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An exploration of point, annual, and lifetime prevalence in characterizing recurrent aphthous stomatitis in USA children and youths

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BACKGROUND: This report presents and contrasts the prevalence of recurrent aphthous stomatitis (RAS) in 51 471 children and adolescents from two major studies: the Third National Health and Nutrition Examination Survey, 1988–1994 (NHANES III) and the National Survey of Oral Health in USA Schoolchildren, 1986–1987 (OHSC), large USA studies based on multistage probability sampling.

METHODS: Prevalence proportions, 95% confidence limits and multivariate logistic regression models were constructed for point, 12-month, and lifetime RAS prevalence using SAS-callable SUDAAN 8.0.2.

RESULTS: Examinations were performed on 51 471 children and adolescents. Point prevalence was 1.51% (NHANES III) and 1.21% (OHSC); annual prevalence was 19.84% (NHANES III); and lifetime prevalence was 40.18% (OHSC). Multivariate logistic models showed that being white, having a history of herpes labialis, (NHANES III), and being white and an adolescent (OHSC) were predictors of RAS.

CONCLUSIONS: Caution should be used in interpreting 12-month and lifetime RAS prevalence based a subject's recall.

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Keywords: children and adolescents; Third National Health and Nutrition Examination Survey; NHANES III; oral epidemiology; oral mucosal lesions; recurrent aphthous stomatitis

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Introduction

Recurrent aphthous stomatitis (RAS) is the most common inflammatory ulcerative condition of the oral cavity in North America (1). Lesions range from minor: well-defined, shallow ulcers < 1 cm deep that resolve within 7–14 days without a scar; major: larger, deeper ulcers that heal within 6 weeks leaving scars; or herpetiform: small (1–2 cm) numerous lesions that heal within 7–10 days (2). While the etiology is uncertain, RAS has been associated with socioeconomic status (3); vitamins B_2 (4), B_6 (4) B_{12} (5, 6), C (7), calcium (7); iron (7, 8), ferritin (8); vitamin B_1 (7, 9); deficiencies, stress (10, 11), hormonal factors (12), trauma (13), microorganisms, food hypersensitivity (14), immune disorders (13), recurrent herpes labialis (RHL) (15, 16), and family history (17). Tobacco, on the other hand, has been identified as a protective factor in some studies (18, 19).

Lesion occurrence has been described using point prevalence: direct evidence from clinical examinations, and self-reported (period) prevalence. Subjects are given a description of RAS and asked if they have experienced one or more episodes within a specified period (typically, 12 months, 24 months, or lifetime). Point prevalence in children and youth has been reported as 2.24% in Spanish 6 year olds (20); 1.0% among 4–13-year-old girls and 2% among boys in an affluent Buenos Aires school and 18% in boys and 20% in girls in a suburban school in an indigent area (21). This wide range of reported point prevalences is due to the variety of locations, patient selection methods, and diagnostic criteria used. Moreover, standard errors are generally not provided so that even assuming generally comparable diagnostic and sampling methods, comparisons between studies is problematic. Most studies of RAS among children and youth have been based on convenience samples and rarely has probability sampling been used.

Kleinman et al. (22) reported the results of oral mucosal examinations on a probability sample of 40 693 USA schoolchildren performed as part of the National

Survey of Oral Health in USA Schoolchildren, 1986–1987 (OHSC). The point prevalence of RAS was 1.23% while lifetime prevalence was 36.5% (22). The Third National Health and Nutrition Examination Survey (NHANES III), 1988–1994 also included oral mucosal examinations (23) although the results have yet to be reported. While both studies collected point prevalence data, OHSC collected lifetime prevalence while NHANES III collected 12-month prevalence. This paper examines RAS point and period prevalence in both studies and explores the consistency of the relationship between RAS point and period prevalence within and between the studies.

Materials and methods

NHANES III

Two publicly available data sets were used: NHANES III (23) and OHSC (24). NHANES III was a multistage probability sample of 19 528 USA households in which 33 994 individuals from 2 months to 90 years of age were interviewed; 30 818 were examined in mobile examination centers, and 493 were examined at home. Dentist-examiners used diagnostic criteria derived from World Health Organization's Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases (25). The scarcity of representative oral lesions made standard calibration (i.e. examining patients' oral lesions as part of the training session) infeasible, so examiner training for the diagnostic criteria consisted of a presentation of the written criteria along with color photographs to illustrate the characteristic features of each lesion or condition. A lesion was classified as RAS based on the presence of well-defined grayish-white ulcer(s) on unkeratinized surfaces surrounded by a red halo. Subjects were asked about clinical history and duration including the presence of pain (26). In addition to the oral examination, extensive health, social, medical histories were obtained by interviewing the subjects 8 years of age and older or their parents. Income was measured by the poverty income ratio that relates family income to the poverty level based on the subject's family size (27). The poorest individuals are in the 'low' category. Subjects not falling into the three race-ethnicity categories (non-Hispanic White, non-Hispanic Black, Mexican-American) were excluded from analyses using race-ethnicity resulting in the removal of 487 subjects categorized as 'other' from the few analyses. Subjects 12 years of age and older were asked about tobacco use. Twelve-month RAS prevalence was determined by the response to the question: 'Have you had canker sores in the past 12 months'? Neither photos nor lesion descriptions were provided to the respondents and responses were based on recall. Blood was drawn on subjects 4 years of age and older. A detailed discussion of the survey methods is presented in Drury et al. (28).

OHSC

The OHSC was a national three-stage school-based probability sample representing the USA school-children in kindergarten through 12th grade conducted by the National Institute of Dental Research from 1986 to 1987 (22). The methodology is described fully in National Institutes of Health (29). The relative rarity and variable clinical appearance of the lesions precluded the use of replicate examinations for calibration so the 14 dentist-examiners were shown color transparencies of each lesion of interest (22). Diagnostic criteria for RAS were based on the World Health Organization's Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases (25). A well-defined grayish-white ulcer surrounded with a red halo with a history of pain was classified as RAS (22). To determine lifetime RAS prevalence, subjects were shown photographs of RHL and RAS and were asked if they ever had cold sores or fever blisters on their lips (RHL) or other recurring ulcers inside their mouths (RAS) (22). Questions about tobacco use were asked to subjects in grade 6 (approximately 12 years of age) and above (24).

Analytic methods

Since both surveys used complex sampling designs, SAS-callable SUDAAN 8.0.2 was used for all data analysis. Prevalence calculations are based on weighted counts rather than actual counts and standard errors are adjusted for the design effect. Mean laboratory analyte values between individuals with and without RAS (NHANES III) were compared using *t*-tests. Caution should be used in interpreting the *t*-test results from multiple pairwise comparisons and α-levels should be lowered (30). Bivariate logistic regressions were performed for RAS point, annual, and lifetime prevalence with the previously mentioned covariates. Those with a Wald F-statistic having a *P*-value of < 0.20 were fitted to a multivariate logistic model using forward selection. Covariates and interactions with $P < 0.05$ were retained in the final models. As this study focuses on children and youth, 1487 individuals 18 years and older were removed from the OHSC data set. When data from NHANES III and OHSC results are compared, NHANES III results will not include 4092 children < 5 years of age.

Results

NHANES III

Oral examinations were performed on 12 265 individuals 2–17 years of age representing more than 63 million non-institutionalized children and youth. Table 1 shows the point (PP) and annual (AP) RAS prevalence in the aggregate and for levels of categorical covariates that the literature suggests may be associated with RAS. Overall, PP was 1.51% with no significant differences among levels of gender, income, RHL history; serologic evidence of *Helicobacter pylori* or hepatitis C, and cigarette smoking. Non-Hispanic Blacks (0.84%) had less than half the PP of non-Hispanic Whites (1.73%) or Mexican-Americans. Analyses using race-ethnicity excluded 684 (5.6%) individuals coded as 'other'. Point prevalence increased significantly in older age groups and was almost eight times higher in the 12–17 (2.48%) than 2–4 (0.32%) year groups. When the analysis was

Table 1 Point and annual prevalence of recurrent aphthous stomatitis, children and youth, Third National Health and Nutrition Examination Survey (NHANES III)

	Point prevalence (2–17 years)			*Annual prevalence (8–17 years)*		
	n	*%*	*95% confidence limits*	*n*	*%*	*95% confidence limits*
Gender	12 265	1.51	1.17–1.86	4657	19.84	17.31–22.36
Male	6045	1.61	1.10–2.12	2280	18.29	15.44–21.14
Female	6220	1.41	0.81–2.01	2377	21.46	18.07–24.84
Race/ethnicity	11 581	1.59[b]	1.22–1.96	4439	21.21[c]	18.48–23.93
Non-Hispanic White	3895	1.73	1.23–2.23	1203	26.29	22.45–30.12
Non-Hispanic Black	3731	0.84	0.44–1.23	1629	4.46	3.09–5.83
Mexican-American	3955	1.93	1.06–2.79	1607	11.69	9.29–14.09
Age (years)	12 265	1.51[c]	1.17–1.86	4657	19.84	17.31–22.36
2–4	4092	0.32	0.04–0.59			
5–7	2711	0.89	0.39–1.38			
8–11	2973	1.63	0.83–2.44	2180	18.14	14.52–21.75
12–17	2489	2.48	1.59–3.37	2477	21.02	17.71–24.33
Poverty income ratio	12 265	1.51	1.17–1.86	4657	19.84[c]	17.31–22.36
Low	5488	1.30	0.67–1.92	2090	11.37	8.16–14.57
Middle	4475	1.91	1.23–2.59	1732	22.13	18.63–25.63
High	2302	1.06	0.42–1.70	835	25.01	20.22–29.81
RHL in past year (≥12 years)	4663	2.13	1.56–2.70	4652	19.85[c]	17.31–22.38
Yes	582	4.15	1.86–6.44	578	39.85	33.06–46.64
No	4081	1.78	1.16–2.40	4074	16.43	13.77–19.08
Hepatitis C (≥4 years)	5002	2.00	1.44–2.55	4078	19.91[a]	17.22–22.61
Yes	12	19.33	−14.20 to 52.87	10	0.00	0.00–0.00
No	4990	1.95	1.39–2.51	4068	19.97	17.27–22.67
Helicobacter pylori (≥4 years)	2252	2.41	1.34–3.47	1805	21.79[a]	17.28–26.29
Yes	707	1.83	0.38–3.28	586	12.49	6.24–18.73
No	1545	2.59	1.21–3.97	1219	24.96	19.33–30.58
Cigarette smoking (≥12 years)	2489	2.48	1.59–3.37	4657	19.84	17.31–22.36
Yes	136	1.10	−1.06 to 3.26	138	18.33	8.77–27.89
No	2353	2.60	1.58–3.62	4519	19.91	17.48–22.34
Smokeless tobacco use	2489	2.48[a]	1.59–3.37	4657	19.84	17.31–22.36
Yes	17	0.00	0.00–0.00	18	0.00	0.00–0.00
No	2472	2.51	1.61–3.41	4639	19.99	17.44–22.55

[a]Chi-square test; $P < 0.05$.
[b]Chi-square test; $P < 0.01$.
[c]Chi-square test; $P < 0.001$.

restricted to children 5 years of age and older, the overall PP was 1.82% (1.40–2.23); 1.94 (1.29–2.58) for males; 1.69 (0.97–2.40) for females; 2.04% (1.46–2.34) for non-Hispanic Whites; 0.98 (0.49–1.47) for non-Hispanic Blacks; and 2.43 (1.29–3.56) for Mexican-Americans (data not in Table).

Overall AP was 19.84%. Non-Hispanic Whites (26.29%) had a fourfold greater RAS prevalence than non-Hispanic Blacks (4.46%). High-income (high PIR) subjects (25.01%) had approximately twice the RAS prevalence than those in the low income (11.37%) category. Subjects with a history of RHL (39.85%) had more than twice the RAS prevalence than those with no RHL history (16.43%). Individuals positive for *H. pylori* (12.49%) had half the AP of those who were *H. pylori*-negative (24.96%). Table 2 compares the mean levels of continuous covariates between individuals with and without RAS. Serum ferritin ($P < 0.022$) and vitamin A ($P < 0.020$) levels were significantly different for PP while vitamin A ($P < 0.015$) was significantly different for AP.

Table 3 shows bivariate and multivariate regression models for RAS PP and AP. Non-Hispanic Whites (odds ratio, OR = 2.09) and Mexican-Americans (OR = 2.34) had more than twice the odds of having a clinically apparent RAS lesion than non-Hispanic Blacks. Subjects 12–17 (OR = 4.93) and 8–11 years of age (OR = 2.97) had higher odds of RAS than those in the youngest (2–7 year) group. Individuals who reported having RHL in the past year (OR = 2.39) had more than twice the odds of RAS than those without a positive RHL history. Individuals who had a positive serologic test for hepatitis C (OR = 12.03) had more than 12 times the odds of having an aphthous lesion than those who were seronegative. The standard error for the OR is large because 12 of 5002 subjects were seropositive; one of whom had a prevalent lesion. When the analysis was restricted to children 5 years of age and older, the overall ORs were: 1.15 (0.61–2.16) for males; 2.10 (1.17–3.78) for non-Hispanic Whites; and 2.51 (1.19–5.27) for Mexican-Americans (data not in Table). The multivariate model for PP consisted of race-ethnicity and RHL history with the ORs substantially unchanged.

Non-Hispanic Whites (OR = 7.64) and Mexican-Americans (OR = 2.84) had greater odds of having a positive lifetime history of RAS than non-Hispanic Blacks. Individuals in the highest (high poverty income ratio) and middle income groups had twice the odds of RAS than those in the high income group (OR = 2.60

Table 2 Mean, standard error, *t*-test for continuous variables used in the analysis (Third National Health and Nutrition Examination Survey, NHANES III)

	Recurrent aphthous stomatitis (RAS) point prevalence				*RAS annual prevalence*			
	n	*Mean*	*SE*	*P(t = 0)*	*n*	*Mean*	*SE*	*P(t = 0)*
Serum ferritin (ng/ml)	8748	37.63	1.12	0.0223	4201	40.81	1.74	0.2075
RAS	117	31.29	2.44		573	38.36	1.91	
No RAS	8631	37.73	1.14		3664	41.42	1.99	
Serum iron (μg/dl)	8792	83.53	0.81	0.2899	4217	87.79	1.08	0.1273
RAS	116	92.75	8.63		538	91.80	3.22	
No RAS	8676	83.38	0.83		3679	86.79	0.96	
Mean corpuscular volume (MCV) (fl)	8722	84.38	0.14	0.0663	4205	85.61	0.16	0.2754
RAS	116	85.42	0.62		534	85.92	0.33	
No RAS	8606	84.37	0.14		3671	85.53	0.17	
Hemoglobin (g/dl)	8722	13.19	0.04	0.0690	4205	13.59	0.04	0.4797
RAS	116	13.52	0.19		534	13.64	13.57	
No RAS	8606	13.18	0.03		3671	13.57	0.04	
Vitamin B_{12} (pg/ml)	3480	642.50	12.71	0.8979	2156	592.01	11.59	0.3646
RAS	55	635.61	51.24		252	576.63	17.70	
No RAS	3425	642.62	13.00		1904	595.57	13.32	
Vitamin C (mg/dl)	4808	0.97	0.02	0.0711	3936	0.94	0.02	0.3404
RAS	96	0.85	0.06		511	0.92	0.04	
No RAS	4712	0.97	0.02		3425	0.94	0.02	
Vitamin A (μg/dl)	6645	40.73	0.29	0.0195	4124	42.87	0.32	0.0145
RAS	111	44.15	1.36		524	44.24	0.69	
No RAS	6534	40.66	0.30		3600	0.69	0.31	
Serum folate (ng/ml)	6911	8.68	0.23	0.0556	4205	7.80	0.26	0.4054
RAS	114	7.61	0.51		535	8.15	0.56	
No RAS	6797	8.70	0.23		3670	7.71	0.25	
RBC folate (ng/ml)	6942	192.53	3.40	0.8691	4606	181.76	3.24	0.3391
RAS	114	194.62	12.74		536	187.83	7.63	
No RAS	6828	192.49	3.43		3670	180.25	3.33	
Hematocrit (%)	8722	13.19	0.04	0.0690	4205	13.59	0.04	0.4797
RAS	116	13.52	0.19		534	13.64	0.09	
No RAS	8606	13.18	0.03		3671	13.57	0.04	

and OR = 2.22, respectively). Individuals who reported having RHL in the past year (OR = 3.37) had more than three times the odds of having RAS in the past year than those without a positive RHL history. The OR for hepatitis C seropositivity could not be estimated since none of the 10 seropositive subjects reported having RAS in the past year.

The multivariate model consisted of race-ethnicity, poverty income ratio, RHL history, and the interaction between RHL history and race-ethnicity. High (AOR = 1.95) and middle income (AOR = 1.75) individuals had higher odds of RAS than those in the low income group. Having a RHL within the past year materially increased the odds of having RAS in the past year for all race-ethnicity groups: non-Hispanic Whites (AOR 24.36 vs. 7.01); Mexican-Americans (AOR 18.42 vs. 2.60); and non-Hispanic Blacks (6.02 vs. 1.00).

OHSC

Oral examinations were performed on 39 206 individuals 5–17 years of age representing more than 43 million schoolchildren. Overall, PP was 1.21%. Table 4 shows the PP and lifetime RAS prevalence (LP) with non-Hispanic Whites having almost four times that of non-Hispanic Blacks. Analyses using race-ethnicity excluded 2133 (5.8%) individuals coded as 'other'. Point prevalence increased significantly in older age groups and was more than three times higher in the 12–17 (1.54%) than 5–7 (0.54%) year groups. Smokeless tobacco (ST) users (0.57%) had a significantly lower RAS PP than non-users (1.29%). Females (41.45%) had a significantly higher RAS LP than males (38.98%) although the actual difference was small. Non-Hispanic Blacks (33.66%) and Mexican-Americans (33.25%) had a significantly lower LP than non-Hispanic Whites (43.86%) although the proportional difference was smaller than it was with PP. Individuals with a lifetime history of RHL (54.79%) had less than twice the RAS LP as those with no history of RHL (31.92%).

Table 5 shows bivariate and multivariate regression models for RAS PP and LP. Non-Hispanic Whites (OR = 3.97) and Mexican-Americans (OR = 3.40) had greater odds of having a lesion than non-Hispanic Blacks. Individuals 12–17 (OR = 2.87) and 8–11 (OR = 2.24) years of age had greater odds of RAS than the youngest group. The multivariate model for PP contained race-ethnicity and age.

Females (OR = 1.10) had greater odds of having a lifetime history of RAS than males although the effect size was small. Individuals 12–17 (OR = 1.60) and 8–11 (OR = 1.54) years of age had greater odds of having a lifetime history of RAS than those in the youngest group. The multivariate model for LP contains lifetime history of RHL, age, gender, and an interaction between RHL history and age. Females [OR = 1.01; 95% confidence interval (CI): 1.01–1.19] than males although

Table 3 Bivariate and multivariate regression models for point and annual RAS prevalence (NHANES III)

	Point prevalence				*Annual prevalence*			
	OR	*95% CL*	*AOR*	*95% CL*	*OR*	*95% CL*	*AOR*	*95% CL*
Gender								
Male	1.14	0.62–2.11			0.82	0.65–1.04		
Female	1.00				1.00			
Race/ethnicity								
Non-Hispanic White	2.09	1.20–3.64	2.33	1.16–4.68	7.64	5.29–11.03	7.01	4.68–10.52
Mexican-American	2.34	1.13–4.82	3.11	1.40–6.92	2.84	1.88–4.28	2.60	1.56–4.36
Non-Hispanic Black	1.00		1.00		1.00		1.00	
Age (years)								
2–4	1.00							
5–7	2.83	0.95–8.39						
8–11	5.24	1.90–14.45			1.00			
12–17	8.04	3.19–20.26			1.20	0.85–1.68		
Poverty income ratio								
Low	1.00				1.00		1.00	
Middle	1.48	0.77–2.82			2.22	1.55–3.17	1.75	1.21–2.53
High	0.82	0.40–1.68			2.60	1.71–3.96	1.95	1.27–3.01
RHL in past year								
Yes	2.39	1.13–5.05	2.23	1.03–4.40	3.37	2.36–4.81	6.48	3.10–13.55
No	1.00				1.00		1.00	
Hepatitis C								
Yes	12.04	1.20–120.77			*			
No	1.00				1.00			
Cigarette smoking								
Yes	0.80	0.10–6.46			0.89	0.47–1.66		
No	1.00				1.00			
Race/ethnicity[a] RHL history								
White and RHL							24.36	14.46–41.06
White and no RHL							7.01	4.68–10.52
Mexican-American and RHL							18.42	10.47–32.42
Mexican-American and no RHL							2.60	1.56–4.36
Black and RHL							6.02	2.91–12.48
Black and no RHL							1.00	

[a]Cannot be estimated.
AOR, adjusted odds ratio; CL, confidence limit; RAS, recurrent aphthous stomatitis; NHANES, Third National Health and Nutrition Examination Survey; RHL, recurrent herpes labialis.

the effect was small. Compared with the referent, individuals 5–7 years of age who had a lifetime history of RHL (AOR = 6.42; 95% CI: 4.46–9.24), had more than six times greater odds of having had RAS; individuals 8–11 years of age who had a lifetime history of RHL (AOR = 5.60; 95% CI: 4.47–7.01); and individuals 12–17 who had a lifetime history of RHL (AOR = 4.54; 95% CI: 3.46–5.95).

Discussion

In both NHANES III and OHSC dentist-examiners were trained to recognize, classify, and record the clinical characteristics of oral mucosal lesions using procedures based on the World Health Organization's Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases (25). Moreover, the studies were close in time (NHANES III: 1988–1994; OHSC: 1986–1987); and both studies had health interview components, which ascertained individual's age, gender, and race-ethnicity and tobacco history. The large number of children and youth sampled (12 265 in NHANES III and 36 257 in OHSC) make multivariate analysis of each study feasible and the presence in both studies of a common set of variables critical to an epidemiologic analysis of mucosal lesions (i.e. gender, age, race-ethnicity, point and period RAS and RHL prevalence, tobacco history) make comparing the multivariate models a useful means for validation. Although sampling for OHSC was school-based and that for NHANES III was household-based, the major difference between the studies was that the oral examination component of NHANES III was part of an extensive health and nutrition study providing access to covariates not ordinarily available for analysis. For example, suggested associations between RAS and *H. pylori*, deficiencies of folate, vitamins A, B_{12}, C, and income could now be investigated adjusting for suspected covariates.

Analysis of the NHANES III PP data did not support the suggested association between RAS and gender, family income, cigarette smoking or ST use, vitamin deficiency, hematologic factors (ferritin, iron, hemoglobin) or *H. pylori*. Seropositivity for hepatitis C was associated with RAS PP (OR = 12.04; 95% CI: 1.20–120.77) but since only one of the 12 seropositives had RAS, the resulting instability in cell sizes precluded its use in the multivariate analysis. While the data suggest protective effect from ST and cigarettes in NHANES III (Table 1) and OHSC (Table 4), prevalences were low, and standard errors large. Consequently, the bivariate

Table 4 Point and lifetime prevalence of recurrent aphthous stomatitis, children and youth, OHSC

	Point prevalence			*Lifetime prevalence*		
	n	*%*	*95% confidence limits*	*n*	*%*	*95% confidence limits*
Gender	39 206	1.21	0.99–1.42	36 257	40.18[b]	36.06–44.29
Male	19 257	1.23	0.96–1.50	17 810	38.98	34.58–43.35
Female	19 949	1.19	0.96–1.41	18 447	41.45	37.43–45.47
Race/ethnicity	37 073	1.22[c]	1.02–1.42	34 336	40.80[b]	36.72–44.89
Non-Hispanic White	28 070	1.44	1.18–1.70	26 104	43.86	40.10–47.62
Non-Hispanic Black	4765	0.37	0.20–0.54	4358	33.66	20.73–45.99
Mexican-American	4238	1.24	0.85–1.62	3874	33.25	27.65–38.86
Age (years)	39 206	1.21[c]	0.99–1.42	36 257	40.18[b]	36.06–44.29
5–7	8098	0.54	0.34–0.75	6363	31.69	23.74–39.65
8–11	13 523	1.21	0.88–1.53	12 899	41.63	37.26–46.00
12–17	17 585	1.54	1.28–1.80	16 995	42.65	38.77–46.52
RHL history (lifetime)	36 344	1.24	1.01–1.47	36 224	40.11[c]	35.91–44.31
Yes	13 377	1.42	0.94–1.90	13 333	54.79	49.78–59.80
No	22 967	1.13	0.88–1.40	22 891	31.92	28.55–35.28
Cigarette smoking	18 950	1.26	1.51–1.76	18 337	42.69	38.85–46.53
Yes	1123	1.04	0.08–2.00	1082	45.54	40.57–50.52
No	17 827	1.28	1.53–1.79	17 255	42.50	38.56–46.44
Smokeless tobacco use	17 268	1.29[b]	1.55–1.81	16 697	42.74	38.85–46.64
Yes	591	0.57	−0.11 to 1.26	562	46.09	40.68–51.49
No	16 677	1.31	1.58–1.85	16 135	42.64	38.66–46.61

[a]Chi-square test; $P < 0.05$.
[b]Chi-square test; $P < 0.01$.
[c]Chi-square test; $P < 0.001$.
OHSC, Oral Health in USA Schoolchildren; RHL, recurrent herpes labialis.

OR for cigarette smoking in NHANES III (OR = 0.80; 95% CI: 0.10–6.46) was not significantly different from the null and the OR for ST use could not be computed since none of the subjects who used ST had RAS. Similarly, ORs for cigarette smokers (0.67; 0.26–1.74) and ST users (0.36; 0.10–1.24) from the OHSC are not significantly different from the null.

Multivariate models for PP and AP based on NHANES III data were consistent in the inclusion of race-ethnicity and RHL history. RHL was a predictor of RAS PP and AP. Whether this is due to a common pathophysiologic mechanism or an artifact of the study design remains to be seen. Katz and Peretz (16) suggest that to the extent that stress is associated with RAS and RHL PP it may confound the relationship. Moreover, the RAS-RHL association with respect to period prevalence may be due to an individual's conflating the two lesions (16). The AP model contained family income level and a race/ethnicity–RHL interaction. High and middle income individuals had significantly higher odds of RAS AP than subjects with lower incomes. This is in contrast to findings that children of low socioeconomic status groups had more systemic and oral health problems than those in higher socioeconomic status groups (31).

The interaction (effect modification) of RHL and race-ethnicity is not surprising since in the USA, Blacks and Mexican-Americans of all ages have a higher HSV-1 seroprevalence than Whites (32). Furthermore, it is not surprising that more variables were statistically significant in the AP model since 924 of 4657 subjects (19.8%) reported having RAS in the past year and only 185 of 12 265 (1.51%) had a prevalent RAS lesion. The AP model had greater statistical power.

Multivariate models for PP and LP based on OHSC data were different although both models included age group. Race-ethnicity, while significant in the PP model, dropped out of the LP model perhaps due to the effect of RHL lifetime prevalence which may be a partial surrogate for race-ethnicity. In addition, the LP model contained an age group–RHL interaction. As with the NHANES III models, the LP model had more statistical power since 474 of 39 206 subjects (1.21%) had a clinically apparent lesion and 14 568 of 36 257 subjects (40.2%) had a lifetime history of RAS.

When NHANES III is restricted to subjects 5 years of age and older to make it comparable to OHSC, overall PP was higher in NHANES III (1.82%; 1.40–2.28) compared with OHSC (1.20%; 0.99–1.41) as well as for all levels of variables the studies had in common. This 82 percentage point (39%) difference in overall PP is significant at the $\alpha = 0.05$ level since the prevalences for each study fall outside 95% confidence limits of the other.

Multivariate models for PP have only race-ethnicity and age group in common with Whites and Mexican-Americans having greater odds of RAS in both studies. On the contrary, 12-month RHL history was significant in the NHANES III model and age group was significant in the OHSC model. While gender was not significantly associated with RAS PP in both studies and with AP in NHANES III, it was it associated with LP, although the effect was weak. Perhaps females have a lower threshold for noticing small lesions than males. Comparing the NHANES III and OHSC period prevalence models is problematic since the periods are different: annual for NHANES III and lifetime for OHSC. Moreover, since LP is higher than AP, the OSSC model has greater statistical power.

Table 5 Bivariate logistic and multivariate regression models for point and lifetime RAS prevalence (OHSC)

	Point prevalence				*Lifetime prevalence*			
	OR	*95% CL*	*AOR*	*95% CL*	*OR*	*95% CL*	*AOR*	*95% CL*
Gender								
Male	1.00				1.00		1.00	
Female	0.97	0.80–1.20			1.10	1.03–1.20	1.10	1.01–1.19
Race/ethnicity								
Non-Hispanic White	3.97	2.44–6.45	3.90	2.41–6.32	1.56	0.88–2.78		
Mexican-American	3.40	1.88–6.15	3.52	1.94–6.38	1.00	0.54–1.87		
Non-Hispanic Black	1.00		1.00		1.00			
Age (years)								
5–7	1.00		1.00		1.00		1.00	
8–11	2.24	1.49–3.37	2.42	1.61–3.64	1.54	1.16–2.03	2.15	1.79–2.50
12–17	2.87	2.07–3.98	3.03	2.11–4.36	1.60	1.13–2.27	2.53	2.07–3.10
RHL history (lifetime)								
Yes	1.25	0.81–1.94			1.25	0.81–1.94	6.42	4.46–9.24
No	1.00				1.00		1.00	
Cigarette smoking								
Yes	0.67	0.26–1.74			1.13	0.92–1.39		
No	1.00				1.00			
Smokeless tobacco use								
Yes	0.36	0.10–1.24			1.15	0.90–1.47		
No	1.00				1.00			
Age (years)[a] RHL history								
5–7 and no RHL							1.00	
5–7 and RHL							6.42	4.46–9.24
8–11 and RHL							5.60	4.47–7.01
8–11 and no RHL							2.15	1.79–2.50
12–17 and RHL							4.54	3.46–5.95
12–17 and no RHL							2.53	2.07–3.10

RAS, recurrent aphthous stomatitis; OHSC, Oral Health in USA Schoolchildren; AOR, adjusted odds ratio; CL, confidence limit; RHL, recurrent herpes labialis.

Given the similarity of the study designs and their relative contemporaneousness, how does one explain the significant differences in overall and stratum-specific point prevalence? First, it is possible that despite the similarity in diagnostic criteria, the absence of formal calibration on both studies [although the services of an oral pathologist consultant were used in the OHSC (22)] might have introduced bias – although one would expect the bias to be random. Perhaps the NHANES III examiners used conservative criteria; that is not calling an almost-resolved lesion as RAS.

The NHANES III measured both PP and AP. Kleinman et al. (33) suggest that point prevalence measured from cross-sectional surveys understates the true prevalence of recurrent lesions since active lesions may not be present at the time of examination and the use of annual prevalence lessens this problem. While this is undoubtedly true, reported annual prevalence may be subject to recall or reporting bias (34), or subjects may attribute the lesion to an incorrect time period (35). Moreover, they may conflate RAS and RHL lesions, especially since NHANES III subjects were not shown photographs of RHL and RAS.

To explore the relationship between PP (1.51%; 1.17–1.86) and AP (19.84%; 17.31–22.36) in NHANES III, assume that the typical RAS lesion is clinically observable for 10 days. An individual reporting the RAS episode in the past year would have 10 chances in 365 (2.74%) of having the lesion identified at the oral mucosal examination. If all (19.84%) individuals who reported having RAS in the past year (NHANES III) had only one lesion during the year, the projected point prevalence would be $19.84 \times 2.74\%$, or 0.54%. This is outside 95% CI for the NHANES III or OHSC (1.21%; 0.99–1.42) point prevalence. If one takes PP to be the 'gold standard', how can this be explained? The PP imputed from AP is less than half that of NHANES III and OHSC. Further, to the extent that individuals had more than one RAS episode per year, PP would be higher. The hypothesis here is that AP overstates true prevalence.

While both studies measured point prevalence, their measures of period prevalence differed; with NHANES III using AP and OHSC using LP. This makes comparison of the point prevalence results problematic. For example, in OHSC, PP increases from 0.54 (5–7 years) to 1.21 (8–11 years) to 1.54 (12–17 years). Similarly, in NHANES III, PP increases from 0.89 (5–7 years) to 1.63 (8–11 years) to 2.48 (12–17 years). Differences in AP between 8–11 and 12–17 years are not significant (18.14%; 14.52–21.75 and 21.02%; 17.77–24.33). While PP is consistently higher in OHSC, the trends are the same – suggesting that a physiologic mechanism is responsible for higher prevalences in older children. Lifetime prevalence increases with age although the difference between 8–11 (41.63%; 37.26–46.00) and 12–17 years (42.65%; 38.77–46.52) is not significant. This is in apparent conflict with the trends for PP in both studies. The hypothesis here is that LP overstates true prevalence.

While NHANES III and OHSC are large probability samples from a national population, they are not without limitations. They are both cross-sectional and may be used to explore associations, not causation. While the large sample sizes make multivariate analysis possible, the low point prevalence of RAS quickly results in small cell sizes and reduced statistical power as the number of covariates increases. Consequently, associations that are not significant for PP may be for AP and *a fortiori* for LP. While NHANES III measured many laboratory analytes, there was no physiologic measure of stress such as serum cortisol – leaving the RAS–stress relationship for future studies. In addition, the association between RAS and vitamins is only among individuals with clinical deficiencies, population-based samples (even one as large as NHANES III) may not yield enough clinically deficient individuals for a multivariate analysis to have sufficient power.

Because of the similarity in design NHANES III and OHSC should be viewed together – where the multivariate models agree, one can be confident in the association. So, for example, the existence of racial-ethnic differences and the lack of gender differences in RAS PP in both multivariate models can be considered dispositive. Where the multivariate models diverge, for example, with age but the bivariate relationships agree, the difference is likely due to a lack of statistical power.

The literature addressing RAS prevalence among youth and adolescents is limited to bivariate analyses. This paper shows that the results of bivariate analyses should be taken with caution as significant bivariate associations do not always remain in a multivariate model either due to lack of statistical power (in which case the association is unresolved) or confounding (in which case the association is spurious).

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