Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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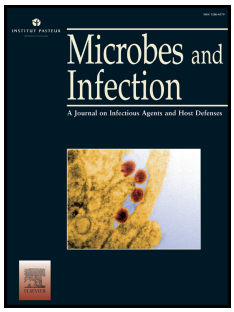

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A systematical association analysis of 25 common virus infection and genetic susceptibility of COVID-19 infection

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Abstract

Objectives: Previous studies identified a number of diseases were associated with 2019 coronavirus disease (COVID-19). However, the associations between these diseases related viral infections and COVID-19 remains unknown now.

Methods: In this study, we utilized single nucleotide polymorphisms (SNPs) related to COVID-19 from genome-wide association study (GWAS) and individual-level genotype data from the UK biobank to calculate polygenic risk scores (PRS) of 487,409 subjects for eight COVID-19 clinical phenotypes. Then, multiple logistic regression models were established to assess the correlation between serological measurements (positive/negative) of 25 viruses and the PRS of eight COVID-19 clinical phenotypes. And we performed stratified analyses by age and gender.

Results: In whole population, we identified 12 viruses associated with the PRS of COVID-19 clinical phenotypes, such as *VZV seropositivity for Varicella Zoster Virus* (Unscreened/Exposed_Negative: $\beta = 0.1361$, $P = 0.0142$; Hospitalized/Unscreened: $\beta = 0.1167$, $P = 0.0385$) and *MCV seropositivity for Merkel Cell Polyomavirus* (Unscreened/Exposed_Negative: $\beta = -0.0614$, $P = 0.0478$). After age stratification, we identified seven viruses associated with the PRS of eight COVID-19 clinical phenotypes. After gender stratification, we identified five viruses associated with the PRS of eight COVID-19 clinical phenotypes in the women group.

Conclusion: Our study findings suggest that the genetic susceptibility to different COVID-19 clinical phenotypes is associated with the infection status of various common viruses.

Keywords: common viral infections, coronavirus disease 2019, positive serological measurements, genetic susceptibility, genome-wide association study

1. Introduction

The coronavirus disease 2019 (COVID-19) pandemic has resulted in over 603 million infections and more than 6.4 million deaths worldwide as of July 31, 2022, casuing a significant disease burden for countries around the world[1]. COVID-19 is caused by the highly contagious severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which presents with a wide range of clinical symptoms, from asymptomatic infection or mild illness to serious illness requiring hospitalization and mechanical ventilation[2]. Previous study has found that clinical variation in COVID-19 severity and symptom presentation may be due to differences in host genetic factors associated with immune response[3]. Therefore, changes in immune responses may be linked to different clinical manifestations of COVID-19. As research on COVID-19 infection has progressed, several single nucleotide polymorphisms (SNPs) and genes associated with different aspects of susceptibility to infection or disease severity have been identified[4], suggesting that genetic factors in the host could influence its susceptibility and severity to the virus[4, 5].

As COVID-19 prevention measures become normalized, identifying co-infection with one or more respiratory viruses can help us understand the infection status of SARS-CoV-2. During the COVID-19 pandemic, there have been increasing reports of co-infection with other pathogens in COVID-19 patients[6, 7]. A retrospective study found that 242 (94.2%) patients had co-infected with one or more pathogens, the most frequent of which were the Epstein virus Barr virus(EBV), the rhinovirus, and the adenovirus[8]. Herpes simplex virus 1 (HSV-1) and varicella zoster virus (VZV) are DNA viruses of the neurotropic alpha human herpesvirus subfamily (HHV)[9]. The virus remains dormant in the body after recovery from the initial

infection and reactivates when the immune system is compromised, causing significant damage to the host organism[10]. Although few case reports of VZV and HSV in patients with COVID-19 have been published, studies have suggested that VZV may be an indicator of potential COVID-19 infection[11]. Previous studies have identified associations between host polymorphisms in genes related to cell entry, cytokine production, and immune response with multiple viruses, and antibody responses have been found to be highly heritable (32%−48%) [12]. The HLA-B*46:01 allele in East Asian patients was associated with infection severity during the 2003 severe acute respiratory syndrome (SARS) outbreak caused by the SARS-CoV-2-related β coronavirus[13].

Researchers have discovered an association between the prevalence of COVID-19 and other viral infections[14]. In addition to age, obesity, hypertension and other common risk factors associated with increased COVID-19 severity[15], a study found that cytomegalovirus (CMV) seropositivity was associated with more than twice the risk of hospitalization due to SARS-CoV-2 infection[14]. Potential CMV infection influences future infection with other viruses and shapes the distribution of adaptive immune cell populations[16, 17]. In SARS-CoV-2 infection, CMV seropositivity results in a severe immunological signature, which is the activation of T_{EMRA} cells[18].

The aim of our study was to investigate which viral infections are associated with the genetic susceptibility to COVID-19 by using polygenic risk scores (PRS) for COVID-19 eight clinical phenotypes. PRS is a score that aggregates genetic variants to predict disease risk. In this work, we used data from the UK Biobank cohort study and established multiple logistic regression models to assess the correlation between serological results of 25 viral infections

and the PRS of COVID-19 eight clinical phenotypes.

2. Material and methods

2.1 UK Biobank Cohort

The UK Biobank cohort is a large prospective cohort study that recruited approximately 500,000 participants aged 40−69 between 2006 and 2010 (https://www.ukbiobank.ac.uk/learn-more-about-uk-biobank). Participant characteristics and other health-related indicators were collected through touchscreen questionnaires, short interviews, and a series of body measurements at 22 assessment centers in the United Kingdom[19]. The UK Biobank study was approved by the National Health Service National Research Ethics Service(11/NW/0382), and all participants provided written informed consent to participate[20]. This study was conducted with the permission from the UK Biobank (application number: 46,478).

Multi-batch genotyping was performed using two slightly different arrays, the Applied Biosystems UK BiLEVE Axiom Array from Affymetrix and the Applied Biosystems UK Biobank Axiom Array. For quality control, sex mismatches, departures from Hardy–Weinberg equilibrium, missing genotype rate >0.05 or imputation accuracy score <0.3 were excluded. Samples identified as outliers for heterozygosity and missing rates were removed. Detailed array design, genotyping and quality control procedures can be found in previous studies[19].

2.2 Common Virus Serological Measurements

In this study, we selected serological measurements of 25 common viruses from the UK Biobank (UK Biobank data fields: 23,050–23,071, 23,073–23,075). Detailed information was shown in the Supplemental tables (Table S1). The serological measurements were defined as positive or negative for each virus.

2.3 Genome-wide Association Study (GWAS) Data of COVID-19 Clinical Phenotypes

The GWAS data of COVID-19 were derived from a genetic association study of the expanded phenotypic definition of COVID-19, including eight clinical phenotypes associated with COVID-19 outcomes[5]. Detailed information of eight clinical phenotypes was presented in Supplementary tables (Table S2). Power analysis of case-control discrete traits was performed using the Purcell power calculator. Array-based genotyping and SNP calling were performed by Illumina with the GenotypeStudio platform or Quest/Athena Diagnostics. Genetic principal components were calculated to include in the association studies to control residual population structure and were computed using FlashPCA 2.0.2. Inbred-related participants were removed by using AncestryDNA. Details of the array design, genotyping, and quality control procedures have been described previously[5].

2.4 Polygenic Risk Scores (PRS) Analysis

In this study, we calculated the PRS of eight COVID-19 clinical phenotypes for each subject. SNPs of $P < 1.00\times10^{-5}$ were selected. The PRS of eight COVID-19 clinical phenotype was calculated by PLINK2.0[21], according to the formula[22]:

$$\mathrm{PRS}_m = \sum_{\mathrm{i}=1}^{\mathrm{n}} \beta_{\mathrm{i}}\, \mathrm{SNP}_{\mathrm{im}}$$

$\mathrm{PRS}_{\mathrm{m}}$ represents the PRS value of COVID-19 clinical phenotypes of the mth subject; n denotes the total number of sample size; β_{i} is the effect parameter of risk allele of the ith significant SNP associated with COVID-19 clinical phenotypes, which was obtained from the GWAS of COVID-19 clinical phenotypes; and SNPim denotes the dosage (0, 1, 2) of the risk allele of the ith SNP for the mth individual[22, 23]. The PRS of eight COVID-19 clinical phenotypes were used as instrumental variables to participate in the subsequent statistical

analysis.

2.5 Statistical Analysis

We used logistic regression models to evaluate the correlation between common viral infections and genetic predisposition to COVID-19. Serological measurements of common viruses were used as outcome variables, while the calculated PRS of eight COVID-19 clinical phenotypes was used as instrumental variable. Age, sex, Townsend deprivation index(TDI), frequency of alcohol drinking per week, frequency of smoking per day, body mass index (BMI) and 10 principal components of population structure were used as covariates. We also conducted a stratified analysis of age and gender. We set a threshold of $P < 0.05$ for suggestive significance. All statistical analyses were performed using R software.

3. Results

3.1 Descriptive characteristics of study participants

For *C. trachomatis Definition II seropositivity for Chlamydia trachomatis*, 3887 subjects were selected, 50.14% of them were woman, mean age was 57.30 years, standard deviation(SD) was 7.91. For *H. pylori Definition I seropositivity for Helicobacter pylori*, 2394 subjects were selected, 53.88% of them were woman, mean age was 56.81 (SD:7.88) years. For the other viruses, 4800 subjects were selected, 52.92% of them were women, mean age was 56.95 (SD: 7.94) years.

3.2 Viruses Associated with COVID-19 Phenotypes in the Whole Population

We first performed the logistic analysis in the whole population and identified 12 viruses associated with the PRS of COVID-19 clinical phenotypes. For example, *VZV seropositivity for Varicella Zoster Virus* was associated with *Unscreened/Exposed_Negative* (β = 0.1361, P =

0.0142), and *C. trachomatis Definition II seropositivity for Chlamydia trachomatis* was associated with *Positive/Unscreened* ($\beta = 0.2174$, $P = 0.0185$). The detailed results were shown in Table 1.

3.3 Viruses Associated with COVID-19 Phenotype After Age Stratification

In the age $\leq$ 65 years group, we identified seven viruses associated with PRS of the COVID-19 clinical phenotypes. For example, the association between *HSV-2 seropositivity for Herpes Simplex virus-2* and *Exposed_Positive/Exposed_Negative* ($\beta = 0.1017$, $P = 0.0177$) was significant. Besides, *HSV-2 seropositivity for Herpes Simplex virus-2* infection was also associated with *Positive/Negative* ($\beta = -0.0987$, $P = 0.0242$). In the age > 65 years group, we found 10 viruses associated with PRS of the COVID-19 clinical phenotypes. For example, *HSV-2 seropositivity for Herpes Simplex virus-2* was associated with *Continuous_Severity_Score* ($\beta = 0.3132$, $P = 0.0084$). In addition, *HSV-2 seropositivity for Herpes Simplex virus-2* was also associated with *Symptomatic/Paucisymptomatic* ($\beta = 0.2436$, $P = 0.0426$). The detailed results were shown in Table 2.

3.4 Viruses Significantly Associated with COVID-19 Phenotype After Gender Stratification

In the women group, we found five viruses associated with the PRS of COVID-19 clinical phenotypes. For example, *HPV 16 Definition II seropositivity for Human Papillomavirus type-16* was associated with *Exposed_Positive /Exposed_ Negative* ($\beta = -0.2766$, $P = 0.0026$), and *HPV 18 seropositivity for Human Papillomavirus type-18* was associated with *Continuous_Severity_Score* ($\beta = -0.3710$, $P = 0.0054$). In the men group, we found 14 viruses associated with the PRS of COVID-19 clinical phenotypes, such as the association between

177 *HSV-2 seropositivity for Herpes Simplex virus-2* and *Positive/Negative* (β = −0.1881, P =
178 0.0017), and the association between *JCV seropositivity for Human Polyomavirus JCV* and
179 *Exposed_Positive/Exposed_Negative* (β = 0.1237, P = 0.0023). The detailed results were
180 shown in Table 3.

181 **4. Discussion**

182 A previous study found that the severity of COVID-19 infection is influenced by host genetic
183 factors[24]. We are curious if there is a potential correlation between COVID-19-related genetic
184 information and the infection status of other viruses. In this work, we used PRS to represent an
185 individual's genetic susceptibility to COVID-19. Logistic regression models were used to
186 assess the association between multiple common viral infections and the PRS of COVID-19
187 clinical phenotypes. Our study aimed to detect which viral infections were associated with
188 genetic susceptibility to COVID-19.

189 Our study builds upon previous research by adding covariates to logistic regression models
190 for correction, in order to explore whether genetic susceptibility to COVID-19 influences the
191 risk of infection by other common viruses. We found that VZV had a significant association
192 with *Unscreened/Exposed_Negative* in the whole population. Herpes zoster is a viral skin
193 disease in which herpes zoster remains dormant in the dorsal root ganglion of the cutaneous
194 nerve after chickenpox infection[25]. Among reported COVID-19 cases, infected patients
195 exhibited diverse skin manifestations, with varicella-like lesions being one of the major skin
196 manifestations during the COVID-19 outbreak[26]. Cases of herpes zoster infection have been
197 identified in recent symptomatic COVID-19 infections[27]. It is possible that this is SARS-
198 CoV-2 could directly infect lymphocytes and promote apoptosis of lymphocytes, leading to

lymphopenia and impaired antiviral response, which may further favor herpes virus recurrence[28].

It has been found that some viruses exhibit a change in incidence with age. For example, the zoster virus demonstrates a steady increase in incidence starting at age 50 years, with the higher incidence in people over 65 years[29]. Therefore, in our study we performed a stratified analysis by controlling for age. After controlling for age variables, we found that the significant associations were not the same between the age $\leq$ 65 years group and the age > 65 years group. In the age $\leq$ 65 years group, the most significant association was found between *HSV-2 seropositivity for Herpes Simplex virus-2* and *Exposed_Positive/Exposed_Negative*. However, in the age > 65 years group, the most significant association was found between *HSV-2 seropositivity for Herpes Simplex virus-2* and *Continuous_Severity_Score*. HSV-2 causes ulcerative lesions in adults and primarily affects the genital region through sexual transmission[30]. Following primary infection, Herpes simplex virus enters the latent state in the ganglion and may emerge later, leading to recurrent active infection[31]. Recent studies been found that individuals infected with HSV could affect SARS-CoV-2 IgM/IgG serologic results due to direct binding of IgM antibodies to otherwise detected surface-modified polystyrene particles[32].

The prevalence of common viruses is also gender-dependent. For example, the epidemiology of HSV-2 differs between women and men, with a greater probability of transmission from male-to-female than female-to-male[33]. Therefore, we conducted a gender stratified analysis. After stratifying, we found more virus in the men group may be affected by the genetic susceptibility of COVID-19. For example, 14 significant associations were found

in the men group, such as HSV-2 and *Positive/Negative*, which also consist with previous studies[32]. In the women group, human papillomavirus (HPV)-associated virus infection is associated with genetic susceptibility to COVID-19. In addition, we found human herpesvirus (HHV) is also associated with genetic susceptibility to COVID-19. HHV reactivation was considered a positive polymerase chain reaction result taken at the time of COVID-19 infection[34]. The reactivation of HSV is associated with an increased risk of hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP)[35]. Overall, co-infection with herpes viruses leads to poor clinical outcomes, particularly in critically ill COVID-19 patients[11, 36].

This is a new study that explores which viral infections are associated with genetic susceptibility to COVID-19. Our study finally identified several viral infections that are associated with genetic susceptibility to COVID-19. However, there are some limitations to consider when interpreting these findings. First, our data comes from a UK biobank, which only includes information from people of European descent. Therefore, our conclusions are limited in their applicability to other racial and ethnic populations. Second, our work is only exploratory, and the results can only demonstrate correlation rather than causation. Third, although we controlled for confounding factors, there may still be potential confounding factors that we did not account for. Therefore, the association between viral infections and genetic susceptibility should be interpreted with caution. Finally, more large-scale prospective and biological studies are needed to confirm our results and elucidate the specific mechanisms involved.

In summary, our work identified viral infections that are associated with genetic susceptibility to COVID-19. These findings may help clinicians to prevent and detect the

recurrence of other viruses closely related to COVID-19 in a timely manner. Moreover, this association might assist clinicians in identifying patients with a poorer prognosis.

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Institutional Review Board Statement

This study has been approved by UK Biobank (Application number: 46478) and obtained health-related records of participants.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Disclosure

All authors report no biomedical financial interests or potential conflicts of interest.

Author contributions

Na Zhang: Writing – original draft, Conceptualization, Formal analysis. **Yujing Chen**: Writing – review & editing, Formal analysis. **Chun'e Li**: Formal analysis. **Xiaoyue Qin**: Writing – review & editing. **Dan He**: Methodology. **Wenming Wei**: Validation. **Yijing Zhao**: Software. **Qingqing Cai**: Software. **Sirong Shi**: Visualization. **Xiaoge Chu**: Visualization. **Yan Wen**: Investigation. **Yumeng Jia**: Investigation. **Feng Zhang**: Supervision, Project administration.

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Legends for Figures and Tables

Figure 1: Forest plots of the results of logistic regression analysis in the whole population.

(a) *Continuous_Severity_Score*;

(b) *Exposed_Positive/Exposed_ Negative*;

(c) *Hospitalized/Not_Hospitalized*;

(d) *Hospitalized/Unscreened*

Note: Odds ratio (OR) forest plot of the PRS of COVID-19 clinical phenotypes . Use forest plot to visualize logistic regression analysis. The outcome variables were serological measurements of 25 viruses. The instrumental variables were the PRS of COVID-19 clinical phenotypes.

Figure 2: Forest plots of the results of logistic regression analysis in the whole population.

(a) *Positive/Negative*;

(b) *Positive/Unscreened*;

(c) *Symptomatic/Paucisymptomatic*;

(d) *Unscreened/Exposed_Negative*

Note: Odds ratio (OR) forest plot of the PRS of COVID-19 clinical phenotypes . Use forest plot to visualize logistic regression analysis. The outcome variables were serological measurements of 25 viruses. The instrumental variables were the PRS of COVID-19 clinical phenotypes.

Table 1: Viral infections associated with COVID-19 clinical phenotypes in the whole population

Table 2: Viral infections associated with COVID-19 clinical phenotypes in the age < 65 years group and the age > 65 years group

Table 3: Viral infections associated with COVID-19 clinical phenotypes in the women group

393 and the men group

Table 1: Viral infections associated with COVID-19 clinical phenotypes in whole population

Outcome Variable	Instrumental Variable	β	P
Unscreened/Exposed_Negative	VZV seropositivity for Varicella Zoster Virus	0.1361	0.0142
Positive/Unscreened	C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.2174	0.0185
Exposed_Positive/Exposed_Negative	HSV-2 seropositivity for Herpes Simplex virus-2	0.0935	0.0192
Positive/Negative	HSV-1 seropositivity for Herpes Simplex virus-1	0.0718	0.0213
Exposed_Positive/Exposed_Negative	HBV seropositivity for Hepatitis B Virus	0.2722	0.0219
Hospitalized/Unscreened	VZV seropositivity for Varicella Zoster Virus	0.1167	0.0385
Positive/Unscreened	HCV seropositivity for Hepatitis C Virus	0.7220	0.0398
Exposed_Positive/Exposed_Negative	KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	-0.1044	0.0444
Positive/Negative	HSV-2 seropositivity for Herpes Simplex virus-2	-0.0814	0.0446
Unscreened/Exposed_Negative	MCV seropositivity for Merkel Cell Polyomavirus	-0.0614	0.0478
Unscreened/Exposed_Negative	T. gondii seropositivity for Toxoplasma gondii	0.0677	0.0481
Unscreened/Exposed_Negative	HSV-2 seropositivity for Herpes Simplex virus-2	0.0817	0.0493

Note: The threshold of significance is $P < 0.05$.

Table 2: Viral infections associated with COVID-19 clinical phenotypes in the age ≤ 65 years group and the age > 65 years group

Group	Outcome Variable	Instrumental Variable	β	P
Age ≤ 65 years	Exposed_Positive/Exposed_Negative	HSV-2 seropositivity for Herpes Simplex virus-2	0.1017	0.0177
	Positive/Negative	HHV-6B seropositivity for Human Herpesvirus-6	-0.0869	0.0226
	Positive/Negative	HSV-2 seropositivity for Herpes Simplex virus-2	-0.0987	0.0242
	Positive/Negative	HSV-1 seropositivity for Herpes Simplex virus-1	0.0748	0.0270
	Exposed_Positive/Exposed_Negative	KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	-0.1208	0.0353
	Unscreened/Exposed_Negative	VZV seropositivity for Varicella Zoster Virus	0.1206	0.0432
	Hospitalized/Not_Hospitalized	HBV seropositivity for Hepatitis B Virus	-0.2565	0.0464
Age > 65 years	Continuous_Severity_Score	HSV-2 seropositivity for Herpes Simplex virus-2	0.3132	0.0084
	Positive/Negative	HHV-6B seropositivity for Human Herpesvirus-6	0.2150	0.0149
	Hospitalized/Unscreened	KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	-0.3371	0.0171
	Unscreened/Exposed_Negative	BKV seropositivity for Human Polyomavirus BKV	0.3491	0.0208
	Continuous_Severity_Score	HHV-6 overall seropositivity for Human Herpesvirus-6	-0.2731	0.0323
	Exposed_Positive/Exposed_Negative	HPV 18 seropositivity for Human Papillomavirus type-18	-0.5712	0.0343
	Hospitalized/Not_Hospitalized	C. trachomatis Definition I seropositivity for Chlamydia trachomatis	-0.2309	0.0367
	Symptomatic/Paucisymptomatic	HPV 16 Definition I seropositivity for Human Papillomavirus type-16	-0.5834	0.0368
	Symptomatic/Paucisymptomatic	HSV-2 seropositivity for Herpes Simplex virus-2	0.2436	0.0426
	Positive/Unscreened	HHV-6B seropositivity for Human Herpesvirus-6	0.1801	0.0465

Note: The threshold of significance is $P < 0.05$.

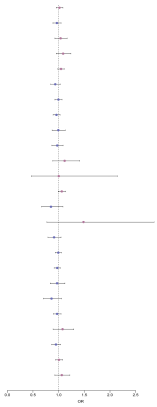
Table 3: Viral infections associated with COVID-19 clinical phenotypes in the women group and the men group

Group	Outcome Variable	Instrumental Variable	*β*	*P*
Women	Exposed_Positive/Exposed_Negative	HPV 16 Definition II seropositivity for Human Papillomavirus type-16	-0.2766	0.0026
	Continuous_Severity_Score	HPV 18 seropositivity for Human Papillomavirus type-18	-0.3710	0.0054
	Hospitalized/Not_Hospitalized	HHV-7 seropositivity for Human Herpesvirus-7	-0.2380	0.0230
	Symptomatic/Paucisymptomatic	HPV 16 Definition II seropositivity for Human Papillomavirus type-16	-0.2105	0.0252
	Hospitalized/Unscreened	BKV seropositivity for Human Polyomavirus BKV	-0.1802	0.0356
Men	Positive/Negative	HSV-2 seropositivity for Herpes Simplex virus-2	-0.1881	0.0017
	Exposed_Positive/Exposed_Negative	JCV seropositivity for Human Polyomavirus JCV	0.1237	0.0023
	Positive/Negative	HHV-6 overall seropositivity for Human Herpesvirus-6	-0.1986	0.0048
	Positive/Unscreened	C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.3021	0.0078
	Unscreened/Exposed_Negative	T. gondii seropositivity for Toxoplasma gondii	0.1269	0.0122
	Positive/Negative	KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	-0.1936	0.0126
	Unscreened/Exposed_Negative	H. pylori Definition I seropositivity for Helicobacter pylori	0.1633	0.0162
	Positive/Unscreened	HPV 16 Definition II seropositivity for Human Papillomavirus type-16	0.2164	0.0256
	Positive/Negative	HSV-1 seropositivity for Herpes Simplex virus-1	0.0989	0.0285
	Positive/Negative	HHV-6A seropositivity for Human Herpesvirus-6	-0.1090	0.0308
	Exposed_Positive/Exposed_Negative	H. pylori Definition I seropositivity for Helicobacter pylori	0.1312	0.0333
	Unscreened/Exposed_Negative	VZV seropositivity for Varicella Zoster Virus	0.1913	0.0364
	Hospitalized/Not_Hospitalized	JCV seropositivity for Human Polyomavirus JCV	-0.0876	0.0417
	Exposed_Positive/Exposed_Negative	HSV-2 seropositivity for Herpes Simplex virus-2	0.1158	0.0445

Note: The threshold of significance is $P < 0.05$.

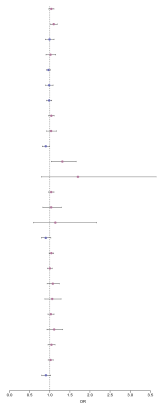
(a)

Virus	P	OR(95%CI)
HSV-1 seropositivity for Herpes Simplex virus-1	0.639	1.015(0.953- 1.082)
HSV-2 seropositivity for Herpes Simplex virus-2	0.397	0.965(0.888- 1.048)
VZV seropositivity for Varicella Zoster Virus	0.518	1.038(0.926- 1.164)
EBV seropositivity for Epstein-Barr Virus	0.211	1.087(0.954- 1.237)
CMV seropositivity for Human Cytomegalovirus	0.144	1.046(0.985- 1.110)
HHV-6 overall seropositivity for Human Herpesvirus-6	0.175	0.934(0.846- 1.031)
HHV-6A seropositivity for Human Herpesvirus-6	0.884	0.995(0.928- 1.067)
HHV-6B seropositivity for Human Herpesvirus-6	0.227	0.957(0.892- 1.028)
HHV-7 seropositivity for Human Herpesvirus-7	0.914	0.993(0.873- 1.130)
KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	0.615	0.972(0.868- 1.087)
HBV seropositivity for Hepatitis B Virus	0.349	1.117(0.886- 1.408)
HCV seropositivity for Hepatitis C Virus	0.996	1.002(0.468- 2.144)
T. gondii seropositivity for Toxoplasma gondii	0.090	1.061(0.991- 1.135)
HTLV-1 seropositivity for Human T-Lymphotropic Virus 1	0.191	0.850(0.665- 1.085)
HIV-1 seropositivity for Human Immunodeficiency Virus	0.239	1.484(0.769- 2.861)
BKV seropositivity for Human Polyomavirus BKV	0.184	0.911(0.793- 1.045)
JCV seropositivity for Human Polyomavirus JCV	0.805	0.993(0.935- 1.053)
MCV seropositivity for Merkel Cell Polyomavirus	0.366	0.972(0.913- 1.034)
HPV 16 Definition I seropositivity for Human Papillomavirus type-16	0.673	0.969(0.836- 1.123)
HPV 18 seropositivity for Human Papillomavirus type-18	0.149	0.861(0.703- 1.055)
C. trachomatis Definition I seropositivity for Chlamydia trachomatis	0.412	0.969(0.897- 1.046)
C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.441	1.076(0.893- 1.295)
H. pylori Definition I seropositivity for Helicobacter pylori	0.235	0.947(0.865- 1.036)
H. pylori Definition II seropositivity for Helicobacter pylori	0.856	1.006(0.941- 1.076)
HPV 16 Definition II seropositivity for Human Papillomavirus type-16	0.398	1.061(0.925- 1.217)



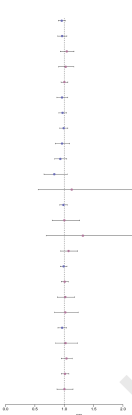
(b)

P	OR(95%CI)
0.204	1.039(0.979- 1.103)
0.019	1.098(1.015- 1.187)
0.912	0.994(0.893- 1.106)
0.762	1.018(0.905- 1.146)
0.247	0.968(0.915- 1.023)
0.748	0.985(0.898- 1.081)
0.634	0.984(0.922- 1.051)
0.259	1.039(0.972- 1.110)
0.586	1.033(0.918- 1.163)
0.044	0.901(0.814- 0.997)
0.022	1.313(1.040- 1.657)
0.173	1.700(0.792- 3.649)
0.280	1.036(0.972- 1.104)
0.760	1.035(0.830- 1.291)
0.691	1.139(0.600- 2.161)
0.123	0.901(0.789- 1.029)
0.167	1.040(0.984- 1.099)
0.934	1.002(0.946- 1.062)
0.306	1.076(0.935- 1.238)
0.539	1.061(0.878- 1.283)
0.452	1.028(0.957- 1.105)
0.251	1.109(0.930- 1.323)
0.333	1.042(0.958- 1.134)
0.507	1.021(0.960- 1.087)
0.117	0.905(0.798- 1.025)



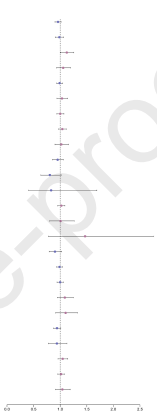
(c)

Virus	P	OR(95%CI)
HSV-1 seropositivity for Herpes Simplex virus-1	0.166	0.957(0.899- 1.018)
HSV-2 seropositivity for Herpes Simplex virus-2	0.368	0.964(0.889- 1.045)
VZV seropositivity for Varicella Zoster Virus	0.456	1.043(0.933- 1.166)
EBV seropositivity for Epstein-Barr Virus	0.701	1.025(0.904- 1.163)
CMV seropositivity for Human Cytomegalovirus	0.949	1.002(0.945- 1.062)
HHV-6 overall seropositivity for Human Herpesvirus-6	0.430	0.952(0.874- 1.059)
HHV-6A seropositivity for Human Herpesvirus-6	0.393	0.971(0.907- 1.039)
HHV-6B seropositivity for Human Herpesvirus-6	0.779	0.990(0.924- 1.061)
HHV-7 seropositivity for Human Herpesvirus-7	0.548	0.952(0.849- 1.091)
KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	0.220	0.933(0.836- 1.042)
HBV seropositivity for Hepatitis B Virus	0.119	0.830(0.656- 1.050)
HCV seropositivity for Hepatitis C Virus	0.738	1.127(0.557- 2.280)
T. gondii seropositivity for Toxoplasma gondii	0.675	0.986(0.922- 1.054)
HTLV-1 seropositivity for Human T-Lymphotropic Virus 1	0.992	1.001(0.794- 1.262)
HIV-1 seropositivity for Human Immunodeficiency Virus	0.400	1.317(0.694- 2.499)
BKV seropositivity for Human Polyomavirus BKV	0.309	1.073(0.937- 1.230)
JCV seropositivity for Human Polyomavirus JCV	0.699	0.989(0.933- 1.048)
MCV seropositivity for Merkel Cell Polyomavirus	0.823	1.007(0.948- 1.070)
HPV 16 Definition I seropositivity for Human Papillomavirus type-16	0.811	1.018(0.881- 1.176)
HPV 18 seropositivity for Human Papillomavirus type-18	0.866	1.017(0.837- 1.236)
C. trachomatis Definition I seropositivity for Chlamydia trachomatis	0.341	0.964(0.894- 1.039)
C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.810	1.022(0.853- 1.226)
H. pylori Definition I seropositivity for Helicobacter pylori	0.410	1.038(0.949- 1.136)
H. pylori Definition II seropositivity for Helicobacter pylori	0.709	1.012(0.949- 1.080)
HPV 16 Definition II seropositivity for Human Papillomavirus type-16	0.964	1.003(0.877- 1.148)



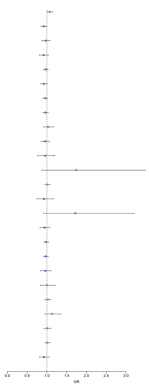
(d)

P	OR(95%CI)
0.178	0.959(0.902- 1.019)
0.681	0.984(0.908- 1.065)
0.038	1.124(1.006- 1.255)
0.392	1.056(0.932- 1.196)
0.696	0.989(0.933- 1.047)
0.486	1.034(0.940- 1.138)
0.978	1.001(0.936- 1.070)
0.269	1.040(0.971- 1.113)
0.737	1.022(0.902- 1.157)
0.369	0.952(0.854- 1.060)
0.073	0.805(0.634- 1.020)
0.605	0.829(0.407- 1.688)
0.530	1.021(0.957- 1.090)
0.954	1.007(0.801- 1.266)
0.234	1.468(0.780- 2.761)
0.121	0.902(0.792- 1.028)
0.672	0.988(0.933- 1.046)
0.972	0.999(0.941- 1.060)
0.235	1.087(0.947- 1.248)
0.309	1.102(0.914- 1.328)
0.102	0.940(0.874- 1.012)
0.498	0.938(0.780- 1.128)
0.303	1.047(0.958- 1.143)
0.604	1.017(0.954- 1.084)
0.549	1.041(0.912- 1.188)



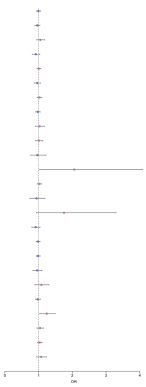
(a)

Virus	P	OR(95%CI)
HSV-1 seropositivity for Herpes Simplex virus-1	0.021	1.075(1.011- 1.142)
HSV-2 seropositivity for Herpes Simplex virus-2	0.045	0.922(0.852- 0.998)
VZV seropositivity for Varicella Zoster Virus	0.563	0.969(0.869- 1.079)
EBV seropositivity for Epstein-Barr Virus	0.158	0.916(0.810- 1.035)
CMV seropositivity for Human Cytomegalovirus	0.301	0.970(0.916- 1.028)
HHV-6 overall seropositivity for Human Herpesvirus-6	0.088	0.921(0.838- 1.012)
HHV-6A seropositivity for Human Herpesvirus-6	0.207	0.958(0.896- 1.024)
HHV-6B seropositivity for Human Herpesvirus-6	0.272	0.963(0.899- 1.030)
HHV-7 seropositivity for Human Herpesvirus-7	0.618	1.032(0.912- 1.168)
KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	0.394	0.954(0.857- 1.063)
HBV seropositivity for Hepatitis B Virus	0.695	0.956(0.761- 1.199)
HCV seropositivity for Hepatitis C Virus	0.118	1.742(0.868- 3.497)
T. gondii seropositivity for Toxoplasma gondii	0.721	1.012(0.948- 1.080)
HTLV-1 seropositivity for Human T-Lymphotropic Virus 1	0.489	0.923(0.735- 1.158)
HIV-1 seropositivity for Human Immunodeficiency Virus	0.089	1.719(0.920- 3.210)
BKV seropositivity for Human Polyomavirus BKV	0.371	0.941(0.824- 1.075)
JCV seropositivity for Human Polyomavirus JCV	0.498	0.981(0.926- 1.038)
MCV seropositivity for Merkel Cell Polyomavirus	0.342	0.972(0.916- 1.031)
HPV 16 Definition I seropositivity for Human Papillomavirus type-16	0.537	0.957(0.832- 1.101)
HPV 18 seropositivity for Human Papillomavirus type-18	0.985	1.002(0.828- 1.213)
C. trachomatis Definition I seropositivity for Chlamydia trachomatis	0.616	1.019(0.947- 1.096)
C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.182	1.131(0.944- 1.355)
H. pylori Definition I seropositivity for Helicobacter pylori	0.865	1.008(0.921- 1.102)
H. pylori Definition II seropositivity for Helicobacter pylori	0.697	1.013(0.950- 1.080)
HPV 16 Definition II seropositivity for Human Papillomavirus type-16	0.242	0.924(0.809- 1.055)



(b)

P	OR(95%CI)
0.861	0.995(0.935- 1.058)
0.316	0.960(0.888- 1.040)
0.353	1.053(0.944- 1.176)
0.163	0.916(0.809- 1.036)
0.777	1.008(0.952- 1.069)
0.379	0.958(0.871- 1.054)
0.488	1.024(0.957- 1.096)
0.519	0.978(0.913- 1.047)
0.644	1.030(0.908- 1.169)
0.836	1.012(0.907- 1.127)
0.773	0.967(0.768- 1.217)
0.040	2.059(1.034- 4.098)
0.502	1.023(0.958- 1.093)
0.598	0.939(0.743- 1.187)
0.081	1.754(0.933- 3.296)
0.185	0.914(0.800- 1.044)
0.636	0.986(0.931- 1.044)
0.617	0.985(0.928- 1.046)
0.533	0.956(0.830- 1.101)
0.423	1.081(0.894- 1.306)
0.519	0.976(0.907- 1.051)
0.018	1.243(1.037- 1.489)
0.360	1.043(0.954- 1.140)
0.309	1.034(0.969- 1.103)
0.291	1.074(0.941- 1.227)



(c)

Virus	P	OR(95%CI)
HSV-1 seropositivity for Herpes Simplex virus-1	0.246	0.964(0.907- 1.026)
HSV-2 seropositivity for Herpes Simplex virus-2	0.434	0.969(0.895- 1.049)
VZV seropositivity for Varicella Zoster Virus	0.723	1.020(0.915- 1.137)
EBV seropositivity for Epstein-Barr Virus	0.509	0.959(0.845- 1.087)
CMV seropositivity for Human Cytomegalovirus	0.970	0.999(0.943- 1.058)
HHV-6 overall seropositivity for Human Herpesvirus-6	0.556	1.029(0.936- 1.132)
HHV-6A seropositivity for Human Herpesvirus-6	0.521	1.022(0.956- 1.093)
HHV-6B seropositivity for Human Herpesvirus-6	0.855	0.994(0.928- 1.064)
HHV-7 seropositivity for Human Herpesvirus-7	0.887	1.009(0.890- 1.144)
KSHV seropositivity for Kaposi's Sarcoma-Associated Herpesvirus	0.500	1.038(0.931- 1.157)
HBV seropositivity for Hepatitis B Virus	0.405	1.104(0.875- 1.392)
HCV seropositivity for Hepatitis C Virus	0.948	1.024(0.495- 2.122)
T. gondii seropositivity for Toxoplasma gondii	0.927	1.003(0.939- 1.071)
HTLV-1 seropositivity for Human T-Lymphotropic Virus 1	0.603	0.941(0.747- 1.185)
HIV-1 seropositivity for Human Immunodeficiency Virus	0.933	0.972(0.507- 1.865)
BKV seropositivity for Human Polyomavirus BKV	0.607	0.965(0.844- 1.104)
JCV seropositivity for Human Polyomavirus JCV	0.773	1.008(0.952- 1.068)
MCV seropositivity for Merkel Cell Polyomavirus	0.640	0.986(0.929- 1.047)
HPV 16 Definition I seropositivity for Human Papillomavirus type-16	0.293	0.928(0.807- 1.067)
HPV 18 seropositivity for Human Papillomavirus type-18	0.325	0.910(0.754- 1.098)
C. trachomatis Definition I seropositivity for Chlamydia trachomatis	0.791	0.990(0.920- 1.066)
C. trachomatis Definition II seropositivity for Chlamydia trachomatis	0.352	0.918(0.767- 1.099)
H. pylori Definition I seropositivity for Helicobacter pylori	0.950	1.003(0.919- 1.095)
H. pylori Definition II seropositivity for Helicobacter pylori	0.867	1.006(0.943- 1.073)
HPV 16 Definition II seropositivity for Human Papillomavirus type-16	0.132	0.904(0.793- 1.031)

(d)

P	OR(95%CI)
0.446	1.024(0.963- 1.090)
0.049	1.085(1.000- 1.177)
0.014	1.146(1.028- 1.278)
0.779	1.018(0.898- 1.155)
0.670	0.987(0.931- 1.047)
0.933	1.004(0.911- 1.106)
0.964	0.994(0.929- 1.064)
0.213	1.045(0.975- 1.120)
0.749	1.021(0.900- 1.159)
0.499	1.039(0.930- 1.160)
0.439	1.097(0.868- 1.387)
0.394	0.739(0.370- 1.480)
0.048	1.070(1.001- 1.144)
0.466	1.093(0.861- 1.386)
0.634	0.857(0.453- 1.620)
0.524	1.045(0.913- 1.195)
0.820	1.007(0.950- 1.067)
0.048	0.941(0.885- 0.999)
0.998	1.000(0.867- 1.153)
0.762	0.971(0.800- 1.177)
0.123	1.061(0.984- 1.143)
0.705	1.036(0.861- 1.247)
0.188	1.062(0.971- 1.162)
0.432	1.027(0.962- 1.096)
0.938	1.005(0.878- 1.151)