Psychological Stress and Other Potential Triggers for Recurrences of Herpes Simplex Virus Eye Infections

Herpetic Eye Disease Study Group

Objectlve: To assess psychological stress and other factors as possible triggers of ocular herpes simplex virus (HSY) recurrences.

Design: A prospective cohort study nested in a randomized, placebo-controlled, clinical trial.

Setting: Fifty-eight community-based or university sites.

Participants: lmmunocompetent adults (N = 308), aged 18 years or older, with a documented history of ocular HSY disease in the prior year and observed for up to 15 months.

Exposure Varlables: Psychological stress, systemic infection, sunlight exposure, menstrual period, contact lens wear, and eye injury recorded on a weekly log. The exposure period was considered to be the week before symptomatic onset of a recurrence.

Main Outcome Measure: The first documented recurrence of ocular HSY disease, with exclusion of cases in which the exposure week log was completed late after the onset of symptoms.

Results: Thirty-three participants experienced a study outcome meeting these criteria. Higher levels of psychological stress were not associated with an increased risk of recurrence (rate ratio, 0.58; 95% confidence interval, 0.32-1.05; P=.07). No association was found between any of the other exposure variables and recurrence. When an analysis was performed including only the recurrences (n=26) for which the exposure week log was completed late and after symptom onset, there was a clear indication of retrospective overreporting of high stress (P = .03) and systemic infection (P= .01). Not excluding these cases could have produced incorrect conclusions due to recall bias.

Concluslons: Psychological stress does not appear to be a trigger of recurrences of ocular HSY disease. If not accounted for, recall bias can substantially overestimate the importance of factors that do not have a causal association with HSY infection.

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HERPESSIMPLEXvirus (HSY) is a leading cause of eye infections and visual loss.[1,2] An important contributor to visual loss from HSY infection is its recurring nature. Several factors have been suggested as potential triggers of recurrent ocular, orofacial, or genital HSY disease, including upper respiratory tract infection,[3,4] fever,[5,6] sunlight,[7,8] seasonal conditions,[3,9-11] emotional factors,[12-15] psychological stress,[14,16-19] trauma,[20] and menstruation.[21] However, results from these studies have been inconsistent, and only a few studies have assessed ocular HSY recurrences.

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In a randomized, placebo-controlled, clinical trial, we found that 12 months of oral acyclovir therapy was beneficial in reducing the incidence of ocular HSY recurrences in participants with a recent history of active ocular HSY disease. In both treatment groups, the number of prior episodes of HSY eye disease was the only baseline or historical factor that was a strong predictor of a recurrence.[22] Herein, we report the results of a prospective cohort study, nested within this clinical trial, that assessed psychological stress and other factors as possible triggers of recurrent HSY eye disease.

A complete list of the members of the Herpetic Eye Disease Study Group appears in a box on page 1624. None of the authors has a proprietary interest in any of the drugs used in this study.

RESULTS

COHORT DESCRIPTION

All 308 participants had experienced at least 1 prior ocular HSY disease episode (as per eligibility requirements); 50% had experienced 3 or more episodes (Table I). When compared with the 229 patients in

PARTICIPANTS AND METHODS

An institutional review board approved the study protocol and informed consent forms for each site, and an independent Data Safety and Monitoring Committee provided study oversight.

PARTICIPANTS

To be eligible for the treatment trial, a participant must have experienced active HSY eye disease within the previous 12 months that was inactive and untreated for at least 30 days before trial enrollment. In the treatment trial, participants received either oral acyclovir or placebo for 12 months and then were observed for 6 months while not receiving treatment.[22]

Additional eligibility criteria for this recurrence factors study cohort included the following: (1) age 18 years or older, (2) 10th grade or greater educational level, and (3) ability to read and write English. Eligible participants were asked to enroll in the recurrence factors study by the end of the first month of the treatment trial but could be enrolled as late as 9 months into the trial. The median time from enrollment into the treatment trial to enrollment in the recurrence factors study was 3 weeks (25th percentile, 10 days; and 75th percentile, 4 weeks). Data collection for the recurrence factors study ended when the participant had completed 15 months of the treatment trial.

Fifty-eight of the 74 clinical sites involved in the treatment trial participated in the recurrence factors study. At these sites, among the 565 participants enrolled in the treatment trial who were also eligible for the recurrence factors study, 336 (60%) agreed to participate. Participants were excluded from analysis if they developed active HSY eye disease either before enrollment into the recurrence factors study (n = 7) or shortly after study enrollment such that either a symptom-onset date could not be determined or a weekly log for the exposure week was not available (n = 5). Also excluded were 15 participants who completed baseline information only and dropped out before submitting any subsequent logs and 1 participant who was subsequently deemed to be ineligible for the treatment trial. These exclusions left a sample of 308 for analysis. Among the 308 patients, 155 were in the acyclovir group and 153 were in the placebo group.

BASELINE DATA COLLECTION

In addition to the data available from the treatment trial, data were obtained on occupation, income, living situation, and the psychological constructs of negative affectivity and social desirability. *Negative affectivity,* defined as the disposition to experience aversive emotional states,[23] was assessed by use of a 20-item version of the Taylor Manifest Anxiety Scale. This instrument has been shown to correlate highly with the full Taylor Manifest Anxiety Scale (Pearson r = 0.91) and to exhibit adequate reliability (Cronbach α = .76).[24] Social desirability was assessed with a 20-item version of the Marlowe-Crowne Social Desirability Scale, which taps defensiveness and the tendency to show a positively biased self-image.[25,26] The short form has shown adequate reliability (Pearson r = 0.73-0.87).[27]

WEEKLY DATA COLLECTION

Participants completed a log at home once a week (for most participants, each Sunday) on which they reported experiences during the prior 7 days. This included rating their psychological stress and reporting on illnesses, sun exposure, contact lens wear, eye injury, and the onset of a menstrual period. The "weekly logs" were mailed directly to the Data Coordinating Center.

Logs were considered valid only if they were completed no more than 2 days before and no more than 6 days after the end of the log week. In addition, for logs completed for the exposure week of participants with a recurrence (as defined later), the log was considered invalid if the completion date was on or after the date of onset of symptoms of a confirmed recurrence. Only data from logs deemed to be valid were included in the primary analysis.

Psychological Stress

The weekly log included 3 measures of stress: a global stress rating scale, an open-ended question about chronic stress (asking participants to describe situations that had been stressful for ≥2 weeks), and the Life Arenas Stress Measure. Our primary stress measure was the global stress rating scale, which consisted of a single question: "Overall, how stressed have you felt this past week?," with a 1 to 7 Likert-type rating scale for responses. For the primary analysis, we collapsed these 7 levels into 3 levels according to the response labels "not at all," which appeared above 1 to 2; "moderately," which appeared above 3 to 5; and "extremely," which appeared above 6 to 7. An average stress level across the study was calculated from the global stress rating across all logs for participants submitting at least 5 valid logs (excluding the exposure week for participants with a recurrence). The presence of chronic stress was assessed in analyses as a weekly indicator variable.

The Life Arenas Stress Measure consisted of a similar 7-point scale on which participants rated stressfulness in 11 areas of daily life: health; financial; home situation; personal goals; relationships outside the home; and if applicable, relationships inside the home; problems with friends and family; school-related stress; work-related stress; unemployment-related stress; and retirement-related stress. The Life Arenas Stress Measure was assessed previously for construct validity, via a correlation with a global measure of stress (r = 0.56), and convergent validity, as indicated by hypothesized positive correlations between specific life arena stress scores and corresponding stress arena scores derived from log-based stressor descriptions and ratings (F. C., unpublished data, November 1996). Two variables derived from the Life Arenas Stress Measure were used in secondary analyses: the sum of the first 5 life arenas previously listed plus the work-related arena (life arenas sum) and the maximum rating among all 11 life arenas (maximum stress). These 2 measures derived from the Life Arenas Stress Measure were highly correlated with the global stress rating scale (Spearman rank correlation coefficient [r,] = 0.84 and 0.89, respectively), and were also highly correlated with each other (r, = 0.85).

the treatment trial who were eligible for but did not enroll in the recurrence factors study, the 308 participants were more likely to be white (85% vs 71%; P<.001), but were similar in sex, age, and number of past episodes of HSY eye disease. The baseline characteristics of the 238 participants enrolled within 4 weeks of enrollment into the treatment trial were similar to those of the 70 participants enrolled later.

Other Variables

Self-reported symptoms suggestive of an infectious s$_{y\ n}$drome were assessed by a checklist and an "other illness" write-in response (to be referred to as "systemic illness"). Illness was considered to have been present when one of the following was checked as being present-cold or respiratory tract infection; stomach flu, vomiting, or diarrhea; or fever--or when participants wrote in names of illnesses suggestive of a systemic bacterial or viral infection (eg, hepatitis or pneumonia).

Unprotected sunlight exposure was assessed by the participant's response to the question, "In the past week, approximately how many total hours did you spend outdoors unprotected by a brimmed hat or other protective clothing?" Respondents selected from one of the following categories: 0 to 7, 8 to 14, 15 to 21, 22 to 28, or 29 or more hours. For analysis, the 5 categories were collapsed into 2: 0 to 21 and 22 or more hours.

Participants also were queried on each weekly log via yes/no questions as to: (1) the occurrence of an eye injury; (2) the use of contact lenses; and (3) for premenopausal women, whether the menstrual period began in the last 7 days. The menstrual cycle analysis included only the 64 women younger than 50 years reporting at least 1 menstrual cycle during follow-up.

OUTCOME

The study outcome was defined as the first recurrence of active HSV eye disease in any form (blepharitis, conjunctivitis, epithelial keratitis, stromal keratitis, and/or iridocyclitis) confirmed on examination by a certified study ophthalmologist using slitlamp biomicroscopy. Clinical examinations were performed after treatment trial months 1, 3, 6, 9, 12, 13, and 15 and at additional times when a participant reported new ocular symptoms. Recurrences were dated at the onset of participant symptoms, as described later. For the primary analysis, only recurrences associated with a valid exposure week log were included.

EXPOSURE PERIOD

The symptom-onset date was determined from the earliest symptom onset reported on a valid weekly log from the 4 weeks before the examination documenting the recurrence, from the study examination form, or from medical records completed on the date of the examination. When different symptom-onset dates were recorded on a valid weekly log and the examination form, the date recorded on the weekly log was used. For participants without symptom-onset data from any of these sources, symptom onset was imputed to be 7 days before the documented recurrence. This imputation was based on the data available for the 59 participants with a documented recurrence who had a recorded symptom-onset date (45 [76%] had the onset of symptoms in the prior week).

The exposure period for assessment of each time-dependent variable was considered to be the week before symptom onset. Because exposure data were gathered weekly, the exposure period consisted of a 7-day period that varied in relationship to the date of symptom onset according to the day of the week on which symptoms first developed. The exposure period thus ranged from the period 1 to 7 days before symptom onset (eg, weekly log completed on Sunday and symptom onset occurred the next day on Monday) to the period 7 to 13 days before symptom onset (eg, weekly log completed on Sunday and symptom onset occurred on the following Sunday).

STATISTICAL ANALYSIS

Comparisons between eligible nonenrolled participants and enrolled participants and between participants who completed follow-up and those who did not were made using *t* tests, Wilcoxon rank sum tests, or X^2 tests as appropriate. Correlations between the different psychological stress measures were made using r_s, treating follow-up weeks as independent observations.

A discrete-time proportional hazards model[28] fit by pooled logistic regression[29] was used to assess the relationship between the exposure variables and an ocular HSV recurrence. The weekly measure of global psychological stress was specified as a time-dependent covariate. A change in psychological stress was modeled by evaluating the weekly global stress while controlling for the participant's average stress across the study, thereby making a within-person assessment. Data for participants with incomplete follow-up were censored after the last weekly log received, and data for participants with invalid recurrences (because of an invalid exposure week log, see previous information) were censored at the beginning of the exposure week (the week that preceded the recurrence).

The global stress variable was first assessed in a univariate model and then in models adjusting for treatment group, self-reported illness, demographics, and other relevant baseline variables. The univariate and full models are reported; 95% confidence intervals were computed for all measures. Models including subsets of the covariates produced similar results. Effect modification (interaction terms with an associated $P < .10$ retained for further screening) and confounding (a change in the effect estimate b y > 10%[30]) were assessed. There was no evidence of interaction between the global stress variable and treatment group. Linear and curvilinear effects were assessed by use of continuous variables and pol$_{y\ n}$omial effects, respectively.

Available-case and complete-case methods of analysis with missing data were used for the univariate and multivariable analyses, respectively.[31,32] No appreciable differences were observed when analysis was restricted to participants with 80% or more weekly log completion.

The chronic stress indicator variable, other exposure variables (systemic infection, sunlight exposure, contact lens use, and the onset of menses), and fixed trait characteristics (negative affectivity and social desirability) were assessed in similar discrete-time proportional hazards models as previously described.

A case-crossover analysis[33] also was performed. In the case-crossover analysis, in which data were limited to the 33 participants with a valid recurrence, each participant

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The baseline global stress scores were positively correlated with the measure of negative affectivity (r_5 0.40, $P<.001$) and inversely correlated with the measure of social desirability (r_5 -0.19, P .002). The baseline scores were slightly higher than the scores from the follow-up logs (3.4± 1.8 vs 3.0± 1.6; $P<.001$) (Table 2). A participant's weekly stress scores were strongly correlated with the participant's average stress for all weeks (r_5 0.81,

becomes a separate stratum in a discrete-time proportional hazards model, and the participant's mean stress level in the control period (the period before the exposure period) is compared with the participant's stress in the *exposure* period (the week before symptom onset). Thus, the method assesses a within-person change in stress, while removing any possibility of between-person confounding.

Analyses were replicated using only recurrences with invalid exposure week logs (completed late after symptom onset). For this analysis, data from participants with valid recurrences were censored at the beginning of the exposure week log.

Analyses were performed using statistical software.34 All P values are 2-sided. Data are given as mean± SD unless otherwise indicated.

The sample size for the recurrence factors study was a function of the treatment trial sample size. We estimated that there was 80% power (assuming a 2-sided type I error rate of .05) to detect a rate ratio of recurrence of 2 or greater for moderate or high stress exposure (levels 3-7) compared with low stress (levels 1-2) and 99% power to detect a rate ratio of 2.5 or greater. This was based on an estimated recurrence rate of 14% related to low stress exposure.

P<.001). The reporting on a weekly log of a chronic (≥2 weeks) stressful situation was associated with a higher global stress score (4.0± 1.5 vs 2.4± 1.4; P<.001).

COMPLETENESS OF FOLLOW-UP

The study was *completed* (defined as the development of documented active HSV eye disease or completion of the 15-month follow-up period) by 223 (72%) of the 308 participants (Figure). For 16 of the 85 "noncompleters," early termination was related to termination from the treatment trial, and for the other 69, termination was related to the participant's decision to stop completing the weekly logs. The median length of study completion for the noncompleters was 22 weeks (25th percentile, 8 weeks; and 75th percentile, 47 weeks). The 223 "completers" were older (52± 15 vs 44± 16 years; P<.001) and more likely to be retired (30% vs 14%; P=.009) than the 85 noncompleters.

The log completion rate was 93% (10459 of 11213 possible logs) for the 223 completers and 78% (1777 of 2276 possible logs before termination) for the 85 noncompleters. Of the submitted logs, 10% were considered invalid (ie, completed > 2 days before or > 6 days after the end of the log week) for the completers and 16% for the noncompleters.

RECURRENCES OF OCULAR HSV DISEASE

A documented recurrence of ocular HSV disease developed in 67 (22%) of the 308 participants. Two of the 67 participants did not submit a log for the *exposure week* (the week before symptom onset). Among the other 65 participants with a recurrence, the exposure week log was considered invalid for 30 (completed late, after symptom onset, in 26 cases and completed > 2 days early in 4). For the remaining 35 participants with a recurrence whose exposure week log was valid, the symptom-onset date was determined from the weekly logs for 10, from the ocular examination form for 18, and by imputation (see the "Exposure Period" subsection of the "Participants and Methods" section) for 7. Two participants with valid exposure week logs were missing the global stress score, which reduced the effective number of valid recurrences to 33 in the analyses of the global stress variable.

Table 1. Characteristics of the 308 Participants*

Characteristic	% of Participants†
Female sex	48
Age, mean (SD), y	49 (16)
Ethnicity	
White	85
African American	7
Hispanic	6
Asian	2
Income,$	
<10000	7
10 000-24 999	18
25 000-49 999	29
>49999	46
Occupation	
Professional	45
Nonprofessional	19
Retired	27
Other‡	10
Taylor Manifest Anxiety Scale score, mean (SD)§	6.4 (4.2)
Marlowe-Crowne Social Desirability Scale score, mean (SD)‖	12.7 (3.7)
Living situation	
Alone	19
Spouse or partner	39
Spouse or partner and children	28
Children and no spouse or partner	5
Other relatives	3
Roommate(s)	3
Other	2
No. of past episodes of HSV eye disease, median (quartiles)	3 (1, 5)
Time from the last ocular HSV episode to the first weekly log, median (quartiles), wk	23 (13, 44)

**There were missing data for income (n = 59), occupation (n = 37), the Taylor Manifest Anxiety Scale (n = 6), the Marlowe-Crowne Social Desirability Scale (n = 6), and living situation (n = 42). HSV indicates herpes simplex virus.*

† Unless otherwise indicated. Percentages may not total 100 because of rounding.

‡ Including student, homemaker, and unemployed.

§ A higher score represents higher anxiety (norm, 5.9).35

‖ A higher score represents higher social desirability (norm, 9.1; SD, 3.9).36

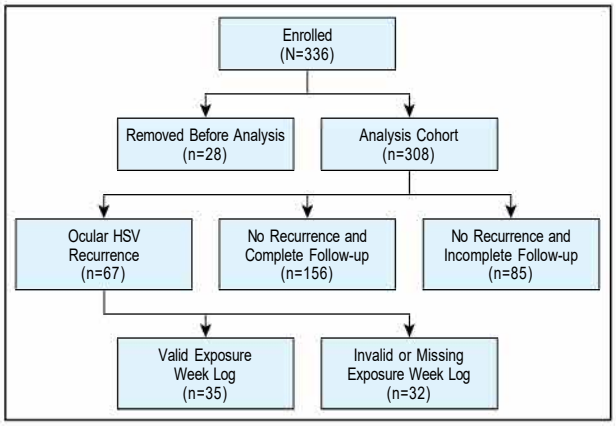
ASSOCIATION OF PSYCHOLOGICAL STRESS AND OCULAR HSV RECURRENCE

High global stress (when evaluated as a 3-level continuous variable) was not associated with an increased risk of recurrence in the discrete-time proportional hazards model. Covariate adjustment provided no meaningful difference in the estimate of this association (Table 3). Similar re-

Table 2. Baseline and Follow-up Global Stress Ratings*

Global Stress Score	No. (%) of Participants		
	Baseline Rating (n = 285)	Follow-up Ratings (n = 9939)	Exposure Week Ratings (n = 33)
1	50 (18)	2337 (24)	8 (24)
2	54 (19)	1964 (20)	10 (30)
3	50 (18)	2110(21)	8 (24)
4	54 (19)	1684 (17)	3 (9)
5	40 (14)	1007 (10)	4 (12)
6	21 (7)	548 (6)	0 (0)
7	16 (6)	289 (3)	0 (0)
Mean± SD	3.4 ± 1.8	3.0 ± 1.6	2.5 ± 1.3

**Includes valid logs only (see "Weekly Data Collection" subsection of the "Participants and Methods" section for definition). Percentages may not total 100 because of rounding.*



Patient flowchart. For the 28 patients removed before analysis, a baseline log only was available tor 15, a preenrollment outcome occurred in 7, the exposure week was unattainable due to an early recurrence in 5, and ineligibility occurred in 1. HSV indicates herpes simplex virus.

sults were obtained when the global stress scores were analyzed as a 1 to 7 continuous variable and for the Life Arenas Stress Measure sum and maximum (data not shown).

The mean of the average global stress scores (computed across all weeks for participants with at least 5 valid logs) was 2.6 ± 1.1 in the 29 participants with a valid recurrence (and a nonmissing exposure week stress score) and 3.1 ±1.3 in the 221 who did not experience a recurrence (P=.06). Among these 29 participants with a valid recurrence, the exposure week stress score was similar to their average stress in all other weeks (2.5 ± 1.2 vs 2.6±1.1; P=.20, paired *t* test), and the correlation between their exposure week stress scores and their average of the prior weeks was 0.84. In accord with the weekly global stress measure, a high average stress score was not associated with increased risk of recurrence (unadjusted rate ratio for a 1-SD increase in average stress, 0.74; 95% confidence interval, 0.50-1.10; *P*=.14).

Also in accord with the other measures of stress, there was no indication of an association between an increased risk of a recurrence and either a change in global stress (assessed in a model including the weekly global stress scores and average stress) (Table 3) or presence of a chronic (2:2 weeks) stressful situation (unadjusted rate ratio, 0.46; 95% confidence interval, 0.20-1.05; P=.07). There was also no association between recurrence and personality measures of negative affectivity (unadjusted rate ratio for a 1-SD increase, 0.98; 95% confidence interval, 0.70-1.38; P=.91) or social desirability (unadjusted rate ratio for a 1-SD increase, 0.92; 95% confidence interval, 0.66-1.28; P=.61).

Analyses of the global stress scores conducted using the case-crossover method, which limits the data to those participants who had a valid recurrence (n=33), produced results similar to those of the discrete-time proportional hazards model (Table 4).

ASSOCIATION OF OTHER POTENTIAL TRIGGERS AND OCULAR HSV RECURRENCE

During the study, a systemic infection was reported on 13% of the weekly logs, sun exposure of more than 21 hours in a week on 7%, and contact lens wear on 10%. None of these potential triggers were found to be associated with recurrences in either the discrete-time proportional hazards analysis (Table S) or the case-crossover analysis (data not shown).

Among the 64 women younger than 50 years who reported at least 1 menstrual period during the study, there were only 7 valid recurrences. Although no association was found between the onset of the menstrual period and a recurrence, the study's power was too low for any meaningful assessment. Similarly, eye injuries were reported too infrequently (reported on only 0.8% of the logs) to assess an association with recurrence.

COMPARISON OF STRESS AND SYSTEMIC INFECTION REPORTING ON VALID AND INVAUD EXPOSURE WEEK LOGS

For comparison purposes, we also examined the 26 recurrences excluded because the exposure week log was completed after the onset of symptoms of a recurrence. The baseline characteristics of the 26 participants with an invalid recurrence were similar to those of the 33 participants with a valid recurrence. Analyses revealed that both high global stress and systemic illness were reported more frequently on exposure week logs completed late after the onset of symptoms of the HSY recurrence than on logs completed properly before the onset of symptoms. High stress was reported on none of the 33 valid exposure week logs (with nonmissing stress scores) and on 4 (16%) of the 25 invalid logs with a stress score (P = .03, Fisher exact test). Systemic illness was reported on 3 (9%) of the 35 valid logs and on 10 (38%) of the 26 invalid logs (P= .01, Fisher exact test).

When the discrete-time proportional hazards model analysis was conducted using only the 26 recurrences in which the exposure week log was completed after symptom onset, the computed rate ratios differed considerably from those estimated for the valid recurrences, showing a strong association between systemic infection and a recurrence (rate ratio, 4.14; 95% confidence interval, 1.88-9.15; P<.001) and suggesting a possible association between high stress and a recurrence (rate ratio for high stress compared with moderate or low stress, 2.04; 95% confidence interval, 0.70-5.95; P=.19). Analyses conducted by the case-crossover method gave similar results (rate ratio

Table 3. Cohort Analysis of the Association of Psychological Stress and Ocular HSV Recurrence in the 308 Participants*

Global Stress Score†	Exposure Week Reporting for Patients With Recurrences‡	No. of Weeks With Logs for All Patients	Rate Ratio (95% CI)			
			Weekly Global Stress		Change From Average Global Stress	
			Unadjusted§	Adjusted§‖	Unadjusted¶	Adjusted§#
Low	18	4405	1.0	1.0	1.0	1.0
Moderate	15	4945	0.74 (0.37-1.48)	0.65 (0.31-1 .39)	0.83 (0.30-2.27)	0.77 (0.27-2.17)
High	0	874	0	0	0	0
Overall**	...	...	0.58 (0.32-1.05)	0.51 (0.26-1.01)	0.63 (0.25-1.57)	0.59 (0.23-1.54)
*P***	...	...	.07	.05	.32	.28

**HSV indicates herpes simplex virus; CI, confidence interval; and ellipses, data not applicable.*

† Low indicates a stress rating of 1 to 2; moderate, 3 to 5; and high, 6 to 7.

‡Distribution of global stress scores in exposure week for the 33 patients with a "valid" recurrence and a reported stress score (stress score missing for 2 patients).

§From a person-time formulation of a discrete-time proportional hazards model, with the global stress scores modeled as dummy variables. The adjusted model included age, sex, ethnicity (white and Asian vs African American and Hispanic), number of past ocular HSV episodes, negative affectivity (Taylor Manifest Anxiety Scale), social desirability (Marlowe-Crowne Social Desirability Scale), living situation (alone vs with others [missing recoded as with others]), acyclovir treatment group, self-reported illness, and study time.

‖One hundred sixty-six logs (including 2 recurrences) were not included in the analysis because of missing covariate data.

¶Eighty-four logs (including 4 recurrences) were not included in the analysis because of missing data on average global stress during follow-up.

 # Two hundred fifty logs (including 6 recurrences) were not included in the analysis because of missing covariate data.

*** From a model with global stress score as a 3-level continuous variable.*

Table 4. Case-Crossover Analysis of the Association of Psychological Stress and Ocular HSV Recurrence in 33 Participants*

Global Stress Score†	Exposure Week Reporting for Patients With Recurrences‡	Risk Ratio (95%CI)
Low	18	1.0
Moderate	15	0.88 (0.32-2.46)
High	0	0
Overall§	...	0.66 (0.27-1.62)
P§	...	.36

**HSV indicates herpes simplex virus; CI, confidence interval; and ellipses, data not applicable.*

† Low indicates a stress rating of 1 to 2; moderate, 3 to 5; and high, 6 to 7.

‡Distribution of global stress scores in exposure week for the 33 patients with a recurrence and a reported stress score on a valid exposure week log (stress score missing for 2 patients).

§From a model including exposure week stress as a 3-level continuous variable.

for systemic infection, 5.08; 95% confidence interval, 1.94-13.30; P<.001; and rate ratio for high stress, 3.52; 95% confidence interval, 0.69-17.92; P=.13).

When the 26 invalid recurrences were included in an analysis with the 33 valid recurrences, the unadjusted rate ratio for the 3-level global stress variable was 0.77 (95% confidence interval, 0.50-1.17; P=.22); for systemic infection, it was 1.80 (95% confidence interval, 0.97-3.33; P=.06).

In this prospective cohort study, we found no association between high psychological stress or a change in psychological stress and a recurrence of HSV infections in the eye. We also found no clear association of a recurrence with systemic infection or with sunlight exposure. However, we did find that considerable bias would have been present in the estimate of the exposure-disease association for systemic infection had we not limited our primary analysis to those recurrences in which the time-order relationship between exposure reporting and symptom onset was preserved.

We can state with reasonable certainty that high stress is unlikely to be associated with the activation of HSV eye disease. Even if an association exists but was not identified in our study, the relationship is almost certainly weak. The upper limit of the 95% confidence interval extends to 1.05, indicating that if our study is unbiased, a true association is unlikely to have a rate ratio of a clinically meaningful magnitude that is appreciably greater than 1.0.

Among the participants who developed an ocular HSV recurrence, none reported high stress on a valid exposure week log, and recurrences occurred more often in those reporting low stress during the exposure week (observed rate ratio, 0.58). Although this suggestion of an association between low stress and an increased incidence of recurrences is probably due to chance, another possible explanation could be that those reporting low stress levels were individuals who deny feeling stressed in stressful circumstances, even though physiologically they are having a strong stress response.[37] However, after categorizing the subjects into repressors (low anxiety and high social desirability), sensitizers (high anxiety), and those thought to be "truly low anxious" (low anxiety and low social desirability) using a method based on one previously described,[38-40] we found that the participants reporting low stress in the exposure week of a recurrence included fairly equal numbers of all 3 defensive style groups (35% repressor, 29% sensitizer, and 35% true low anxious), arguing against this possible explanation.

Strengths of our study include a large sample size, prospective data collection (which provides evidence for time order and limits the possibility of recall bias), weekly ex-

Table 5. Cohort Analysis of the Association of Other Variables and Ocular HSV Recurrence in the 308 Participants*

Exposure Reported on Weekly Log	Exposure Week Reporting for Patients With Recurrences†	No. of Weeks With Logs for All Patients	Rate Ratio (95% CI)‡	*p*
Systemic infection				
No	32	9399	1.0	.42
Yes	3	1417	0.62 (0.19-2.02)	
Sun exposure, h				
≤21	31	9778	1.0	.22
>21	4	677	1.93 (0.68-5.49)	
Contact lens use§				
No	28	9490	1.0	.58
Yes	4	1012	1.35 (0.47-3.86)	

*HSV indicates herpes simplex virus; CI, confidence interval.
†Distribution of variables in exposure week for patients with a recurrence and a valid exposure week log.
‡Unadjusted rate ratio from univariate discrete-time proportional hazards models.
§Exposure week data missing for 3 participants.

posure measurement (which reduces exposure misclassification among time-varying exposures), and physician confirmation of recurrence (which reduces outcome misclassification). However, even with the extensive efforts we undertook to try to assure compliance with the protocol, many logs were completed late. For most weeks, completing the log a few days late did not pose a problem. However, for recurrences, even a few days delay in completing the log from the week covering the exposure period could mean that the exposure data were not recorded until after symptoms of the recurrence had begun. Our results strongly indicate that both high stress and systemic infection, particularly the latter, were overreported when logs were completed after symptoms of a recurrence appeared. We found no evidence to indicate that having a systemic illness or high stress level might have been the reason a log was completed late; logs reporting one of these occurrences during nonexposure weeks were no more likely to be late than other logs (data not shown). If we had not excluded recurrences in which this time order was violated, we could have erroneously concluded that systemic infection was associated with a recurrence. Exclusion of these recurrences, which was necessary to minimize bias, had the unwanted but unavoidable effect of reducing the power of the study.

Our finding that psychological stress did not increase the risk of a recurrence was consistent in all models that were assessed with both the discrete-time proportional hazards model and case-crossover methods and when alternate measures of stress were evaluated, including the maximum stress reported on the Life Arenas Stress Measure on a weekly log, reporting of chronic stress on a weekly log, and a participant's average global stress across all logs. There was no evidence of confounding being present. Despite this consistency, consideration must be given to whether the measure of stress we used was reliable and valid for our purposes and to whether the exposure period we assessed was appropriate.

Although the global stress score we used has not been formally validated, other similar scales have been validated. Using similar single-item global measures of psychological stress, Watson[41] provided estimates of reliability (Pearson $r=0.71$) and construct validity by correlation with a measure of negative emotion (Pearson r=0.44), and Cohen and Williamson[42] reported a correlation of 0.39 with the Perceived Stress Scale among disease-free adult subjects.

Even with the intensive weekly data collection that resulted in the submission of 12236 logs by the 308 participants, the data collection may have been too infrequent for optimal assessment of the stress-disease relationship. Little is known about the timing of this relationship. We a priori selected the exposure week for the stress assessment such that it fully preceded the onset of symptoms of a recurrence of HSY eye disease. Depending on the day of the week that the symptoms started, the 7-day period for exposure could have been as long as 7 to 13 days before symptom onset or as short as 1 to 7 days before symptom onset. Thus, the measured exposure period may not have included the *critical exposure period* (the period before the induction period during which stress could have a causal effect on recurrence). It is also possible that the critical exposure period is less than 7 days and, thus, the measured exposure period included background information irrelevant to the stress-disease relationship. We evaluated exposure periods 2 and 3 weeks before symptom onset and again found no association between high stress and a recurrence (data not shown).

An additional potential source of error is lack of precision in determining the symptom-onset date. We used the weekly logs and the examination records to increase the accuracy of this determination. However, in some cases, the symptom-onset date was not available and needed to be imputed based on the date of examination documentation of the recurrence. In these cases and potentially others, it is possible that inaccuracies in the symptom-onset date could result in selection of the wrong exposure week log for analysis. This would tend to bias away from detecting true exposure-disease associations.

To our knowledge, there is no prior study of the association of stress and ocular HSY recurrences for comparison with our results. Several studies have assessed the association between stress and nonocular HSY recurrences. No consistent finding has been reported. Prospective studies by Kemeny et al,[43] Hoon et al,[18] and Rand et al[44] found no clear association between psychological stress

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and recurrence of genital herpes via monthly, weekly, and daily exposure assessment, respectively. Cohen et al,[19] using weekly stress assessment in a prospective study, found that persistent but not acute stress was associated with increased genital herpes recurrence. Goldmeier et al[12] examined the time to first recurrence in patients in whom genital herpes was newly dia$_{gn}$osed and found that the General Health Questionnaire (a measure of psychiatric symptoms) was associated with an increased recurrence rate (rate ratio [10-U increase in the General Health Questionnaire score], 1.27; P<.02), but found no evidence of an association with a measure of stressful life events. Schmidt et al[16] found an increase in stressful life events and hassles during the week before an oral herpes recurrence compared with a dormant week; however, stress was assessed after symptoms began (ie, within 3 days of the onset of the vesicular eruption). Padgett and colleagues,[45] in a study of recurrence ofHSV-1-associated keratitis in mice, found that only 1 type of stress paradigm (social stress, not restraint stress) led to recrudescence in these animals. However, the biological mechanisms underlying reactivation and recrudescence could not be determined and are thought to be complex.[43]

Our assessments of eye injury, contact lens wear, and the onset of a menstrual cycle were of insufficient power for any meaningful conclusions. For systemic infection and sunlight exposure, interpretation of the study results is limited by imprecise measurement of the exposure.

Early experimental results of induced fever suggest a 24-hour induction period before the onset of orofacial herpes symptoms.[5] In view of the potential that this critical exposure period was obscured or missed in our measured exposure period, we may have missed a true association between a systemic infection and the development of an ocular HSV recurrence.

The literature[7] suggests that an intense, short, UV light exposure may trigger HSV recurrence. Experimental UV light exposure among patients with orofaciaF or genital[8]

herpes has shown an average induction period of 4 days. Although our data suggest the possibility of an association of extensive sunlight exposure and HSV eye disease, in retrospect, our measure of sunlight exposure was inadequate. Assuming a 4-day or shorter induction period for our participants whose symptoms began on Friday and continued through Sunday (assuming log completion on the previous Sunday), the critical exposure period would not have been included in the weekly log designated as the measured exposure period. Furthermore, our study assessed weekly sun exposure rather than intense episodes of sunlight exposure and, therefore, our measure was insensitive to single intense exposures of short duration that could be sufficient to trigger a recurrence.

High psychological stress does not appear to be a trigger of recurrences of HSV eye disease. Although our results suggest either that low stress may be associated with an increased risk of a recurrence or that high stress may be associated with a decreased risk, this finding is not supported by previous studies of oral and genital herpes recurrences. Without a credible mechanism for this and replication in other studies, this association should not be accepted as plausible. Our finding of a strong potential bias toward overreporting of systemic infection and high stress when there was violation of the time-order requirements (for exposure reporting before symptom onset) makes suspect the results of HSV risk factor studies in which this time-order is not clearly established. If not accounted for, recall bias can substantially overestimate the importance of factors that do not have a causal association with HSV infection.

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