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Perceived stress and incident sexually transmitted infections in a prospective cohort

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ABSTRACT

Purpose: Psychosocial stress has been associated with susceptibility to many infectious pathogens. We evaluated the association between perceived stress and incident sexually transmitted infections (STIs; *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, and *Trichomonas vaginalis* genital infections) in a prospective study of women. Stress may increase vulnerability to STIs by suppressing immune function and altering the protective vaginal microbiota.
Methods: Using the 1999 Longitudinal Study of Vaginal Flora ($n = 2439$), a primarily African American cohort of women, we fitted Cox proportional hazards models to examine the association between perceived stress and incident STIs. We tested bacterial vaginosis (measured by Nugent Score) and sexual behaviors (condom use, number of partners, and partner concurrence) as mediators using VanderWeele's difference method.
Results: Baseline perceived stress was associated with incident STIs both before and after adjusting for confounders (adjusted hazard ratio = 1.015; 95% confidence interval, 1.005–1.026). Nugent score and sexual behaviors significantly mediated 21% and 65% of this adjusted association, respectively, and 78% when included together in the adjusted model.
Conclusions: This study advances understanding of the relationship between perceived stress and STIs and identifies high-risk sexual behaviors and development of bacterial vaginosis—both known risk factors for STIs—as mechanisms underlying this association.

Introduction

According to 2016 Centers for Disease Control estimates, there are approximately 20 million new sexually transmitted infections (STIs) in the United States each year [1]. In 2008, the annual national burden of STIs was in excess of $16 billion in direct medical costs to the health care system [2,3]. In addition to their own morbidities, STIs such as genital Neisseria gonorrhoeae (GC), Chlamydia trachomatis (CT), and Trichomonas vaginalis (TV) are risk factors for infertility [4] and acquisition of human immunodeficiency virus (HIV) [5]. Population-based surveys show marked and persistent racial or ethnic disparities in the STI and HIV prevalence [6–8]. Individual risk behaviors, such as number of sexual partners and a lack of condom use, do not fully account for the high rate of infection among African Americans in the United States [9–15]. Perceived stress is a well-known psychosocial factor that increases risk for many health outcomes [16], as stress can impair multiple physiological systems [17,18] and increase the likelihood of high-risk behaviors [19,20]. Limited research has examined psychosocial stress in relation to vulnerability to STIs, although extensive research indicates that high psychosocial stress is associated immune suppression, leading to heightened

Obtaining data: Longitudinal Study of Vaginal Flora data are available by submitting a request to the NICHD/DIPHR Biospecimen Repository Access and Data Sharing program.

The authors have no conflicts of interest to disclose.

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infection susceptibility, severity, and persistence of infections [16,21–27].

Perceived stress refers to thoughts or feelings one has about their level of experienced stress. It is associated with STI risk because of multiple biological and behavioral mechanisms. On the biological front, several studies—including one with participants from the Longitudinal Study of Vaginal Flora (LSVF; the same cohort used in the present study)—have documented an independent association between psychosocial stress and greater prevalence and incidence of bacterial vaginosis (BV), a dysbiosis of the vaginal microbiota [25–27]. Amabebe and Anumba also recently reviewed how cortisol, a biologic measure of stress, can potentially affect vaginal health [28]. BV has been linked to an approximately two-fold increased risk for acquisition of STIs, including HIV, GC, CT, TV, herpes simplex virus, and human papillomaviruses [29–35]. The vaginal microbiome offers protection in part through the influential action of Lactobacillus spp. Species of vaginal Lactobacillus spp. can provide broad-spectrum protection through production of copious amounts of lactic acid [36], bacteriocins [29,32,37–39], antagonistic bacteriocin-like substances [40], and biosurfactants [41] and through their ability to adhere to mucus, forming a physical barrier against incoming pathogens [42] and disrupting biofilms [43].

Considering behavioral pathways, high perceived stress has been associated with a 2.4-fold greater odds of reporting problems using condoms, and depression was associated with 50% lower odds of using condoms consistently [44]. A longitudinal study of 155 adolescents reported that perceived stress was significantly associated with emotional distress, which in turn, was associated with a higher number of sexual partners and high-risk sexual partners [45]. Perceived stress may also influence STI risk through changes in partners: a study found that among 1002 women in South Africa, baseline depression was marginally associated ($P = .073$) with increased sexual partner concurrence in the following 12 months [46].

There are limited longitudinal data examining links between psychosocial stressors and STI [20,47–49]. In one prospective study of 627 African American female adolescents (aged 14–20 years), chronic socioeconomic strain was associated with STI acquisition and reinfection over 36 months [20]. In a 14-year study of nearly 1 million women in the Swedish Multi-Generation Register, death of a close relative was associated with incident STI [49]. In a study of 130 heterosexual dyads (aged 14–24 years) with discordant chlamydia status, depressive symptoms were associated with increased STI risk in the non-infected partner [50].

The objective of this study was to evaluate the associations between psychosocial stress and incident STIs (genital CT, GC, TV), testing BV and sexual behaviors as mediators. To our knowledge, no prior studies have examined potential behavioral and microbiotal mediators of the association between perceived stress and incident STIs.

Materials and methods

Sample

From August 1999 to February 2002, 3620 nonpregnant women (aged 15–44 years) were recruited to the LSVF through family planning and wellness clinics in the Birmingham, Alabama area [51]. Exclusion criteria were immunocompromised status, hysterectomy, menopause, pelvic radiotherapy, antibiotic therapy greater than 30 days, nonfluency in English, plans to move within the next 12 months, participation in a clinical trial using antibiotics or genital microbicides, and mental or intellectual limitations preventing informed consent. Participants were followed for approximately 12 months with clinical examinations and surveys. Participants who had a positive test for genital GC, CT or TV at baseline (screening described below) were excluded from our analytic sample (752 excluded). Next, we excluded participants with no visits after baseline (413 excluded). Of the remaining sample, there was less than 1% missing data for all baseline measures other than income, which was imputed. All observations with incomplete baseline measures other than income were excluded (16 excluded). The final sample consisted of 2439 participants (32.3% excluded).

All participants gave written informed consent, and the study was approved by the Institutional Review Boards of the National Institute of Child Health and Human Development, the Jefferson County Department of Health, the University of Alabama at Birmingham, as well as secondary data analysis at the University of Maryland School of Medicine.

Measures

Perceived stress

Perceived stress was measured at baseline using Cohen's 10-item Perceived Stress Scale (PSS), a well-validated measure of an individual's appraisal of stress in the past 30 days [52–54]. Each of the items has a 5-point Likert response format, and the scale covers dimensions of overload, uncontrollability, and ability to cope, including questions such as “In the last month, how often have you been upset because of something that happened unexpectedly?” This scale demonstrated good internal consistency (Cronbach's alpha = 0.85). We used this measure as a continuous score in our main analyses.

Incident STI

Participants were tested for GC, CT, and TV at each study visit. An endocervical swab was used to inoculate Thayer–Martin agar plates for culture of GC, whereas CT testing was performed by ligase chain reaction (Abbott Laboratories, Abbott Park, IL). TV was determined by means of a positive finding on either culture (InPouch) or microscopic evaluation for trichomonads. Participants were removed from the risk set after their first observed incident STI, as there were very few cases with multiple distinct STIs during the study. For participants without an observed incident STI, their last study visit was used as the right-censoring time.

Bacterial vaginosis

BV was measured at each visit using Nugent's scoring of a vaginal Gram stain (0–10) [55]. Nugent score was categorized as low, intermediate, or high (0–3, 4–6, 7–10, respectively) based on standard scoring criteria. Time-varying measures for Nugent category were used up to the time point of the first incident STI or right censoring. For each time point, the Nugent category at the previous wave was used to assess BV as a mediator of incident STI. This ensured that Nugent scores reflect the period after the end of the baseline stress period and before incident STI or right censoring. This also makes the Nugent Score concurrent with the beginning of the reference period for each sexual behavior, which extends 3 months before the time of measurement.

Sexual risk behaviors

Sexual risk behaviors were measured at each visit. Respondents reported on their number of sexual partners in the past 3 months (0–1, 2, or more), frequency of condom use (never, seldom, half the time, most of the time, and always), and sexual concurrence of their partners (none, unlikely concurrence, possible concurrence, and definite concurrence). Partner concurrence was assessed with the question “Do you think any of these sexual partners had sex with anyone else?” We used time-varying measures for all sexual behaviors up to first incident STI or right censoring.

Other risk factors for STIs

We used potential confounders measured at the baseline interview, including self-identified race (Black, White, and other), education (high school and under, above high school), marital status (married and not married), monthly income (<$500, $500–$800, $800–$3000, >$3000), and age (continuous years). A literature-based approach was used to select confounders that have been shown in previous research to confound the association between stress and STI or have been independently associated with both stress and incident STI [19,44,45,49].

Statistical analysis

First, we compared baseline demographics, BV, and sexual behaviors between participants with and without incident STI using chi-square tests for categorical variables, and Satterthwaite *t* tests for continuous variables. We used Cochran-Armitage tests of trend to test differences in proportions of ordinal variables. We also compared the theorized mediators across perceived stress. We also tested differences in survival rates between perceived stress quartiles (≤11, 12–17, 18–23, ≥24) using log-rank tests for trend. To assess linearity of the PSS, we also analyzed the quartile-categorized PSS, using both adjusted and unadjusted Cox proportional hazards models. Categories of 0 and 1 for number of sexual partners were collapsed to account for potential unreported partner overlap for participants reporting 0 and 1 partners at adjacent visits. Adjacent categories of 0 and 1 was a commonly observed phenomenon in our data. To assess the validity of combining these categories, we also tested for differences between these categories in a post-hoc analysis.

Cox proportional hazards models were used to test the association between perceived stress and incident STIs. We used sequential model building, where the first model only included the perceived stress term (Model 1). We then added terms for potential demographic confounders (Model 2). We then added time-varying terms for Nugent score and sexual behaviors (Model 3). The Kolmogorov-type supremum test was used to assess the proportional hazards assumption for all models.

Next, we tested sexual risk behaviors and Nugent score as mediators by calculating indirect association estimates for these variables both separately and combined. The indirect association estimates, adjusted for the same covariates included in Model 2, describe the proportion of the association between perceived stress and incident STI that is explained by the set of mediators. VanderWeele's difference method was used to estimate indirect associations of Nugent score, sexual behaviors, and both mediators combined by calculating the change in the association estimate when including each potential mediator in the model [56]. To

Table 1
Baseline demographic and behavioral measures and Nugent score before event, stratified by incident STI status ($n = 2439$)

Measure	Total		No observed incident STI		Observed incident STI		*P*
	Mean	SD	Mean	SD	Mean	SD	
Perceived Stress Scale, past 3 mo*	17.12	7.5	16.77	7.6	18.02	7.0	<.001
Age (y)*	25.70	7.1	26.05	7.1	24.76	7.0	<.001
	n	%	*n*	%	*n*	%	
Marital status†							<.001
Not married	1998	81.9	1395	79.1	603	89.3	
Married	441	18.1	369	20.9	72	10.7	
Race†							<.001
Black	1908	78.2	1290	73.1	618	91.6	
White	495	20.3	443	25.1	52	7.7	
Other	36	1.5	31	1.8	5	0.7	
Education level†							<.001
≤High school	1739	71.3	1203	68.2	536	79.4	
>High school	700	28.7	561	31.8	139	20.6	
Monthly income‡							
<$500	447	19.9	301	18.4	146	23.9	<.001
$500–$800	659	29.3	440	26.9	219	35.8	
$800–$3000	962	42.8	746	45.7	216	35.3	
>$3000	178	7.9	147	9.0	31	5.1	
Nugent score‡,§							
Low (0–3)	982	40.3	792	44.9	190	28.3	<.001
Medium (4–6)	515	21.4	362	20.6	153	22.8	
High (7–10)	939	38.6	610	34.5	329	49.0	
Condom use, past 3 mo‡,§							<.001
Never	1531	63.0	1165	66.3	366	54.5	
Seldom	112	4.6	77	4.4	35	5.2	
Half the time	85	3.5	56	3.2	29	4.3	
Most of the time	201	8.3	141	8.0	60	8.9	
Always	501	20.6	319	18.2	182	27.1	
Number of sex partners, past 3 mo†,§							<.001
0–1	2309	94.7	1690	95.6	619	91.7	
≥2	130	5.3	74	4.2	56	8.3	
Partner concurrence†,§							<.001
No concurrence	725	33.4	574	36.6	153	25.8	
Unlikely concurrence	1121	51.6	805	51.3	307	51.7	
Possibly concurrent	171	7.9	104	6.6	64	10.8	
Definitely concurrent	154	7.1	85	5.4	70	11.8	

* *P* calculated using Satterthwaite *t* test.
† *P* calculated using χ^2 test.
‡ *P* calculated using Cochran-Armitage trend test.
§ Nugent score is used from wave before observed incident STI or right censoring. Condom use, number of sexual partners, and sexual partner concurrence are used at wave of incident STI or right censoring. All other variables are used from baseline.

calculate each indirect association, the beta estimate for the PSS term in each adjusted model containing mediators was subtracted from the beta estimate for the PSS term in the total adjusted model. Each percentage of mediated association was calculated from this. We used bootstrapping to generate 95% confidence intervals (CIs) for each indirect association. All analyses were conducted using SAS Version 9.4 (SAS Institute, Cary, NC).

Missing data

There was less than 5% missingness for all time-varying measures and less than 1% missing data for all baseline measures except income, which had 8% missingness. To address this, monotone multiple imputation was used to generate 10 imputed datasets that were used for all model analyses. We imputed income using nonmissing data from race, age, education level, and marital status. These variables were selected as they demonstrated significant associations with income in our dataset.

Results

Sample

The 2439 participants contributed a total 1855.55 person-years. The person-time contributed by each participant ranged from 48 to 405 days. The PSS score ranged from 0 to 40 and was normally distributed (Supplement 1). In both unadjusted and adjusted models using the quartile-stratified PSS, we found clear evidence of dose–response, consistent with linearity (Supplement 2). Perceived stress was relatively stable over the follow-up period: 85% of participants remained within one stress quartile of their baseline stress quartile across all visits, with strong positive correlation between perceived stress measures across visits (Median $r = .62$; see Appendix 1). Women in our study were predominantly Black/African American (78%) and unmarried (82%); most women had more than a high school education (71%), and 72% had monthly income between $500 and $3000. There were 675 (27% of the sample) incident STI cases in the cohort across 1855.55 person-years, equating to an incidence rate of 36.4 cases per 100 person-years. Among incident STI cases, 46.4% were Chlamydia only, 35.7% were Trichomonas only, 10.2% were GC only, 3.0% were GC and Chlamydia, 1.3% were GC and Trichomonas, 3.1% were Chlamydia and Trichomonas, and 0.3% were all three infections.

Bivariate

Greater perceived stress was associated with incident STI ($P < .001$; Table 1). Those with incident STI were more likely to be younger, Black, unmarried, and have elevated Nugent score, lower income, education of high school or less, sexual partner concurrence, multiple sexual partners, and frequent condom use. In addition, greater perceived stress was associated with elevated Nugent score, multiple sexual partners, and sexual partner concurrence (Table 2). A Kaplan–Meier plot (Fig. 1) demonstrates differences in survival between the four perceived stress quartiles. As shown, the lowest quartile of stress has lower risk of STI than any of the other quartiles. A log-rank test for trend indicated a significantly increasing risk of STI with increasing stress quartiles ($P < .001$).

Cox proportional hazards models

Perceived stress was associated with incident STI (Table 3), with an approximate 2% increase in risk of incident STI with each 1-unit increase in perceived stress. At the highest values of perceived stress (40), this equates to nearly twice the risk of incident STI compared with those at the lowest values of perceived stress (0).

Table 2
Mean baseline perceived stress scale across behavioral measures and Nugent score before event ($n = 2439$)

Measure	Perceived stress scale, past 3 mo		*P*
	Mean	SD	
Nugent score*,†			.031
Low (0–3)	16.78	7.7	
Intermediate (4–6)	17.17	7.3	
High (7–10)	17.46	7.3	
Condom use*,†			.165
Never	18.89	7.6	
Seldom	18.61	7.3	
Half the time	18.12	7.7	
Most of the time	17.49	7.3	
Always	17.13	7.3	
Number of sex partners, past 3 mo†,‡			<.001
0–1	16.93	7.4	
≥2	20.31	7.5	
Partner concurrence*,†			<.001
No concurrence	16.49	7.4	
Unlikely concurrence	17.17	7.3	
Possibly concurrent	18.73	7.3	
Definitely concurrent	18.99	7.9	

* *P* calculated using Spearman's rank-sum correlation.
† Nugent score is used from wave before observed incident STI or right censoring. Condom use, number of sexual partners, and sexual partner concurrence are used at wave of incident STI or right censoring.
‡ *P* calculated using Satterthwaite *t* test.

When adjusting for confounders in Model 2, this was attenuated to approximately a 1.5% increase in risk of incident STI with each 1-unit increase in perceived stress. The association between perceived stress and incident STIs was further attenuated after incorporating potential mediators and was no longer statistically significant. Among mediators, intermediate Nugent score, high Nugent score, and partner sexual concurrence were associated with greater risk of STI. Significant demographic factors included race and education of high school or less. The Kolmogorov-type supremum test did not indicate a significant deviation from proportional hazards for any of the terms used ($P > .05$).

Mediation Analyses

Mediation analysis revealed significant indirect effects of Nugent score, sexual behaviors, and both combined (Table 4). Of the total association of stress with incident STI, 21% was mediated through Nugent score, 65% was mediated through sexual behaviors,

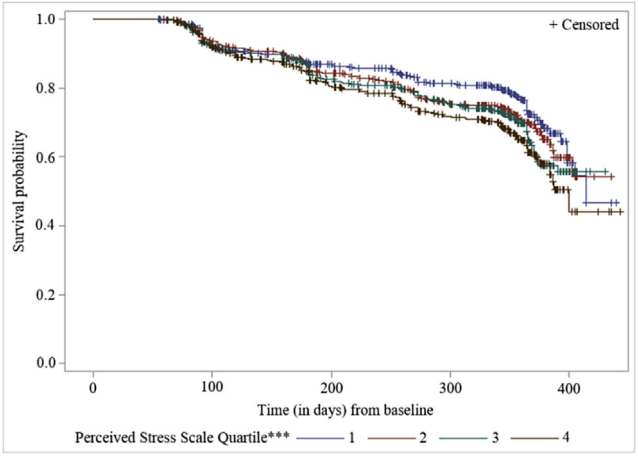

Fig. 1. Kaplan–Meier plot of survival probability (of no incident STI) over time in days stratified by baseline stress quartile ($n = 2439$, $^{***}P < .001$).

Table 3
Hazard ratios (and 95% confidence intervals) for the association of perceived stress and incident STI ($n = 2439$)

Measure	Model 1: unadjusted total stress association	Model 2: adjusted total stress association	Model 3: adjusted direct stress association
Perceived Stress Scale, past 3 mo			
Continuous (0–40)	**1.019 (1.009, 1.029)**	**1.015 (1.005, 1.026)**	1.003 (0.990, 1.016)
Education			
>High school degree		1.00	1.00
≤High school degree		**1.456 (1.195, 1.773)**	**1.460 (1.153, 1.848)**
Monthly income			
<$500		1.00	1.00
$500–$800		1.021 (0.844, 1.235)	0.920 (0.724, 1.169)
$800–$3000		**0.795 (0.635, 0.968)**	**0.730 (0.572, 0.931)**
>$3000		**0.637 (0.435, 0.934)**	0.778 (0.507, 1.195)
Race*			
Black		1.00	1.00
White		**0.354 (0.266, 0.473)**	**0.416 (0.295, 0.585)**
Age (y)		0.990 (0.979, 1.002)	0.997 (0.982, 1.012)
Marital status			
Not married		1.00	1.00
Married		**0.745 (0.576, 0.964)**	0.795 (0.584, 1.073)
Nugent score			
Low (0–3)			1.00
Intermediate (4–6)			**1.595 (1.230, 2.068)**
High (7–10)			**1.612 (1.280, 2.029)**
Condom use, past 3 mo			
Always			1.00
Most of the time			0.996 (0.712, 1.393)
Half the time			1.443 (0.969, 2.148)
Seldom			1.138 (0.747, 1.735)
Never			0.949 (0.748, 1.202)
Number of sex partners, past 3 mo			
0–1			1.00
≥2			1.295 (0.900, 1.865)
Partner concurrence			
No concurrence			1.00
Unlikely concurrence			**1.490 (1.186, 1.872)**
Possibly concurrent			**1.709 (1.176, 2.483)**
Definitely concurrent			**1.911 (1.325, 2.756)**

Bold indicates statistically significant hazard ratio at $P < .05$.
* Terms for other racial groups not reported due to insufficient sample size in each group ($n < 20$).

and combined, Nugent score and sexual behaviors mediated 78% of the observed association (Fig. 2).

Post-Hoc Analyses

Using the two-category number of sexual partners variable (0–1, 2+) did not result in any substantial change (<1% difference in indirect associations) compared with models using the three-category number of sexual partners variable (0, 1, and 2+). Sexual behaviors were a significant mediator using both categorizations for number of sexual partners, both in conjunction with and independent of Nugent score.

Discussion

In this longitudinal study of 2450 reproductive-age women, baseline perceived stress was associated with incident STI over approximately a year, independent of major confounders. This is consistent with cross-sectional studies indicating that stress is associated with higher prevalence of STIs [20,44,49]. In addition, approximately one-fifth of the association of stress with incident STI was mediated through Nugent score. This finding unites two previous studies from the LSVF study team documenting an association between perceived stress and both development and prevalence of BV and an association between BV and incident STI [27,30]. One-third of the mediating effects of Nugent score was independent of sexual behaviors; this may suggest direct impacts of stress on the dysbiosis of vaginal microbiota. The analysis of mediators allows for a more complete understanding of mechanisms of our observed association. Although the analysis excluding mediators is useful for assessing the total effect of stress on incident STI, the model including mediators more clearly parses how this association manifests. This is an especially important approach to risk assessment, as it identifies specific factors to target for

Table 4
Estimates (and bootstrap-generated two-sided 95% confidence intervals) for mediation effects of the association between perceived stress and incident STI: Longitudinal Study of Vaginal Flora, 1999–2002, among $n = 2439$ women STI-free at baseline

Estimate	Model: stress and only confounders*	Model: stress, confounders,* Nugent score, and sexual behaviors†	Model: stress, confounders,* and Nugent score	Model: stress, confounders,* and sexual behaviors†
Stress β	0.0150	0.0033	0.0121	0.0053
Indirect Effect	—	**0.0117 (0.0091, 0.0156)**	**0.0029 (0.0014, 0.0048)**	**0.0097 (0.0065, 0.0134)**
Percent mediated	—	**78%**	**21%**	**65%**
P	—	**<.01**	**.03**	**<.01**

Indirect effects are the difference in estimates compared with the model with stress and only confounders. Bold indicates statistically significant estimate at $P < .05$.
* Confounders include age, race, income, education level, and marital status.
† Sexual behaviors include condom use, number of sexual partners, and sexual partner concurrence.

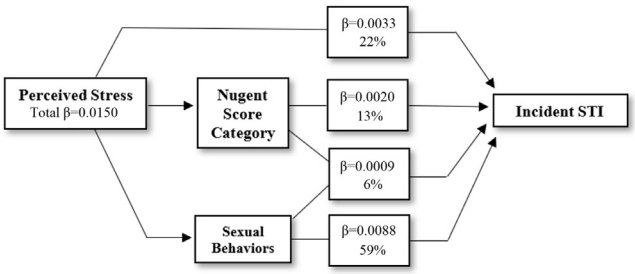

Fig. 2. Directed acyclic graph of the association of perceived stress with incident STI and mediating paths, adjusted for age, race, marital status, education, and income (n = 2439).

intervention. Although the confidence intervals for the association between stress and incident STI in Model 3 overlapped the null, this only reflects the direct effect of stress, not its total effect. Model 2 reflects the total effect of stress on STI. The substantial decrease in stress estimates in Model 3 indicates that sexual risk behaviors and Nugent score are large mediators of this association (i.e., baseline stress affects STI through changes in sexual behaviors and Nugent score).

Chronic psychological stress can be accompanied by dysregulation in the immune system that may directly affect colonization by an STI and indirectly increase STI susceptibility due to changes in the vaginal microenvironment. Chronic psychological stress has been shown to affect the immune system by activating type-2 cytokine-driven and proinflammatory responses [24]. Chronic stress has been associated with a decrease in natural killer cell cytotoxicity and suppressed lymphocyte proliferative responses [57–59]. Sympathetic fibers that innervate lymphoid tissues can act directly on lymphocytes via beta-adrenergic receptors. Psychological stress may also influence release of corticotropin-releasing hormone from the hypothalamus. Corticotropin-releasing hormone causes release of adrenal corticotropic hormone from the pituitary gland, which induces cortisol secretion from the adrenal cortex. Cortisol can profoundly impair the immune response by blocking T-cell proliferation [60]. These changes may result in a decrease in Th1 cytokines, which are required for active cellular immunity to defend against a wide range of infections and an increase in production of pro-inflammatory Th2 cytokines [24]. Inflammation could then cause destruction of infected epithelial layers, allowing bacterial STIs to access deeper tissues [61,62]. BV has been associated with genital proinflammatory cytokine upregulation, although some studies have found that downregulation of some cytokines also occurs [63–65]. Shifts in immune function due to psychological stress may directly impact susceptibility to STIs through changes in host immune responses and the microbiota.

Stress may also influence additional behavioral risk factors for STI, including sex while using alcohol or other substances. In a prospective study by Seth et al. of 605 African American female adolescents, depressive symptoms were associated with greater likelihood of not using condoms, having multiple sexual partners, having a main partner with concurrent sexual partners, a higher fear of discussing condoms with partners, and sex while influenced by alcohol or drugs [66]. Race demonstrated the strongest association with incident STI, independent of sexual risk behaviors and socioeconomic factors. There are many social and biological factors that converge to cause disproportionately high STI rates among African Americans [66]. This association may reflect differences in sexual network dynamics, network STI prevalence, BV rates, and unmeasured individual, psychosocial, and structural factors affected by racial discrimination [67,68].

There are limitations to the present study. First, the study was limited to clinics in the Birmingham, Alabama area, and was comprised primarily of Black women, so we could not study modification by race. However, Black women living in rural areas are often neglected in STI literature and face increased risk of STI. A potential limitation is that the data were collected approximately 20 years ago. Although specific stressors (e.g., types of discrimination experienced) may vary over time, we are not aware of evidence that the association between perceived stress and STI is likely to differ over time. Our results are consistent with recent studies on the association between stress and prevalent STI [19,26,44,49]. Culture-based screening methods for GC and TV are not as sensitive as modern methods such as polymerase chain reaction, so there may have been some false negatives. Finally, perceived stress is a subjective proxy for physiological stress, and it is possible unobserved variables (e.g., recent major adverse events) may lead some individuals to over- or under-report their stress. Although reporting of stress may differ between Black and White women, as Black women are likely to face additional stressors related to racism (e.g., additional experiences of discrimination and microaggressions), the PSS is highly validated and has been used in many studies across several populations and disciplines [54]. It also allows for the measurement of stress over the last 30 days, as opposed to a narrower measurement such as cortisol. Social desirability bias is also likely to be present for self-reported sexual behaviors, potentially resulting in misclassification [69,70]. In addition, although our study covered multiple measures of sexual behaviors, these variables are not fully comprehensive. There are additional sexual risk factors, such as partner STI status, that were unmeasured and could not be included.

There are a number of strengths to this study. The use of Nugent scoring for BV assessment and laboratory-based screening for STIs, as well as the longitudinal study design, allowed us to assess the association between perceived stress and STIs, as well as estimate relative risk. The use of baseline perceived stress and subsequent sexual risk behaviors, Nugent score, and STI is especially important, as there are several potential bidirectional associations among these variables. For instance, BV may lead to increases in stress, or changes in sexual partners may also lead to later changes in stress. This could result in a mediating pathway where stress mediates the association between these factors and STI. The use of temporally separated measures for baseline stress, intermediate mediators, and incident STI allows for assessment of a single theorized mediating pathway that can be interpreted with observed temporality. Much of the existing research on this topic has used small clinic-based samples and often with predominantly White participants. The use of time-varying mediators and covariates is a strength, as it allowed the most complete incorporation of the data available between the time of the baseline stress exposure and the time of STI or right censoring. Finally, VanderWeele's method is particularly robust for assessing mediation, as it allows for testing multiple mediators and can parse their associations independent of each other.

Conclusions

In this large, 12-month prospective cohort study, perceived stress was associated with incident STIs, and sexual risk behaviors and BV appear to be key mechanisms of this association. To our knowledge, this is the first longitudinal study to assess the association between stress and incident STI and demonstrate how changes in Nugent score and sexual risk behaviors mediate the association between stress and incident STIs. This study highlights perceived stress and the intermediary risk factors as important focal points to consider in the development of STI prevention

programs. Future research into social and biological mechanisms will be useful in further understanding how stress influences risk for genital infections 1and developing strategies to intervene.

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Supplementary data

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