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EDITED BY
Ming Yang,
Sichuan University, China

REVIEWED BY
Yi-Hao Peng,
Asia University Hospital, Taiwan
Jing Kang,
University of Leeds, United Kingdom

*CORRESPONDENCE
Kexing Han
hankexing0329@163.com

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The association between Herpes simplex virus type 2 and asthma: A cross-sectional study from National Health and Nutrition Examination Survey 1999–2016

Xiaofei Zhang[1], Yalin Jiang[1], Hui Qian[1], Xiangkun Qu[1] and Kexing Han[1,2]*

[1]Department of Respiratory Medicine, Bozhou Hospital Affiliated to Anhui Medical University, Bozhou, China, [2]The First Affiliated Hospital of Anhui Medical University, Hefei, China

Background: The association between Herpes simplex virus type 2 (HSV-2) infection, a common infectious disease that increases the incidence of multisystem diseases, and asthma was less well studied. The aim of this study was to investigate the association between HSV-2 infection and the prevalence of asthma.

Materials and methods: We used data from National Health and Nutrition Examination Survey (NHANES) 1999–2016 for analysis. The study population included was limited to those aged 20–45 years and contained complete information on HSV-2 infection and asthma. We calculated the prevalence of HSV-2, asthma, and HSV-2 combined with asthma separately. The association between HSV-2 infection and asthma was analyzed using multiple logistic regression. We also performed stratified analyses to reduce bias and to find sensitive cohorts.

Results: The prevalence of HSV-2 infection was decreasing with change in time period (P for trend < 0.01), but the prevalence of asthma was increasing (P for trend < 0.01). The prevalence of HSV-2 infection was higher in those with asthma than in non-asthma participants. A positive association was found between HSV-2 infection and asthma [odds ratio (OR) $= 1.15$, 95% CI: 1.04–1.27]. Subgroup analysis showed that this positive association was more pronounced in participants who were male, White, 30 years $\leq$ age $\leq$ 40 years, body mass index (BMI) ≤ 28 kg/m^2, $1.39 \leq$ ratio of family income to poverty (PIR) < 3.49 and smokers.

Conclusion: There was a positive association between HSV-2 infection and asthma, and participants who were male, White race, 30 years $\leq$ age $<$ 40 years, BMI ≥ 28 kg/m^2, $1.39 \leq$ PIR < 3.49, and smokers should receive more attention.

KEYWORDS

Herpes simplex virus type 2, asthma, National Health and Nutrition Examination survey (NHANES), cross-sectional study, prevalence

Introduction

HSV-2 infection is a global health problem that affects an estimated 491.5 million people aged 15–49 years worldwide (1). HSV-2 is transmitted primarily through sexual contact, with herpes genitalis being its early clinical manifestation, and can remain latent in the body for a long time after infection, with the potential for recurrence when the infected person's immunity is weakened (2). HSV-2 not only affects the urinary and reproductive systems, but also has been shown to cause psychological and social distress (3). Previous studies suggested that HSV-2 infection may lead to reactivation of the virus from a dormant to a proliferative state in the ganglia after a number of triggering factors (e.g., stress, fatigue, heat, cold or ultraviolet radiation, immunosuppression, etc.), resulting in multiple systemic diseases (2). Many researchers have found the presence of this virus in the lung, brain, liver and throat of people infected with HSV-2 (4–7). This suggests that the multisystemic diseases caused by HSV-2 need to be a concern.

According to the 2015 Global Burden of Disease Study, 358 million people are living with asthma worldwide, a 12.6% increase in prevalence from 1990 (8). Bronchial asthma is a heterogeneous disease characterized by chronic airway inflammation and airway hyperresponsiveness, with pathological changes including airway inflammation, airway remodeling and airway hyperresponsiveness. The main etiological causes include genetic and environmental factors, but its pathogenesis has not yet been fully elucidated (9, 10). In non-allergic asthma, viruses are an important factor in causing asthma and contributing to asthma exacerbations. Viral infections cause T-cell and neutrophil-mediated airway inflammation and may be a potential mechanism for non-allergic asthma (11, 12). Banerjee P showed that herpes simplex virus infection affects T-cell-mediated immune responses, for example, patients with herpes virus infection have a lower T1 cell-dominated immune response and an increased T2 cell-dominated immune response, and an enhanced T2 cell-dominated immune response is strongly associated with asthma exacerbations (13). It is also important to note that patients with acute asthma attacks have an increased chance of immunosuppression and this immunosuppressed state increases the patient's susceptibility to herpes simplex virus (4, 14).

Although many studies have confirmed the association of asthma with viruses, such as rhinovirus (RV) and respiratory syncytial virus (RSV), which are frequently detected in asthma patients (15), studies on the association between herpes simplex virus and asthma were not as well established. Igde M's study demonstrated a positive correlation between atopic status and HSV-1 infection in children with asthma and allergic rhinitis (16), where the mechanism might be due to the disruption of the body's immune homeostasis after HSV-1 infection, a view that would be consistent with that of Zhang J (13). To our knowledge, no studies on the association between HSV-2 and asthma have been conducted, probably because HSV-2 testing is extremely private and although patients do not object to testing regarding HSV-2, they may be conservative in feeding back information to healthcare workers (17). Although the relationship between HSV-2 infection and asthma has been studied rarely, HSV-2 infection can cause alterations in the body's immune response (18), for example, HSV-2 produces a large number of latency-associated transcripts (LATs) during host ganglion latency (19), with five products such as miRNA, sRNA, lncRNA, sncRNA and open reading frames (ORFs). These five products mediate LAT function and play a critical role in HSV-2 reactivation (19), and certain RNAs have been found to be associated with asthma development and asthma severity characteristics, such as hsa-miR-223-3p, a neutrophil-derived microRNA that regulates Toll-like receptors (TLRs)/Th17 signaling and endoplasmic reticulum stress, which causes asthma (20).

Until now, researchers have never stopped exploring the risk factors for asthma. Some studies have shown that the number of genetic loci associated with asthma is continuously increasing, and that changes in many of these loci may be associated with microbial infections, air pollution, and climate change (21). For example, 17q12-21, a genetic locus associated with childhood wheezing asthma, may be strongly associated with a history of viral respiratory infections in early childhood (22). NHANES is a research programme designed to assess the health and nutritional status of the United States population and is often used to conduct cross-sectional studies due to its continuously updated survey data and large sample size. Therefore, we aimed to use data from NHANES 1999–2016 to explore whether there are some notable associations between HSV-2 and asthma.

Materials and methods

Data sources

The NHANES database includes participant demographic information, physical examination information, dietary information, and laboratory test information, and has been kept up to date every 2 years since 1999. NHANES project information is open to outside parties, frequently used to conduct cross-sectional studies with large samples, and ethical clearance is exempt.

Population

All participants included in this study participated in the NHANES survey and the age of participants in this study was restricted to 20–49 years of age in accordance with the NHANES regulations for the age of participants who were given a HSV-2

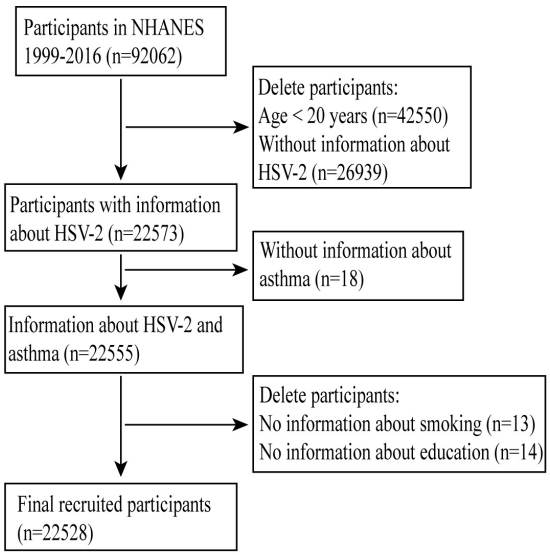

FIGURE 1
Flow chart for participants.

antibody test (the age limit set by this test). All participants included in this study had complete information on HSV-2 antibody test results and whether they had asthma. The study population was screened as shown in **Figure 1**.

Dependent and independent variable

In this study, we explored the association between HSV-2 infection and asthma by using whether the participants were infected with HSV-2 as the independent variable and whether they had asthma as the dependent variable.

A subsample of serum for the presence of glycoprotein-specific HSV-2 (designated as gG-2) was detected using a highly sensitive and specific solid-phase enzymatic type-specific immunospot assay, and a positive antibody was defined as an infection. NHANES 1999–2016 laboratory data section contained complete information on herpes simplex virus antibody testing.

The NHANES 1999–2016 questionnaire included information on medical conditions and participants were asked the question "Have you ever been told have asthma?" Participants who answered "Yes" were defined as asthma sufferers.

Covariates

Based on previous studies (23), we collected age, gender, race, BMI, education, marital status, total household size, PIR, smoking status, alcohol use, sexual behavior, injecting drug use, and as potential influencing factors, and the presence of a close relative with asthma as an influencing factor for asthma. Smoking status, alcohol consumption, sexual behavior and injecting drug use were taken from the questionnaire section. Smokers were defined as having smoked 100 cigarettes in their lifetime, and drinking 12 times in the past year was defined as drinking alcohol. Information on sexual behavior and injecting drug use was obtained from participants' responses to the questions "Ever had vaginal, anal, or oral sex?" and "Ever use a needle to inject illegal drug?"

Statistical analysis

All data extraction and analyses were performed in R[1] and Empowerstats.[2] To make the included information more representative of the entire United States population, we used 2-year sample weights throughout the analyses. Prevalence rates were expressed using weighted rates with 95% confidence intervals (95% CI), while trend tests for rates were conducted on a year-by-year basis. In the cleaning process of the covariate data, we made some allowance for missing data. When the missing data were continuous variables and did not exceed 10% of the total sample, we used the mean as a substitution. When the missing variable was categorical, we defined it as a group that could be independently classified (Unclear group) if the sample size exceeded 10, otherwise it was removed. Multiple logistic regression was used to analyze the relationship between HSV-2 and asthma. Three models were generated by adjusting for different covariates in order to more fully assess the relationship between the independent and response variables. Model 1: non-adjusted model; Model 2: age, gender, and race were adjusted; Model 3: all covariates presented in **Table 1** were adjusted. To find sensitive cohorts, we then conducted a stratified analysis. We set a p-value < 0.05 as statistically different.

Results

Prevalence of Herpes simplex virus type 2 and asthma

NHANES updates data from the survey on a 2-year time period. We calculated prevalence rates for HSV-2, asthma and co-morbidities for 9 time periods in NHANES 1999–2016 and tested for trends in these prevalence rates over the time period. The prevalence of HSV-2 was 21.4% (4825/22573), (95% CI:

1 http://www.R-project.org
2 http://www.empowerstats.com

TABLE 1 Baseline characteristics of included participants.

Characteristic	Without asthma	Asthma	*P*-value
Sample size	19364	3164	
HSV-2 infection (%)			< 0.001
Yes	20.77	25.19	
No	79.23	74.81	
Gender (%)			< 0.001
Male	47.91	40.71	
Female	52.09	59.29	
Age (years)	34.50 ± 8.62	33.23 ± 8.72	< 0.001
Stratified by age (years) (%)			< 0.001
< 30	32.94	39.79	
30–40	33.31	31.64	
≥ 30	33.75	28.57	
Race (%)			< 0.001
Mexican American	22.38	10.49	
White	39.76	48.39	
Black	19.92	24.02	
Other race	17.94	17.10	
Marital status (%)			< 0.001
Live with a partner	61.61	52.88	
Solitude	37.25	46.40	
Unclear	1.13	0.73	
Family members (%)			< 0.001
< 3	45.79	52.50	
≥ 3	54.21	47.50	
BMI (kg/m^2)	28.46 ± 6.80	29.99 ± 8.02	< 0.001
Stratified by BMI (kg/m^2) (%)			< 0.001
< 24	26.80	23.32	
24–27.9	27.14	23.93	
≥ 28	46.05	52.75	
PIR (%)	2.49 ± 1.57	2.37 ± 1.61	< 0.001
Stratified by PIR (%)			< 0.001
< 1.39	32.19	37.33	
1.39–3.49	38.97	34.83	
≥ 3.49	28.84	27.84	
Education (%)			< 0.001
<High school	23.92	18.39	
High school	23.04	21.65	
> High school	53.05	59.96	
Smoker (%)			< 0.001
Yes	39.85	46.21	
No	60.15	53.79	
Alcohol drinking (%)			0.004
Yes	11.69	11.44	
No	11.96	9.99	
Unclear	76.35	78.57	
Sexual intercourse (%)			< 0.001
Yes	84.06	87.55	
No	4.88	3.82	
Unclear	11.07	8.63	
Used injecting drugs (%)			< 0.001
Yes	1.54	2.28	
No	65.46	71.27	
Unclear	33.00	26.45	
Close relatives with asthma (%)			< 0.001
Yes	19.47	45.48	
No	79.01	51.58	
Unclear	1.52	2.94	

Mean + SD for continuous variables: *P*-value was calculated by weighted linear regression model. % for Categorical variables: *P*-value was calculated by weighted Chi-square test. HSV-2, Herpes simplex virus type 2; BMI, Body mass index (kg/m^2); PIR, Ratio of family income to poverty.

20.8–21.9%) during 1999–2016, with a trend test suggested a decreasing trend in the prevalence of HSV-2 over time (P for trend < 0.01). The prevalence of asthma was 13.1% (6457/49463), (95% CI: 12.8–13.4%), but the prevalence was increasing (P for trend < 0.01). The prevalence of co-existing HSV-2 and asthma was 3.4% (798/23555), (95% CI: 3.2–3.6%), and the trend test for the rate was not statistically different (P for trend = 0.26). Results are presented in **Supplementary Tables 1–3** and **Figure 2**.

Baseline characteristics of study participants

A total of 22,528 participants were eventually included, of whom 3,164 were asthmatic and 4,819 were HSV-2 antibody positive. A higher proportion of participants with asthma had HSV-2 infection than non-asthmatic participants ($p < 0.01$) (**Table 1**).

The association between Herpes simplex virus type 2 and asthma

There was a positive association between HSV-2 and asthma (OR = 1.15, 95% CI: 1.04–1.27) (**Table 2**). Stratified analyses suggested that sensitive individuals with statistical differences were male (OR = 1.23, 95% CI: 1.03–1.47), White race (OR = 1.19, 95% CI: 1.01–1.40), 30 ≤ age (years) < 40 (OR = 1.29, 95% CI: 1.09–1.53), BMI ≥ 28 kg/m^2 (OR = 1.30, 95% CI: 1.13–1.48), 1.39 ≤ PIR < 3.49 (OR = 1.23, 95% CI: 1.03, 1.45), and smoking participants (OR = 1.23, 95% CI: 1.06–1.43). In addition, this positive relationship was more pronounced for those with education below high school level than for other education levels (OR = 1.18, 95% CI: 0.94–1.47). The sensitive population in the fully adjusted model condition is shown in **Figure 3**.

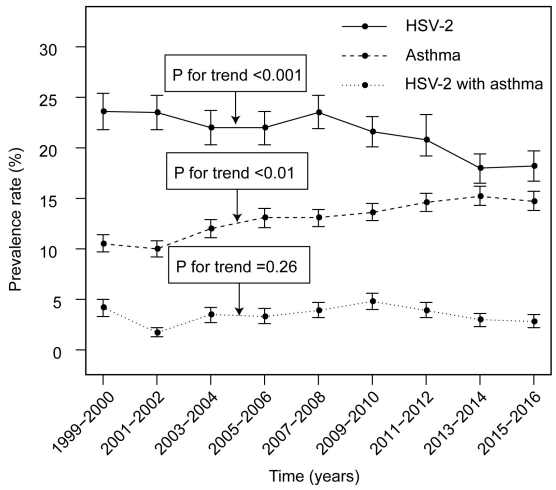

FIGURE 2
Prevalence and trends of HSV-2 infection and asthma. HSV-2, Herpes simplex virus type 2.

TABLE 2 Association between HSV-2 infection and asthma.

Characteristic	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
HSV-2 (–)	1.0	1.0	1.0
HSV-2 (+)	1.28 (1.18, 1.40)	1.27 (1.15, 1.40)	1.15 (1.04, 1.27)
Subgroups			
Gender			
Male	1.13 (0.97, 1.33)	1.28 (1.08, 1.52)	1.23 (1.03, 1.47)
Female	1.28 (1.15, 1.42)	1.26 (1.12, 1.42)	1.09 (0.96, 1.24)
Race			
Mexican American	1.10 (0.81, 1.51)	1.18 (0.85, 1.63)	1.07 (0.76, 1.50)
White	1.28 (1.10, 1.48)	1.33 (1.15, 1.55)	1.19 (1.01, 1.40)
Black	1.12 (0.96, 1.31)	1.16 (0.99, 1.38)	1.16 (0.97, 1.38)
Other race	1.34 (1.08, 1.68)	1.42 (1.13, 1.79)	1.09 (0.84, 1.40)
Age (years)			
< 30	1.27 (1.07, 1.52)	1.15 (0.95, 1.39)	1.10 (0.90, 1.34)
30 ≤ age < 40	1.50 (1.29, 1.74)	1.39 (1.18, 1.64)	1.29 (1.09, 1.53)
≥ 40	1.38 (1.20, 1.60)	1.22 (1.04, 1.43)	1.05 (0.88, 1.24)
BMI (kg/m^2)			
< 24	0.93 (0.75, 1.15)	0.94 (0.75, 1.18)	0.86 (0.68, 1.08)
24–27.9	1.15 (0.96, 1.39)	1.18 (0.96, 1.44)	1.07 (0.86, 1.32)
≥ 28	1.42 (1.27, 1.60)	1.38 (1.21, 1.57)	1.30 (1.13, 1.48)
PIR (%)			
< 1.39	1.33 (1.16, 1.53)	1.20 (1.03, 1.40)	1.09 (0.93, 1.28)
1.39–3.49	1.29 (1.12, 1.50)	1.29 (1.10, 1.52)	1.23 (1.03, 1.45)
≥ 3.49	1.12 (0.93, 1.35)	1.15 (0.94, 1.41)	1.10 (0.89, 1.35)
Education			
< High school	1.61 (1.34, 1.93)	1.32 (1.07, 1.62)	1.18 (0.94, 1.47)
High school	1.22 (1.02, 1.47)	1.25 (1.02, 1.53)	1.14 (0.92, 1.41)
> High school	1.26 (1.12, 1.42)	1.29 (1.13, 1.47)	1.13 (0.99, 1.30)
Smoker			
Yes	1.24 (1.10, 1.41)	1.26 (1.09, 1.45)	1.23 (1.06, 1.43)
No	1.25 (1.11, 1.42)	1.15 (1.00, 1.31)	1.06 (0.92, 1.22)

Model 1: No covariates were adjusted.
Model 2: Age, gender, race were adjusted.
Model 3: Age, gender, race, body mass index, poverty to income ratio, education, marital status, family members, smoker, alcohol drinking, sexual intercourse, used injecting drugs, close relatives with asthma were adjusted.
The model is not adjusted for the stratification variable itself in the subgroup analysis.
HSV-2, Herpes simplex virus type 2; BMI, Body mass index (kg/m^2); PIR, Ratio of family income to poverty.

Discussion

In this study, we first assessed changes in the prevalence of HSV-2, asthma and co-morbidities of both in the United States from 1999–2016. Similar to the results of previous studies, the prevalence of HSV-2 infection showed a decreasing trend over time, which is closely related to past public health efforts (24–26). For asthma, smoking, environmental pollution and climate change may be potential reasons for the continued increase in asthma prevalence (8). In addition, we demonstrated a positive association between HSV-2 and asthma (OR = 1.15, 95% CI: 1.04–1.27) and identified sensitive cohorts.

Although the study by Zein et al. found that the prevalence of asthma would shift from males to females after adolescence (27), the stratified analysis in this study suggested that the positive association between HSV-2 infection and asthma was more pronounced in the male population, and that this positive association may exist because of the higher proportion of males who smoke, which has become known to be a significant factor that can contribute to asthma (28). Neither asthma nor HSV-2 infection appears to be prevalent in populations of white ethnicity (29, 30). However, on the basis of the positive association between the two diseases suggested by this study, White race were more sensitive. Combined with the results of the baseline patient data in **Table 1**, the proportion of patients with asthma in this study was indeed higher for the White race. Although there are still no larger cohort studies that have found similar results, whether HSV-2 infection exhibits a more severe Th2 response (11, 31) and thus causes asthma can explain the greater susceptibility to asthma after HSV-2 infection in White race compared to other races remains to be further validated by subsequent studies.

A study based on the National Center for Health Statistics (NCHS) confirmed that the prevalence of HSV-2 increases with age (age range 14–49 years), with a positive rate of up to 21.2% in the 40–49 age group (30). Although the age cut-off for late-onset asthma is still controversial, the prevailing view is that 50 years is a reasonable value (32). The proportion of the cohort with late-onset asthma is clearly smaller compared to other age groups, and evidence from epidemiological studies has shown that the proportion of patients with asthma decreases progressively with age. This may be the reason why our study found that the positive association between HSV-2

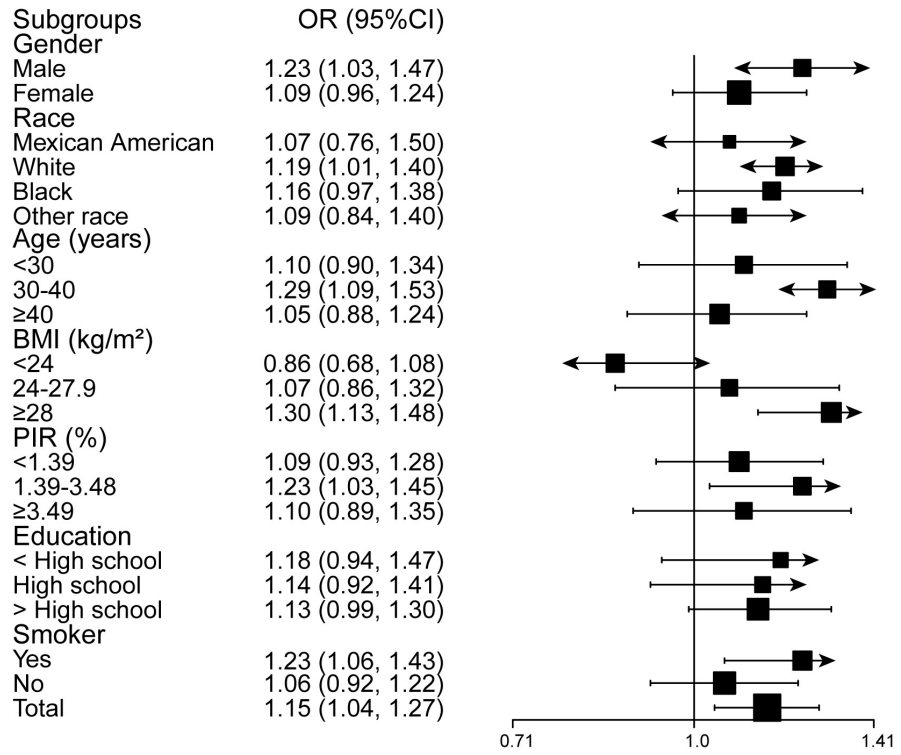

FIGURE 3
Subgroups analyses of the association between HSV-2 and asthma. HSV-2, Herpes simplex virus type 2. All the covariates in **Table 1** were adjusted.

infection and asthma was more pronounced in participants aged 30–39 years.

In our study, we found that the positive association between HSV-2 infection and asthma was more pronounced in obese participants. There is no denying that obesity is closely associated with asthma and that obese asthma patients have more severe clinical symptoms and a poorer quality of life (33). Asthma as a chronic disease imposes a significant financial burden on society and individuals (34), and although children as a high prevalence group of asthma place greater socio-economic pressure, studies have shown that the average cost to individuals for managing asthma increases with age, and for groups with very low financial capacity may choose to discontinue treatment (35). This might explain why the positive association between HSV-2 infection and asthma in our study was more pronounced in participants of moderate financial capacity. Although the stratified analysis in this study did not yield statistically significant differences between the different education levels, the effect sizes of the regression models could somewhat suggest that the positive association between HSV-2 and asthma might improve with increasing education level.

Although cross-sectional studies cannot be used as evidence to explain causality, to our knowledge, our study is the first to explore the relationship between HSV-2 infection and asthma. Although not all cohorts were statistically significant in the stratified analysis, the trend toward a positive association between HSV-2 infection and asthma was stable on the basis of adjustment for different covariates.

However, there were also some limitations to our study. For example, risk factors for asthma are still not fully identified and we could not ensure that the full range of confounding factors were included as covariates in the adjustment. Secondly, due to the characteristics of the available data in NHANES, the diagnosis of asthma in this study was based on participants' responses to a questionnaire, and it might have been difficult for us to discriminate between participants with non-allergic and allergic asthma and to grade their disease severity based on ancillary tests. To further explore the correlation between HSV-2 and asthma, follow-up studies will need to be supplemented with more complete information. In addition, cross-sectional studies are naturally unavoidable in terms of missing variables, and although we have treated missing variables accordingly, the impact of missing variables on the final results might still be difficult to avoid, so conclusions from cross-sectional studies such as these need to be treated with caution. Finally, due to the presence of missing variables, we did not stratify the characteristics of participants with missing variables in order to avoid biasing the results of the stratification analysis by

missing variables and to limit our study from further identifying potential special populations of interest.

Conclusion

A positive correlation existed between HSV-2 infection and asthma. While the trend of HSV-2 infection decreased over time, the prevalence of asthma was on the rise. Male, white race, age 30–40 years, weight $\geq$ 28 kg/m^2, 1.39 $\leq$ PIR $<$ 3.49, smokers should be more cautious in the positive association between HSV-2 infection and asthma.

Data availability statement

The original contributions presented in this study are included in the article/**Supplementary material**, further inquiries can be directed to the corresponding author.

Author contributions

XZ: data analysis. XQ: manuscript writing. HQ and YJ: manuscript editing. KH: study design and quality control. All authors agreed on the journal to which the article was to be submitted and agreed to take responsibility for all aspects of the work.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.943706/full#supplementary-material

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