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Recurrent herpes labialis in US children and youth

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Abstract – *Objectives:* This study reports data from the Third National Health and Nutrition Examination Study, 1988–1994 (NHANES III). *Methods:* NHANES III was a complex, multistage sample of 33 994 civilian, non-institutional individuals from 19 528 households. Dentist examiners were trained to recognize, classify oral mucosal lesions to include recurrent herpes labialis (RHL). Subjects ≥8 years of age were asked if they had cold sores in the past year and serologic tests for herpes virus type 1 (HSV-1) and type 2 (HSV-2) were performed on blood of youth >12 years of age. *Results:* Examinations were performed on 10 032 individuals 2–17 years of age. Overall point prevalence was 1.42% (0.69–2.15); annual prevalence in individuals 8–17 years of age was 14.77% (12.74–16.80); and serologic prevalence of HSV-1 in youth 12–17 years of age was 43.18% (38.88–47.48). When the data were subset to youth 12–17, annual prevalence for seropositives was 24.13% (20.44–27.82) compared with 16.87 (14.16–19.57) for all subjects. Approximately 25% of the seropositive youth had at least one recurrence in the past year. *Conclusion:* As RHL is a recurrent infection, prevalence in a population will be related to the proportion of the population that has been infected with herpes simplex virus. When lesion-specific prevalences are cited in the literature, they should be stratified by covariates known to be associated with them. Future studies should examine RHL prevalence in infected individuals.

Key words: children and adolescents; herpes labialis; herpes simplex virus; NHANES III; oral medicine; oral pathology

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While recurrent herpes labialis (RHL) is a common occurrence in children and youth, estimates of RHL prevalence in this population are rare, and are generally based on atypical or self-selected samples (1, 2). Often, it is not clear whether a reported prevalence is point prevalence (the proportion of subjects presenting with clinically apparent lesions) or period prevalence (1-year, 2-year or lifetime reported disease occurrence).

Recurrent herpes labialis is caused by the activation of a latent infection with herpesvirus type 1 (HSV-1) or type 2 (HSV-2) (3). After the primary infection, the virus lies dormant in the trigeminal ganglia (4) and is often triggered by actinic radiation (5), or other local stimuli such as fever, stress or menstruation (4). Of individuals with a primary infection, 20–40% will have recrudescent infection (6). While HSV-1 generally infects the oral cavity and HSV-2 infects the genitalia, either can appear in the other region (4). Transmission is via direct personal contact between a susceptible individual (one who is seronegative) and an individual who is excreting virus in saliva or other mucocutaneous secretions (e.g. genital or ocular) (7).

In a study of 846 Argentine schoolchildren 4–13 years of age, Crivelli et al. (8) found RHL point prevalence to be 5.2% while De Muñiz et al. (9) found point prevalence of 10.7% among boys 6–13 years of age living in a home for indigent children. In the only national probability sample of oral mucosal lesions of US children and youth in the literature, Kleinman et al. (10) found that the RHL point prevalence among 5–17-year-olds was 0.78%; ranging from 0.36% at age 5 years to 1.06 at age 17 years. Females (0.94%; SE: 0.13) had a significantly higher point prevalence than males (0.63%; SE: 0.12) and RHL was more prevalent in Whites (0.94%; SE: 0.14) than other races (0.25%; SE: 0.09) and in children who did not live in standard metropolitan statistical areas (SMSA) (1.05%; SE:

0.30) compared with those who did (0.70%; SE: 0.11) (10).

Studies of RHL prevalence in adults have been equivocal in identifying risk factors. Higher prevalence in females compared with males has been reported by Reichart (11), Axèll (12) and Shulman et al. (5); however, none of the differences was statistically significant. Furthermore, Diaz-Guzman et al. (13) found RHL prevalence to be higher but not statistically significantly higher (computed from data) in males than females. A study of blood donors found that having a history of recurrent aphthous stomatitis (RAS) (adjusted OR = 1.65; 1.22–2.24), parents or siblings with RHL history (adjusted OR = 2.54; 1.93–3.33), and a tendency for dark suntans as a child (adjusted OR = 1.37; 1.05–1.78) were associated with having a history of RHL (14).

With the availability of the oral mucosal examination data from the Third National Health and Nutrition Survey, 1988–1994 (NHANES III), a nationwide probability sample of US households, RHL point prevalence, annual prevalence, and serologic prevalence and their risk factors can now be described.

Methods

Oral mucosal examinations were performed by dentists using procedures based on the World Health Organization's Guide to Epidemiology and Diagnosis of Oral Mucosal Diseases (15) as part of the NHANES III. The scarcity of representative oral lesions made standard calibration (i.e. examining patients' oral lesions as part of the training session) infeasible, so 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. Examinations were performed using a standard examination and data recording procedure (16). RHL was diagnosed when clusters of vesicles or crusts with duration of less than 3 weeks was present (16). A discussion of the survey methods is presented in Drury et al. (17) and the oral mucosal examination is described in Shulman et al. (1).

From 19 528 randomly selected households, 33 994 subjects 2 months of age and older or their proxies were interviewed, 30 818 were examined in mobile examination centers, and 493 were examined at home. In addition to oral and physical examinations, taking of blood and urine specimens, extensive health, social, and nutritional medical histories were obtained by interviewing the subjects or their parents. Subjects were asked about use of cigarettes, chewing tobacco and snuff in a private setting (20).

This study explores three dimensions of RHL prevalence: point prevalence based on the clinical examination performed on children and youth 2–17 years of age; annual prevalence, based on the response to the question '[Have you] Ever had cold sores in past 12 months?' asked to subjects $\geq$8 years of age. Neither photos nor lesion descriptions were provided to the respondents and responses were based on recall. Serologic prevalence of HSV-1 was based on a test using viral glycoproteins specific for HSV-1 (18). Blood samples were drawn from subjects 4 years of age and older. Serologic tests for HSV-1 were performed on blood samples from subjects 12 years of age and older. As questions about tobacco use were not asked to children younger than 12 years of age, serum cotinine levels (measured on children $\geq$4 years) were used as a proxy for tobacco exposure in these children. Serum cotinine was assayed by isotope dilution-liquid chromatography-tandem mass spectrometry (19). This technique is highly specific and is capable of detecting levels as low as 0.030 ng/mL allowing quantitative measurement of both low levels of tobacco-smoke exposure from environmental tobacco smoke and higher levels of exposure from active smoking (19).

This paper examines the potential association of RHL point and annual prevalence with the following covariates that the literature suggests may be potential risk factors: race-ethnicity (non-Hispanic White, non-Hispanic Black and Mexican-American), gender, age, tobacco exposure, population of county of residence, and income. Income was measured by the poverty income ratio (PIR) that relates family income to the poverty level based on the subject's family size (20). It is computed by dividing the midpoint of the reported family income category by the Census Bureau's poverty threshold for the calendar year the family was interviewed and the age of the family reference person. PIR was categorized as low (0–1.3), middle (1.301–3.50), and high (>3.50). Subjects not falling into the three race-ethnicity categories were excluded from analyses using the race-ethnicity variable resulting in the removal of 487 subjects categorized as 'other' from the some analyses.

As the survey used complex, multistage sampling, SAS-callable SUDAAN 8.0.2 (Research Triangle Institute, Research Triangle Park, NC, USA) was used to compute standard errors for all variables adjusting for the survey design (design effect) as well providing the (weighted) population size to which the prevalence data can be projected. For example, the 10 030 subjects 2–17 years of age who received an oral mucosal examination represent 58 580 750 individuals in the US population (weighted count). Prevalence was based on the projected number of lesions divided by the weighted count rather than the number of individuals with a clinically apparent (or reported) lesion divided by the number of individuals examined.

Prevalence estimates, chi-square and logistic regression results are adjusted for the design effect. Bivariate logistic regressions were performed for RHL point, annual, and serologic prevalence with the previously mentioned covariates. Those with a Wald *F*-statistic having a *P*-value of <0.10 were fitted to a multivariate logistic model using forward selection. Covariates and interactions with $P < 0.05$ were retained in the final models.

Results

Point prevalence

Table 1 shows the number of individuals with RHL lesions, prevalence, 95% confidence interval (CI), bivariate odds ratio (OR), 95% CI, adjusted OR and 95% CI. When adjusted for the design effect, a 1.42% of US children and youth 2–17 years of age had at least one RHL lesion. The prevalence is not significantly greater in males (1.61%) than females (1.22%). Non-Hispanic Whites (1.72%) and Mexican-Americans (1.23%) had higher prevalences than non-Hispanic Blacks (0.57%) and the difference was statistically significant ($P = 0.001$). Individuals living in counties with a population ≥1 million (1.92; 0.48–3.35) had a higher prevalence of RHL than those in counties <1 million (0.97; 0.60–1.34). RHL prevalence was not significantly different among the age groups. Whites and Mexican-Americans had higher odds of having RHL than Blacks (OR = 3.79 and 3.88, respectively). Non-smokers had statistically significantly lower odds of RHL (0.99) but the relationship was distorted by the absence of lesions among the smokers and the

Table 1. Herpes labialis: point prevalence, standard error, 95% confidence interval (CI), bivariate odds ratio (OR), 95% CI, adjusted OR and 95% CI

	n	Prevalence (%)	95% CI	OR	95% CI	Adjusted OR	95% CI
Gender	10 032	1.42	0.69–2.15				
Male	4934	1.61	0.88–2.34	1.32	0.72–2.44		
Female	5098	1.22	0.46–1.98	1.00			
RAS in past year (age ≥ 8)	4574	1.73	0.61–2.85				
Yes	580	3.74	0.40–7.09	3.13	1.35–7.27		
No	3994	1.23	0.45–2.00	1.00			
Race/ethnicity	9545	1.48	0.68–2.28				
Non-Hispanic White	2703	1.72	0.66–2.78	3.05	1.69–5.50	3.30	1.50–7.26
Mexican-American	3498	1.23	0.87–1.59	2.16	1.13–4.11	2.02	0.88–4.61
Non-Hispanic Black	3344	0.57	0.25–0.89	1.00		1.00	
Age (years)	10 032	1.42	0.69–2.15				
2–6	4887	0.69	0.00–1.02[a]	1.00			
7–11	2705	2.29	0.41–4.17	2.48	0.80–7.73		
12–17	2440	1.30	0.35–2.25	1.38	0.58–3.33		
Current cigarette smoking (age ≥ 8 years)	4608	1.72	0.61–2.82				
Yes	58	0.00	0.00–0.00	0.99	0.98–0.99		
No	4550	1.80	0.64–2.96	1.00			
Serum cotinine (ng/mL) (age ≥ 4 years)	6104	1.64	0.66–2.62				
<3	5514	1.83	0.71–2.94	5.78	1.24–26.95	6.06	1.24–29.71
≥3	590	0.32	0.00–0.65[a]	1.00		1.00	
Poverty income ratio	10 032	1.42	0.69–2.15				
Low	4652	1.66	0.80–2.51	1.33	0.55–3.24		
Middle	3608	1.36	0.51–2.20	1.09	0.39–3.04		
High	1772	1.25	0.00–2.52[a]	1.00			
Location	10 032	1.42	0.69–2.15				
≥1 million population	5050	1.92	0.48–3.35	2.00	0.85–4.66		
<1 million population	4982	0.97	0.60–1.34	1.00			

[a]Negative lower limit truncated to zero.

effect was *de minimis*. Subjects with serum cotinine levels <3 ng/mL had more than five times the odds (OR = 5.78; 1.24–26.95) of RHL than those with cotinine levels of ≥3 ng/mL. Smokeless tobacco use was not analyzed as only 15 subjects reported using smokeless tobacco. Only race-ethnicity and cotinine were retained in the multivariate model with their ORs not changing materially.

Annual prevalence

Table 2 shows the number of individuals who reported having cold sores, the annual prevalence, 95% CI, bivariate OR, 95% CI, adjusted OR and 95% CI. When adjusted for the design effect, a 14.77% of US children and youth 2–17 years of age reported having at least one RHL episode in the past year. The prevalence was not significantly greater in males (14.46%) than females (15.10%). Non-Hispanic Whites (16.93%) and Mexican-Americans (11.87%) had significantly higher prevalence than Blacks (7.94%) and the difference was statistically significant ($P = .001$). RHL prevalence was significantly higher (16.87%; 14.17–19.57) in 12–17-year-olds than those 8–11 years of age (11.75%; 9.40–14.10). Low-income individuals had significantly higher RHL prevalence (17.04%; 13.37–20.71) than middle (15.97%, 13.01–18.93), or higher income levels (10.77; 8.56–12.98). Whites and Mexican-Americans had higher odds of having RHL than Blacks (OR = 2.36 and 1.56, respectively); subjects with serum cotinine levels <3 ng/ml had greater odds (OR = 1.62; 1.11–2.37) of RHL than those with cotinine levels of ≥3 ng/mL; and low (OR = 1.75; 1.19–2.56) and middle (OR = 1.67; 1.24–2.26) had higher odds of RHL than individuals with higher incomes. The association between cigarette smoking and RHL was not statistically significant. Race-ethnicity, cotinine level, and poverty level remained in the multivariate model. A history of RAS within the past year was associated with a

Table 2. Herpes labialis: annual prevalence, standard error, 95% confidence interval (CI), bivariate odds ratio (OR), adjusted OR and 95% CI

	n	Prevalence (%)	95% CI	OR	95% CI	Adjusted OR	95% CI
Gender	4580	14.77	12.74–16.80				
Male	2240	14.46	11.95–16.96	0.95	0.73–1.24		
Female	2340	15.10	12.37–17.82	1.00			
RAS in past year	4569	14.67	12.56–16.71				
Yes	580	29.71	22.84–36.58	3.45	2.41–4.93	6.38	3.05–13.31
No	3989	10.92	9.29–12.56	1.00		1.00	
Race/ethnicity	4368	14.94	12.71–17.17				
Non-Hispanic White	1192	16.93	13.85–20.01	2.36	1.66–3.37	2.36	1.62–3.43
Mexican-American	1577	11.87	9.87–13.87	1.56	1.14–2.13	1.18	0.83–1.68
Non-Hispanic Black	1599	7.94	6.22–9.66	1.00		1.00	
Age (years)	4580	14.77	12.73–16.81				
8–11	2149	11.75	9.40–14.10	1.00		1.00	
12–17	2431	16.87	14.17–19.57	1.52	1.15–2.01	1.58	1.18–2.10
Current cigarette smoking	4580	14.76	12.74–16.80				
Yes	570	15.93	8.05–23.83	1.10	0.58–2.08		
No	4010	14.71	12.60–16.82	1.00			
Serum cotinine (ng/ml)	4020	15.06	12.88–17.24				
<3	3620	14.15	11.97–16.33	1.00			
≥3	400	21.05	15.19–26.91	1.62	1.11–2.37		
Poverty income ratio	4368	14.94	12.71–17.17				
Low	1961	17.04	13.37–20.71	1.75	1.19–2.56	2.70	1.81–4.02
Middle	1627	15.97	13.01–18.93	1.67	1.24–2.26	1.67	1.20–2.31
High	780	10.77	8.56–12.98	1.00		1.00	
Location	4368	14.94	12.71–17.17				
≥1 million population	2055	13.28	10.82–15.74	0.79	0.57–1.08		
<1 million population	2313	16.31	12.79–19.84	1.00			
Race-ethnicity × RAS history							
Black and no RAS						1.00	
Black and RAS						6.37	3.05–13.31
White and no RAS						2.36	1.62–3.43
White and RAS						7.63	2.65–22.01
Mexican-American and no RAS						1.18	0.83–1.68
Mexican-American and RAS						9.53	3.02–30.07

sixfold increase in odds of RHL for non-Hispanic Blacks, a greater than twofold increase for non-Hispanic Whites, and an eightfold increase for Mexican-Americans.

Serologic prevalence

Table 3 shows the prevalence of HSV-1 seropositivity in youth 12–17 years of age. Females have higher seroprevalence (45.62%) than males (41.01%) although the difference is not statistically significant. Mexican-Americans have the highest seropositivity (66.61%; 60.80–72.40) compared with non-Hispanic Blacks (54.23%; 48.27–60.19), and non-Hispanic Whites (35.04%; 30.58–39.50). Non-Hispanic Blacks had more than twice the odds of being seropositive than whites (OR = 2.20; 1.64–2.95) and Mexican-Americans had more than 50% higher odds (OR = 3.70; 2.69–5.09) of being seropositive than Blacks. Low-income individuals had almost three times the odds of being HSV-1 positive (OR = 3.24; 1.92–5.47) than higher income individuals. The only variables remaining in the multivariate model were race-ethnicity and poverty level.

Table 4 compares point and annual prevalence estimates of HSV-1 positive individuals to those of all individuals. The analysis is restricted to youth ≥12 years of age as serologic testing was not performed for younger individuals. Approximately 25% of the seropositive youth had at least one recurrence in the past year.

Discussion

Race-ethnicity was a risk factor for RHL point prevalence, annual prevalence, and HSV-1 seroprevalence. The effect of race-ethnicity was not explained by income differences among members of these groups, because the difference in risk remained even after they were taken into account. This is consistent with the findings of Kleinman et al. (10). Mexican-Americans had the highest seroprevalence but not the lowest point prevalence which is not surprising as HSV-1 infection and activation have separate mechanisms. In a study of reported RHL prevalence among Israeli soldiers, Katz et al. (21) found that prolonged exposure to sunlight was associated with RHL reactivation. Spruance et al. (22) showed that RHL can be induced experimentally in volunteers who are susceptible to ultraviolet radiation. A similar finding was made by Shulman et al. (5) who studied soldiers participating in a multiweek desert exercise who found that those with light complexions had 2.5 times greater odds of RHL than soldiers with dark complexions.

Table 3. HSV-1: seropositivity, standard error, 95% confidence interval (CI), bivariate odds ratio (OR), adjusted OR and 95% CI, US youth 12–17 years of age

	n	Prevalence (%)	95% CI	OR	95% CI	Adjusted OR	95% CI
Gender	1795	43.18	38.88–47.48				
Male	859	41.01	35.94–46.06	0.83	0.65–1.05		
Female	936	45.62	40.34–50.89	1.00			
Race/ethnicity	1708	41.39	37.60–41.18				
Non-Hispanic White	448	35.04	30.58–39.50	1.00		1.00	
Mexican-American	653	66.61	60.80–72.40	3.70	2.69–5.09	2.96	2.15–4.06
Non-Hispanic Black	607	54.23	48.27–60.19	2.20	1.64–2.95	1.75	1.30–2.35
Age (years)	1795	43.18	38.78–47.48				
12–14	899	40.47	34.84–43.35	1.00			
15–17	896	45.85	40.10–51.60	1.25	0.91–1.70		
Current cigarette smoking	1795	43.17	38.88–47.48				
Yes	982	54.47	40.20–68.75	1.64	0.92–2.90		
No	813	42.21	38.00–46.43	1.00			
Serum cotinine (ng/mL)	1773	42.84	38.53–47.15				
<3	1516	40.66	35.74–45.58	1.00			
≥3	257	51.88	41.51–62.25	1.57	0.97–2.56		
Poverty income ratio	1795	43.18	38.88–47.48				
Low	778	60.32	53.00–67.64	3.24	1.92–5.47	2.35	1.36–4.06
Middle	687	39.35	34.15–44.56	1.38	0.87–2.20	1.23	0.76–2.00
High	330	31.92	23.62–40.22	1.00		1.00	
Location	1795	43.18	38.89–47.48				
≥1 million population	858	40.79	34.15–47.43	0.82	0.57–1.18		
<1 million population	937	45.53	40.03–51.01	1.00			

Table 4. Point and annual RHL prevalence in all youth 12–17 years of age compared with those who are HSV-1 seropositive

	Point prevalence				Annual prevalence			
	All subjects		HSV-1 seropositive		All subjects		HSV-1 seropositive	
	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Gender	1.30	0.35–2.25	1.28	0.21–2.34	16.87	14.16–19.57	24.13	20.44–27.82
Male	1.93	0.16–3.71	1.36	0.00–3.16[a]	17.71	14.59–20.83	26.31	21.04–31.58
Female	0.63	0.19–1.06	1.20	0.03–2.29	15.97	11.74–20.21	21.93	16.94–26.92
Race/ethnicity	1.23	0.26–2.21	1.43	0.23–2.64	17.22	14.42–20.01	25.76	21.59–29.32
Non-Hispanic White	1.23	0.00–2.59[a]	1.31	0.00–3.22[a]	19.52	15.79–23.25	33.38	27.18–39.58
Mexican-American	1.29	0.04–1.07	0.73	0.00–1.77[a]	9.17	6.86–11.48	11.41	8.17–14.65
Non-Hispanic Black	0.55	1.21–2.87	2.99	1.75–4.22	13.66	10.45–16.87	16.26	11.66–20.85
Age (years)	1.30	0.35–2.25	1.28	0.22–2.34	16.87	14.16–19.57	24.13	20.44–27.82
12–14	1.75	0.04–3.47	1.13	0.01–2.33	15.77	12.21–19.33	21.48	16.60–26.35
15–17	0.83	0.08–1.58	1.41	0.00–3.13[a]	18.01	14.22–21.80	26.45	19.44–33.45
Current cigarette smoking	1.72	0.61–2.82	1.28	0.22–2.34	14.76	12.74–16.80	24.13	20.44–27.82
Yes	0.00	0.00–0.00	0.00	0.00–0.00	15.93	8.05–23.83	30.24	14.54–45.94
No	1.80	0.64–2.96	1.42	0.26–2.58	14.71	12.60–16.82	23.45	19.30–27.60
Serum cotinine (ng/mL)	1.43	0.38–2.48	1.30	0.23–2.37	16.96	14.03–19.89	24.31	20.63–27.99
<3	1.68	0.40–2.37	1.64	0.24–3.04	15.94	12.65–19.23	21.56	17.13–25.99
>3	0.35	0.08–0.92	0.20	0.00–0.60[a]	21.30	15.09–27.51	33.26	22.41–44.11
Poverty income ratio	1.30	0.35–2.25	1.28	0.22–2.35	16.87	14.16–19.57	24.13	20.44–27.82
Low	0.81	0.32–1.30	1.02	0.37–1.96	17.68	12.94–22.43	20.72	14.51–26.94
Middle	1.70	0.00–1.30[a]	1.32	0.00–3.44[a]	19.19	15.31–23.08	27.12	21.42–32.83
High	1.09	0.00–2.54[a]	1.72	0.00–1.97[a]	11.87	8.83–14.92	24.43	14.59–34.26
Location	1.30	0.35–2.25	1.28	0.22–2.18	16.87	14.16–19.57	24.13	20.44–27.82
≥1 million population	1.89	0.04–3.68	1.82	0.00–3.39[a]	15.79	13.01–18.57	21.49	16.70–26.28
<1 million population	0.78	0.21–1.35	0.81	0.39–1.23	17.82	13.44–22.19	26.45	21.23–31.68

[a]Negative lower limit rounded to zero.

Gender was not associated with point, annual or serologic prevalence. This conflicts with the findings of Kleinman et al. (10) who found that females 5–17 years of age had higher point prevalence than males. Among the possible explanations for this difference are variations in the proportions of males and females who are seropositive in the two studies and statistical variation as point prevalences were low and standard errors were relatively large.

Recurrent herpes labialis point prevalence was higher in individuals living in counties with a population ≥1 million than those in counties <1 million. However, this variable did not remain in the multivariate model. This conflicts with Kleinman et al. (10) who found that individuals living in SMSA had lower RHL point prevalence than those living in SMSAs.

Individuals with serum cotinine levels <3 ng/mL had more than six times higher odds of having a herpetic lesion (OR = 6.06; 1.24–29.71) than individuals with cotinine levels ≥3 ng/ml (Table 1), adjusting for the effects of race-ethnicity. This relationship was not present in the multivariate models for annual prevalence or serologic prevalence. In fact, the bivariate logistic regression model (Table 2) shows that individuals with cotinine levels ≥3 ng/ml had odds of having had an herpetic lesion 1.67 in the past 12 months than individuals with serum cotinine levels <3 ng/ml although the cotinine level did meet the $\alpha = 0.05$ retention criterion. Perhaps components of tobacco exert a protective effect on reactivation similar to that hypothesized for RAS (23).

While the association between poverty level and RHL point prevalence was not statistically significant, low-income individuals had higher annual prevalence and seroprevalence than those of high or middle income. To see if the higher annual prevalence was a function of higher underlying infection rates of low-income individuals, the multivariate model shown in Table 2 was rerun excluding individuals who were seronegative. The resulting model for seropositive individuals showed race-ethnicity to be the only significant variable, with non-Hispanic Whites having more than four times the odds (OR = 4.05; 2.44–6.69) of having had an herpetic lesion in the past year than non-Hispanic Blacks. This strongly suggests that much of the reported difference in RHL prevalence

was confounded by failing to control for seropositivity.

As the NHANES III survey collected data for point and annual prevalence, it is instructive to compare the two measures. Kleinman et al. (10) suggest that point prevalence measured from cross-sectional surveys understates the true prevalence of recurrent lesions such as RHL as active lesions may not be present at the time of examination and the use of annual prevalence lessens this problem. However, reported annual prevalence may be subject to recall bias; a form of differential misclassification bias in which risk estimates may be biased toward or away from the null (24); or reporting bias – respondents may have trouble remembering whether they had a lesion in the past year or may assign the lesions to incorrect time periods (25). Moreover, they may confuse cold sores with another orofacial lesion.

Aside from the predictable difference in magnitude of point prevalence and reported annual prevalence, bivariate ORs for gender and location were not significantly different from the null while race-ethnicity, RAS in the past year, and serum cotinine were. However, bivariate ORs for age and PIR were significantly different from the null for annual prevalence but not for point prevalence. Multivariate models differed in that while both contained race-ethnicity and serum cotinine, the annual prevalence model contained age, PIR, RAS, and the interaction between race-ethnicity and RAS.

Recurrent herpes labialis point prevalence for youths 12–17 years of age was 1.30% (0.35–2.25) while annual prevalence was 16.87% (14.16–19.57) (Table 4). If the typical herpetic lesion is clinically observable for 10 days, an individual reporting an RHL episode in the past year would have 10 chances in 365, or a 2.74% chance of having the lesion identified at the oral mucosal examination. If all 16.87% had only one lesion during the year, the projected point prevalence would be 16.87×2.74, or 0.46%; within the 95% CI for point prevalence. To the extent that individuals had more than one episode per year, the projected prevalence would be higher.

As the number of prevalent lesions was small (only two subjects with a prevalent lesion had a serum cotinine level $\geq$3 ng/mL), the inherent instability in cell size substantially reduced the statistical power of the analysis. This may explain why the demographic findings from the point and period prevalence analyses sometimes disagree in this and other studies. While the question of which of the two prevalence measures is superior is beyond the scope of this paper, there is an analytical advantage to using annual prevalence as the standard errors are smaller, with 95% CI more than 100% of the point prevalence but in the 30–40% range for annual prevalence. The result is greater statistical power.

This paper presented prevalence data from a national probability sample that employed trained dentist examiners using standard criteria for defining RHL. While there was no calibration (as there was with the DMF component of NHANES III), experienced dentists using the same diagnostic criteria should be reasonably consistent in identifying RHL. As RHL is a recurrent infection, prevalence in a population will be related to the proportion of the population that has been infected with herpes simplex virus. So, for example, our finding that RHL is more prevalent in males than females would be spurious if males had a higher infection rate. Future studies should examine RHL prevalence in infected individuals.

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