Camila de Barros et al., 2009). The changes in the immune system among patients with mental health conditions, such as depression, may also lead to RAS. A prior study reported that stress usually occurs prior to the onset of a depression (Mazure, 1998). However, depression could also happen without involving stress acting as an antecedent (Beck &

Alford, 2009). In this case, genetic factors or previous depressive episodes have been related to the cause of the depression (Beck & Alford, 2009). Due to the uncertainties involving the mental health measures and their causal sequence impacting the incidence of RAS, assessment of mediation pathway through depression in the relationship between stress and RAS warrants further investigation.

A review of many depression studies reveals findings that there is a different manifestation of depression between Asians and Western people (Kalibatseva and Leong, 2011). While Westerners may “psychologise” depression, Asians tend to somatise depression (Kalibatseva and Leong, 2011). Westerners often describe depression in relation to concepts like guilt, individualism, decision-making, and self-control. On the other hands, Eastern experience of depression may reflect the integration of body and mind, which would explain the widespread occurrence of somatic symptoms. Our findings suggest that RAS among susceptible Indonesians may be one of the somatic symptoms caused by the depression.

This study is among the few reporting the relationship between depression and RAS in a representative sample, and to the best of our knowledge is the first in the Indonesian population. A weakness of this study could be the unweighted analysis; therefore, our estimate may not be generalisable to the entire Indonesian population. However, the high number of data subjects (N=29,029) increases the precision of the estimates for the relationship between depression scores and RAS. Self-reporting of RAS in this study could result in an overestimation of the disease as respondents may not be able to differentiate it from traumatic or other types of ulcers such as manifestations of systemic diseases (e.g., Behçet’s disease). However, Behçet’s disease is quite rare (Nair & Moots, 2017) and trauma could also initiate RAS (Aminabadi, 2008). Moreover, even if RAS was measured inaccurately, this will only be a form of non-differential misclassification of outcome (as outcome measure is non-dependent on exposure measurement) which is likely to bias the estimate towards the null. Hence, the findings may only be an underestimation of true association. Self-reported stress using a single global question has been found to be valid and reliable in the past (Littman et al., 2006). But this could be a limitation as it may not provide as rich a description of stress description as that measured using a validated questionnaire such as the perceived stress scale. Further, even though we tried to adjust for possible confounding, there are still some possibilities that not all variables that have been associated with RAS and depression have been controlled for in this study, potentially resulting in some residual confounding. The cross-sectional nature of the IFLS 2007 data used in this study

could be another limitation as it does not establish temporal ordering between depression and RAS.

CONCLUSIONS

In this large population-based study, the previous month prevalence of RAS among Indonesians was found to be 12%. Higher depressive symptoms were associated with higher odds of RAS even after adjustment for age, gender, and stress levels.

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Tables

Table 1. Characteristics of the study participants

Characteristics	All participants
	Mean[CI] or %[CI]
N = 29,029	
Depression (continuous CES-D score)	4.09[4.05-4.13]
Depression (ordinal scale based on CESD-score)	
Low (0-5)	73.01[72.50-73.52]
Intermediate (6-10)	21.49[21.01-21.96]
High (>10)	5.50[5.24-5.77]
RAS	
Yes	11.95[11.58-12.33]
No	
Age	36.88[36.70-37.06]
Sex	
Male	47.61[47.04-48.19]
Female	52.39[51.81-52.96]
Level of stress	
No stress	62.91[62.24-63.57]
Low stress	31.12[30.48-31.76]
High stress	5.98[5.65-6.31]

CES-D =Center for Epidemiologic Studies Depression; RAS = recurrent aphthous stomatitis; CI =95% Confidence Interval

Table 2. Bivariate analyses (unadjusted analysis) of the associations of RAS with depression and the study covariates

Characteristics	Association with the previous month prevalence of RAS
	% [CI] or OR [CI]
N = 29,029	
Depression (continuous CES-D score)	(OR [CI])=1.09 [1.08-1.09]
Depression (ordinal scale based on CESD-score)	
Low (0-5)	10.10 [9.69-10.50]
Intermediate (6-10)	14.89 [14.00-15.77]
High (>10)	25.06 [22.93-27.19]
Age	(OR [CI])=0.98 [0.98-0.98]
Sex	
Male	11.24 [10.71-11.76]
Female	12.60 [12.08-13.13]
Level of stress	
No stress	10.52 [9.99-11.06]
Low stress	13.58 [12.73-14.43]
High stress	17.46 [15.31-19.60]

Bold= significant in unadjusted analysis; CES-D= Center for Epidemiologic Studies Depression; RAS= recurrent aphthous stomatitis; CI=95% Confidence Interval; OR=Odd Ratio

Table 3. Multivariable analysis of the associations of RAS with depression (continuous CES-D score) and the study covariates

Characteristics	Previous month RAS prevalence	
	Unadjusted model* OR [CI]	Adjusted model* OR [CI]
Depression (continuous CES-D score)	1.09 [1.08-1.09]	1.09 [1.08-1.10]
Age	-	0.98 [0.97-0.98]
Gender		
Female	-	-
Male	-	0.84 [0.77-0.92]
Work stress		
No stress	-	-
Low stress	-	1.20 [1.09-1.31]

	High stress	-	1.36 [1.16-1.61]
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Bold= significant; CES-D= Center for Epidemiologic Studies Depression; RAS= recurrent aphthous stomatitis; CI=95% Confidence Interval; OR=Odd Ratio; *logistic regression model

Table 4. Multivariable analysis of the association of RAS with depression (categorised ordinally) and the study covariates

Characteristics		Previous month RAS prevalence	
		Unadjusted model* OR [CI]	Adjusted model* OR [CI]
Depression (ordinal scale based on CESD-score)			
	Low (0-5)	-	-
	Intermediate (6-10)	1.56 [1.43-1.69]	1.59 [1.44-1.76]
	High (>10)	2.98 [2.64-3.36]	3.01 [2.58-3.50]
Age			0.98 [0.97-0.98]
Gender			
	Female	-	-
	Male	-	0.84 [0.77-0.92]
Work stress			
	No stress	-	-
	Low stress	-	1.20 [1.09-1.32]
	High stress	-	1.38 [1.17-1.63]

Bold= significant; CES-D= Center for Epidemiologic Studies Depression; RAS= recurrent aphthous stomatitis; CI=95% Confidence Interval; OR=Odd Ratio; *logistic regression model

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