

Immune responses to infection and autoimmune diseases in the UK biobank

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ABSTRACT

Background: Infections may trigger autoimmunity, but large-scale studies on antibodies to infections and their associations with autoimmune diseases are limited. We aim to better understand the etiologic role of infection. **Methods:** We analyzed 9429 UK Biobank participants for 45 antibody responses to 20 pathogens. Association between seropositivity and autoimmune diseases was assessed with logistic regression for prevalence and Cox regression for incidence, applying Bonferroni correction. 49 autoimmune diseases were ascertained via International Classification of Diseases codes and self-reported diagnoses, of which 14 were analyzed.

Results: At baseline, 671 (7.1 %, 58 % female) had at least one autoimmune disease. In males, HSV-1 seropositivity was linked to lower odds of rheumatic fever/rheumatic heart disease (odds ratio 0.29 [95 % CI 0.12–0.68]), at Bonferroni significance. At nominal significance ($p < 0.05$), eight associations were observed—positive: HHV-6B–type 1 diabetes, *H. pylori*–sarcoidosis, HPV-18–type 1 diabetes, JCV–psoriasis; inverse: *T. gondii*–celiac disease, *H. pylori*–Crohn’s disease, HSV-1–multiple sclerosis, HHV-7–rheumatoid arthritis. Of 8758 autoimmune disease-free individuals, 627 developed autoimmune diseases. In females, seropositivity to HPV-18 was associated with rheumatoid arthritis (hazard ratio 2.26 [95 % CI 1.34–3.82]), at Bonferroni significance. HRs for 3 nominal seropositivity/autoimmune disease associations (1 inverse, 2 positive) ranged from 0.42 [95 % CI 0.21–0.87] (HHV-6B/vasculitis) to 3.62 [95 % CI 1.29–10.12] (*C. trachomatis*/psoriasis) in both sexes.

Conclusions: This study examined cross-sectional and prospective associations between antibodies to infectious agents and autoimmune diseases. Inverse associations may suggest infections could train the immune system or reflect altered host immunity, while positive associations indicate potential autoimmune triggers. These findings enhance understanding of autoimmune disease etiology and provide a foundation for future mechanistic studies and hypothesis-driven research.

1. Introduction

Infections can influence the immune system, potentially triggering or exacerbating autoimmune diseases or modulating these conditions [1]. Molecular mimicry, where components of pathogens closely resemble human elements, may cause the immune system to attack its own tissue mistakenly [2]. Conversely, infections may promote immune tolerance or dampen inflammatory responses, reducing autoimmune susceptibility. Additionally, infections often modulate type I interferons, which can inhibit or enhance immune cell activity depending on the context, sometimes suppressing pro-inflammatory processes that could drive autoimmune activity [3]. Beyond molecular mimicry and tolerance,

other mechanisms such as epitope spreading and bystander activation also play important roles in infection-driven autoimmunity [4].

Various bacterial and viral infections have been implicated in the development of autoimmune diseases. One of the most well-established associations is between streptococcal infection and acute rheumatic fever (RF), which can progress to rheumatic heart disease (RHD) [5]. Epstein-Barr virus (EBV) has been associated with various autoimmune diseases, including multiple sclerosis (MS), systemic lupus erythematosus, and Sjögren’s disease [6–10]. Furthermore, the COVID-19 pandemic, in which millions experienced acute and chronic infections simultaneously, is prompting extensive research to clarify the links between infection and autoimmune diseases [11].

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Advances in understanding how infectious agents trigger autoimmunity are illuminating the role of infection in common autoimmune diseases, but previous epidemiologic studies primarily focused on the history of infection linked with autoimmune diseases and many were limited by restricted pathogen panels or retrospective study designs [5, 6,9,12]. To our knowledge, large-scale prospective studies on antibodies to infections and their associations with autoimmune diseases are limited. By exploring associations between seropositivity to common human infectious agents and the prevalent and incident autoimmune diseases in UK Biobank, we aim to better understand the etiologic role of infection in autoimmune diseases.

2. Materials and methods

2.1. Study participants

Data were obtained from the UK Biobank, a large-scale prospective study designed to explore genetic, lifestyle, and environmental factors contributing to various diseases in the general UK population [13]. Between January 1, 2006, and December 31, 2010, ~500,000 adults aged 37 to 73 were enrolled at 22 assessment centers across the UK. At baseline, participants completed a questionnaire on sociodemographic, lifestyle, medical history, and medications, and underwent physical measurements.

2.2. Assessment of seropositivity to infectious agents

We utilized serological antibodies to infectious agents, made available through the UK Biobank [14]. The Multiplex Serology panel was developed and validated by the UK Biobank in collaboration with the German Cancer Research Centre (DKFZ), and the 20 pathogens were preselected by that team based on scientific relevance and assay availability. A randomly selected ~10,000 participants had their serum analyzed using the Multiplex Serology panel, a bead-based platform that enhances enzyme-linked immunosorbent assay to measure serum immunoglobulin levels for high-throughput analysis. Each pathogen-specific assay was validated against a gold-standard reference using independent sera, exceeding the 85 % thresholds for sensitivity and specificity (median 97.0 % and 93.7 %, respectively). Further details, including the cut-offs used to determine seropositivity, by Drs. Tim Waterboer and Nicole Brenner are in Table 1 (<https://biobank.ctsu.ox.ac.uk/crystal/crystal/docs/infidisease.pdf>). The panel measured antibody responses against 45 antigens from 20 viral, bacterial, and parasite pathogens. The viral pathogens included herpes simplex virus types 1 and 2 (HSV-1 and HSV-2), varicella-zoster virus (VZV), EBV, human cytomegalovirus (CMV), human herpesviruses 6 and 7 (HHV-6 and HHV-7), Kaposi's sarcoma-associated herpesvirus (KSHV), hepatitis B and C viruses (HBV and HCV), human T-lymphotropic virus 1 (HTLV-1), human immunodeficiency virus 1 (HIV-1), BK and JC polyomaviruses (BKV and JCV), Merkel cell polyomavirus (MCV), and human papillomavirus types 16 and 18 (HPV-16 and HPV-18). The bacterial pathogens included *Chlamydia trachomatis* and *Helicobacter pylori*, while *Toxoplasma gondii* represented a protozoan parasite. All measurements were taken from samples collected during the initial assessment visit.

2.3. Ascertainment of autoimmune diseases

The definition of autoimmune disease was derived from the International Classification of Diseases 9th and 10th Revision codes found in participants' hospital inpatient records and self-reported conditions (Supplementary Table 2). We identified 39 autoimmune diseases, selected based on prior literature and criteria provided by the Autoimmune Registry [15–18]. For the analysis of individual autoimmune diseases, we focused on 14 diseases for prevalence and another 14 for incidence, each disease having at least 11 affected individuals, a

threshold chosen to balance inclusion of rare diseases with the need to ensure minimally stable estimates and avoid analyses based on extremely small case numbers (Supplementary Table 2). The diagnosis date was defined as the date when the ICD-9 or 10 code was first recorded. The comparison group for the prevalent cases consisted of individuals who had no prior diagnosis of any of the 39 autoimmune diseases included in the study.

2.4. Statistical analyses

We used multivariable-adjusted logistic regression to calculate odds ratios (ORs) and 95 % confidence intervals (CIs) for the association between seropositivity and autoimmune disease prevalence. Additionally, we used multivariable-adjusted Cox proportional hazards regression to estimate hazard ratios (HRs) and 95 % confidence intervals (CIs) for the incidence of any and specific autoimmune disease among autoimmune disease-free individuals. Participants were followed up from their recruitment until the earliest occurrence of an autoimmune disease diagnosis, death, follow-up loss, or the study's end date (October 31, 2021). Variables violating chi-squared test assumptions, such as expected cell frequencies to be at least 5, were excluded from both logistic regression and Cox models. All models were adjusted for age at recruitment, sex, race and ethnicity (Asian, Black, mixed, White, Other), socioeconomic status (Townsend deprivation score, continuous), educational level (college or university, other), body mass index (BMI kg/m², continuous), smoking (never, previous, current, unknown) and alcohol drinking status (never, previous, current, unknown). The percentages of unknown status for smoking and alcohol were all less than 1 % and were treated as a missing category. For example, socioeconomic status and education influence healthcare access and infection exposure, while BMI, smoking, and alcohol use can modulate immune responses and inflammatory pathways. Adjusting for these factors helps reduce potential confounding in estimating the association between infections and autoimmunity. To test for sex differences, we first included a sex-by-infection interaction term in the models to obtain p-interaction values, and subsequently conducted sex-stratified analyses to explore differential associations. To minimize the reverse causality, we conducted sensitivity analyses by excluding outcomes that occurred within 2 years of recruitment.

To account for multiple testing, we applied Bonferroni correction based on 22 pathogens ($0.05/22 = p < 0.0028$), treating each antigen as an independent test. We did not correct across autoimmune diseases, as the primary focus was pathogen-specific associations. We also considered nominal significance ($p < 0.05$) to avoid overlooking potential associations. All analyses were conducted using R software (version 4.3.3), and statistical tests were two-sided.

3. Results

3.1. Prevalent autoimmune diseases

A total of 9429 participants (mean [SD] age at recruitment, 56.5 [8.2] years; 56 % females; 94.2 % Whites) were analyzed for prevalent autoimmune diseases (Supplementary Table 3). At baseline, 671 (7.1 %) had at least one autoimmune disease. Participants with autoimmune diseases were older (mean 58.1 vs. 56.4 years old), had higher BMI (mean 28.0 vs. 27.3 kg/m²), were more likely to smoke (former and current combined; 49.7 vs. 43.8 %), and less likely to consume alcohol (former and current combined; 93.9 vs. 95.6 %).

Fig. 1 and Supplementary Table 4 show the associations between seropositivity to infection and prevalent autoimmune disease, for males and females combined. At the Bonferroni threshold, no antibody-autoimmune disease associations showed significance. Four positive nominal associations were observed, including HHV-6B and type 1 diabetes mellitus (T1D) (OR 2.55, 95 % CI 1.11–7.34), *H. pylori* and sarcoidosis (OR 2.38, 95 % CI 1.11–5.14), HPV-18 and T1D (OR 1.92,

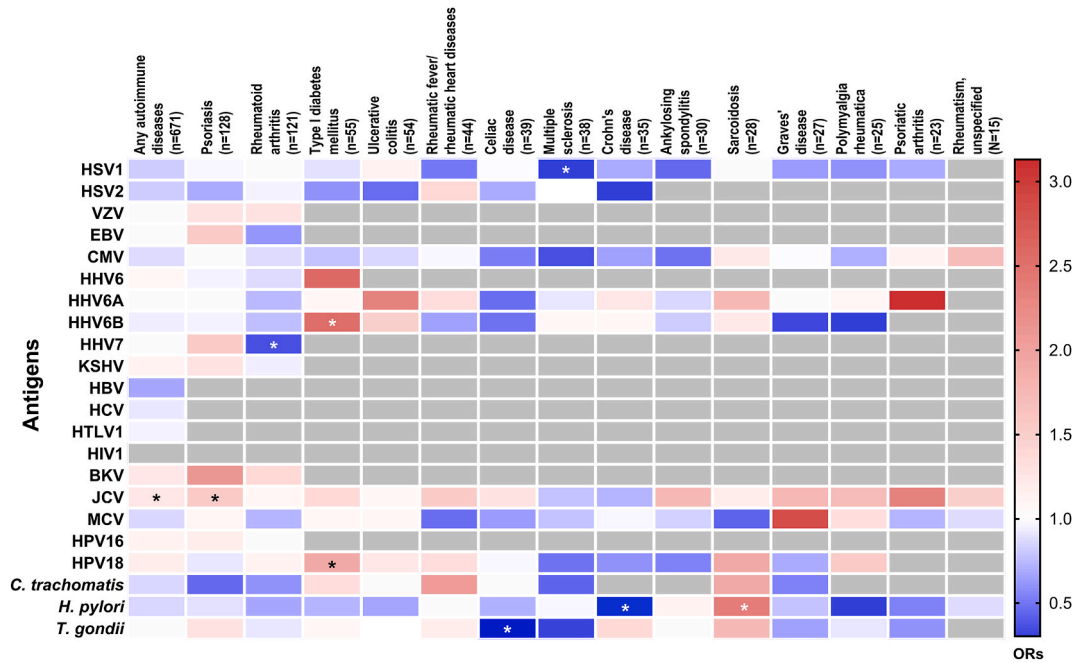


Fig. 1. Associations between seropositivity to infection and prevalent autoimmune disease in male and female combined * Significant at nominal cut-off ($p < 0.05$) ** Significant at Bonferroni cut-off. Abbreviations: HSV1: Herpes Simplex virus-1, HSV2: Herpes Simplex virus-2, VZV: Varicella Zoster Virus, EBV: Epstein-Barr Virus, CMV: Human Cytomegalovirus, HHV6: Human Herpesvirus-6, HHV6A: Human Herpesvirus-6A, HHV6B: Human Herpesvirus-6B, HHV7: Human Herpesvirus-7, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, BKV: Human Polyomavirus BKV, JCV: Human Polyomavirus JCV, MCV: Merkel Cell Polyomavirus MCV, HPV16: Human Papillomavirus type-16, HPV18: Human Papillomavirus type-18, HIV1: Human Immunodeficiency Virus, C. trachomatis: Chlamydia trachomatis, H. pylori: Helicobacter pylori, T. gondii: Toxoplasma gondii Grey colored cells indicate non-estimable ORs.

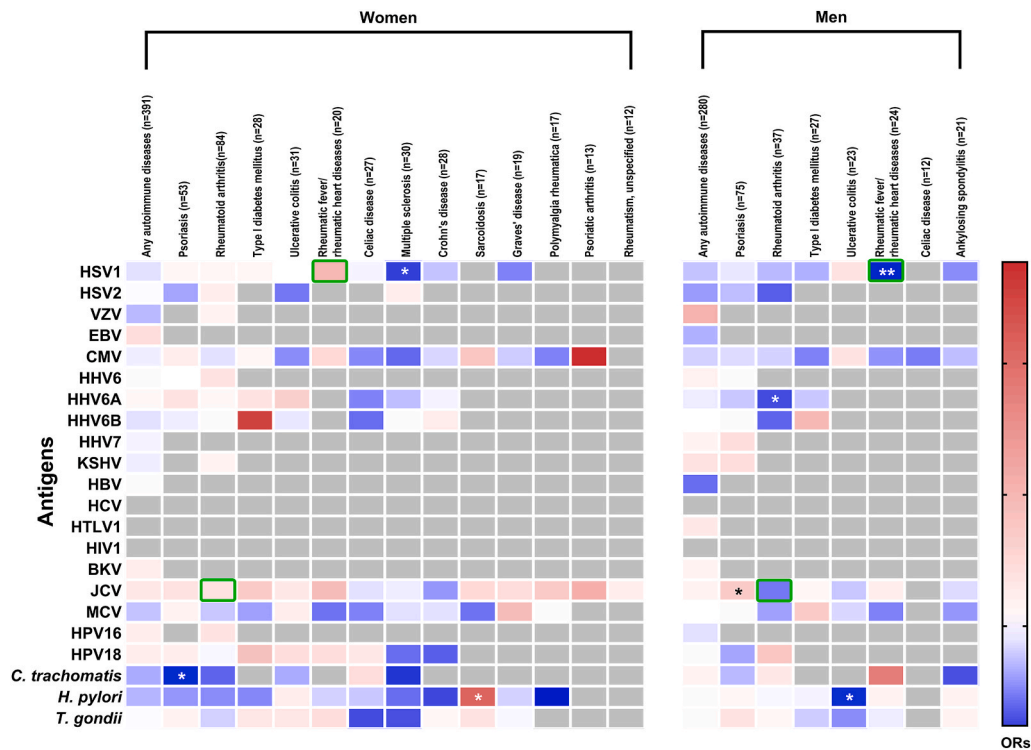


Fig. 2. Associations between seropositivity to infection and prevalent autoimmune disease by sex * Significant at nominal cut-off ($p < 0.05$). ** Significant at Bonferroni cut-off Green outlined boxes denote significant interaction effects. Abbreviations: HSV1: Herpes Simplex virus-1, HSV2: Herpes Simplex virus-2, VZV: Varicella Zoster Virus, EBV: Epstein-Barr Virus, CMV: Human Cytomegalovirus, HHV6: Human Herpesvirus-6, HHV6A: Human Herpesvirus-6A, HHV6B: Human Herpesvirus-6B, HHV7: Human Herpesvirus-7, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, BKV: Human Polyomavirus BKV, JCV: Human Polyomavirus JCV, MCV: Merkel Cell Polyomavirus MCV, HPV16: Human Papillomavirus type-16, HPV18: Human Papillomavirus type-18, HIV1: Human Immunodeficiency Virus, C. trachomatis: Chlamydia trachomatis, H. pylori: Helicobacter pylori, T. gondii: Toxoplasma gondii Grey colored cells indicate non-estimable ORs.

95 % CI 1.04–3.42), JCV and psoriasis (OR 1.54, 95 % CI 1.06–2.26). Additionally, four inverse nominal associations were observed for *T. gondii* and celiac disease (CD) (OR 0.30, 95 % CI 0.09–0.76), *H. pylori* and Crohn's disease (OR 0.38, 95 % CI 0.14–0.87), HSV-1 and MS (OR 0.45, 95 % CI 0.23–0.90), HHV-7 and rheumatoid arthritis (RA) (OR 0.50, 95 % CI 0.28–0.98).

In the sex-stratified analysis (Fig. 2 and Supplementary Tables 5–6), seropositivity to HSV-1 was associated with RF/RHD in males (OR 0.29, 95 % CI 0.12–0.68), Bonferroni-significant, but not in females (OR 2.01, 95 % CI 0.57–7.05; p-interaction=0.02). Although there was no statistical heterogeneity between sexes, three nominal associations were observed only in females: *H. pylori* and sarcoidosis (OR 3.11, 95 % CI 1.16–8.33), HSV-1 and MS (OR 0.41, 95 % CI 0.19–0.87), and *C. trachomatis* and psoriasis (OR 0.32, 95 % CI 0.10–0.98). Similarly, three nominal associations were found only in males: JCV and psoriasis (OR 1.70, 95 % CI 1.01–2.85), HHV-6A and RA (OR 0.45, 95 % CI 0.22–0.90), and *H. pylori* and ulcerative colitis (OR 0.33, 95 % CI 0.11–0.99).

3.2. Incident autoimmune diseases

Incidence analysis included 8758 participants (mean [SD] age, 56.4 [8.2] years; 55.8 % females; 94.1 % Whites) without prior autoimmune disease diagnosis (Supplementary Table 7). Over a median of 12.7-year follow-up (interquartile range 1.4 years), 627 (7.2 %) were diagnosed with at least one incident autoimmune disease. These participants were older (59.8 vs. 56.2 years old), more socioeconomically deprived (Townsend deprivation score –1.0 vs. –1.4), less educated (college or university education; 22.2 vs. 33.0 %), had higher BMI (mean 28.3 vs. 27.2 kg/m²), and were more likely to smoke (47.0 vs. 43.6 %) at baseline.

Fig. 3 and Supplementary Table 8 show associations between seropositivity to infection and incident autoimmune disease for males and females combined. No associations reached Bonferroni significance, but two positive and one inverse nominal associations were observed: *C. trachomatis* and psoriasis (HR 3.62, 95 % CI 1.29–10.12), HPV-18 and RA (HR 1.61, 95 % CI 1.03–2.53), HHV-6B and vasculitis (HR 0.42, 95 % CI 0.21–0.87).

In the sex-stratified analysis (Fig. 4 and Supplementary Tables 9–10), seropositivity to HPV-18 was associated with RA in females (HR 2.26,

95 % CI 1.34–3.82), Bonferroni-significant, but not in males (HR 0.49, 95 % CI 0.14–1.64; p-interaction=0.02). *T. gondii* was nominally associated with RA in females (HR 1.79, 95 % CI 1.08–2.97) but not in males (HR 0.62, 95 % CI 0.28–1.38; p-interaction = 0.03). Although there were no statistical differences between males and females, there was two (HHV-6 and Grave's disease, HR [95 % CI] 0.42 [0.18–0.96]; *H. pylori* and vasculitis, HR 3.81 [95 % CI 1.29–11.20] and one (HPV-18 and RF/RHD, HR [95 % CI] 1.89 [1.06–3.36]) nominal association observed in females and males, respectively.

Sensitivity analyses with a 2-year lag showed consistent HR directions and change <28.6 %, supporting the robustness of our results (Supplementary Table 11 and Fig. 1). Notably, both the main analysis and 2-year lag sensitivity analysis identified a nominal association between *C. trachomatis* and psoriasis, with the main analysis showing HR 3.62 (95 % CI 1.29–10.12) and the 2-year lag analysis showing HR 1.61 (95 % CI 1.28–16.64).

4. Discussion

Our study comprehensively examines antibodies to a wide range of infectious agents and various autoimmune diseases in a large population cohort. At the Bonferroni significance level, there were no significant associations at Bonferroni level between seropositivity to 20 infectious agents and the 14 prevalent and incident autoimmune diseases. However, sex-stratified analysis revealed inverse associations between HSV-1 and prevalent RF/RHD in males, and positive associations between HPV-18 and incident RA in females. At nominal significance level, we identified 6 positive and 8 inverse associations with prevalent autoimmune diseases, as well as 5 positive and 2 inverse associations with incident autoimmune diseases. These identified nominal-level associations suggest potential signals warranting further investigation.

Evaluating prevalent and incident autoimmune diseases separately offers unique insights. In prevalent cases, antibodies reflect past infection but cannot determine if it preceded or followed the autoimmune disease. If infections follow the onset, it could imply that individuals with autoimmune diseases are more susceptible to infections due to their altered immune status [19]. Regardless of the order, identifying associations between seropositivity to infection and autoimmune diseases can offer clues to shared pathophysiological processes [20–22]. In contrast, studying seropositivity and incidence of autoimmune diseases clarifies timing, allowing us to hypothesize that infection may play an etiological role in developing autoimmune diseases later. Consistent findings in both prevalent and incident analyses can simplify interpretations about whether the infections pose a risk or offer protection. However, discrepancies can occur. An inverse association in prevalence but positive in incidence analysis could indicate that the timing or duration of infection is crucial. Early-life infections might train and modulate immunity [23], while frequent or late-life infections could promote autoimmunity through chronic inflammation, molecular mimicry, and exposure to nuclear autoantigens [23–26]. Conversely, initial positive associations in prevalent and inverse associations in incidence analysis might suggest that mechanisms like molecular mimicry initially promote autoimmunity [27], but later, immune tolerance or anergy makes the immune system unresponsive to the infection, appearing protective [28,29]. In our study, we observed an inverse association between *C. trachomatis* and prevalent psoriasis in females but a positive association with incident psoriasis, suggesting its role may vary over time or between different stages of the disease. Interactions with other infections, such as helminthic infections affecting the Th1/Th2 balance, latent infections, or with treatments for infection and autoimmune diseases, can complicate the understanding of the infection-autoimmune disease relationship [30,31]. Additionally, analyzing incident cases without autoimmune diseases might introduce biases such as survivor bias, skewing the results. Lastly, common underlying factors or shared risk exposures may influence these associations.

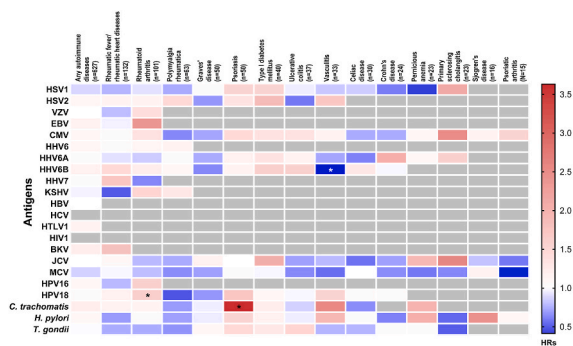


Fig. 3. Associations between seropositivity to infection and incident autoimmune disease in male and female combined * Significant at nominal cut-off (p < 0.05) ** Significant at Bonferroni cut-off HSV1: Herpes Simplex virus-1, HSV2: Herpes Simplex virus-2, VZV: Varicella Zoster Virus, EBV: Epstein-Barr Virus, CMV: Human Cytomegalovirus, HHV6: Human Herpesvirus-6, HHV6A: Human Herpesvirus-6A, HHV6B: Human Herpesvirus-6B, HHV7: Human Herpesvirus-7, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, BKV: Human Polyomavirus BKV, JCV: Human Polyomavirus JCV, MCV: Merkel Cell Polyomavirus MCV, HPV16: Human Papillomavirus type-16, HPV18: Human Papillomavirus type-18, HIV1: Human Immunodeficiency Virus, *C. trachomatis*: Chlamydia trachomatis, *H. pylori*: Helicobacter pylori, *T. gondii*: Toxoplasma gondii Grey colored cells indicate non-estimable Hrs.

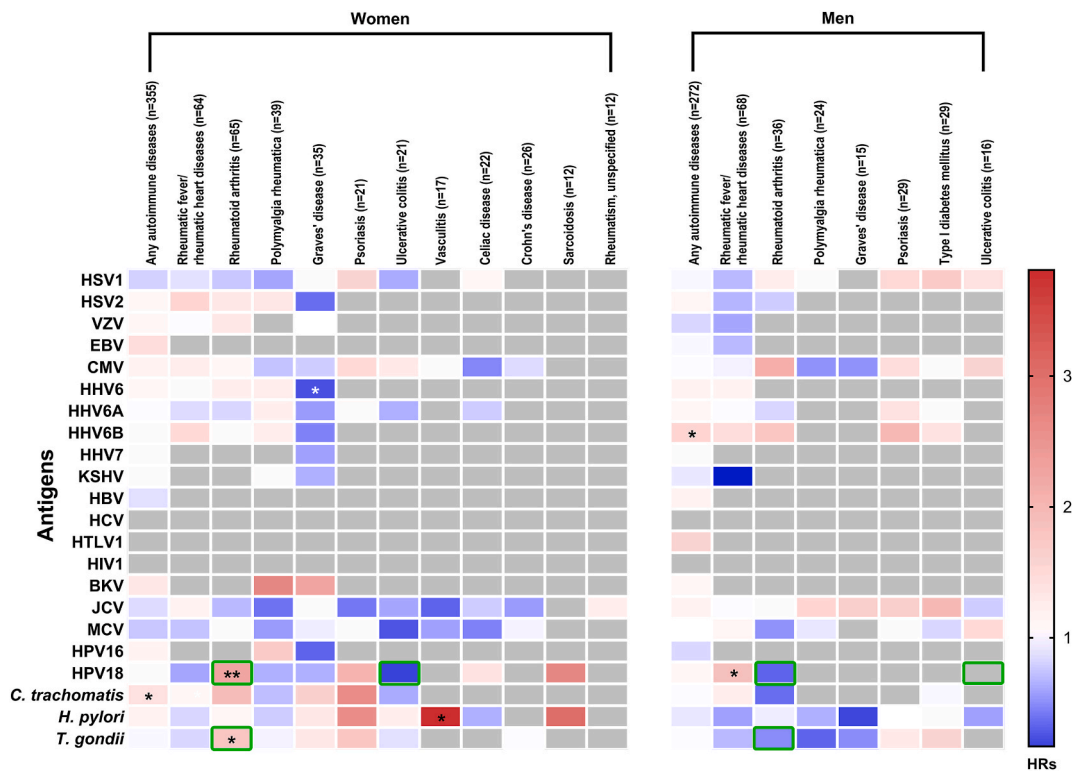


Fig. 4. Associations between seropositivity to infection and incident autoimmune disease in male and female combined * Significant at nominal cut-off ($p < 0.05$) ** Significant at Bonferroni cut-off Green outlined boxes denote significant interaction effects HSV1: Herpes Simplex virus-1, HSV2: Herpes Simplex virus-2, VZV: Varicella Zoster Virus, EBV: Epstein-Barr Virus, CMV: Human Cytomegalovirus, HHV6: Human Herpesvirus-6, HHV6A: Human Herpesvirus-6A, HHV6B: Human Herpesvirus-6B, HHV7: Human Herpesvirus-7, HBV: Hepatitis B Virus, HCV: Hepatitis C Virus, BKV: Human Polyomavirus BKV, JCV: Human Polyomavirus JCV, MCV: Merkel Cell Polyomavirus MCV, HPV16: Human Papillomavirus type-16, HPV18: Human Papillomavirus type-18, HIV1: Human Immunodeficiency Virus, *C. trachomatis*: *Chlamydia trachomatis*, *H. pylori*: *Helicobacter pylori*, *T. gondii*: *Toxoplasma gondii* Grey colored cells indicate non-estimable Hrs.

We have identified potential positive associations between antibodies to infection and autoimmune diseases, possibly due to infections triggering autoimmunity via mechanisms like molecular mimicry [32–34]. As for viruses, we observed a positive nominal association between HHV-6B and prevalent T1D, as well as HPV-18, with both prevalent T1D (nominal significance) and incident RA (adjusted significance). In a previous study, glycoprotein B expression from HHV-6 was higher in the pancreatic tissue of individuals with T1D compared to non-diabetic subjects [35]. Additionally, females with diabetes (type 1 and 2) or prediabetes were shown to have a higher risk of persistent HPV infection [36]. In a nationwide cohort study in Taiwan, HPV-infected individuals, particularly females, exhibited a higher risk of RA compared to non-HPV controls [37], which may be explained by persistent HPV-18 infection delivering viral antigens that mimic joint-associated self-antigens, thereby activating autoreactive B and T cells and promoting the production of anti-citrullinated protein antibodies, ultimately leading to synovial inflammation [38]. As for bacteria, our observation of a positive nominal association between *H. pylori* and prevalent sarcoidosis corroborates earlier findings from a case-control study that reported higher titers of anti-*H. pylori* IgG antibody in sarcoidosis patients [39]. We observed nominal associations between *H. pylori* and incident vasculitis in females, including Henoch-Schönlein Purpura (HSP) and Behçet's disease (BD). Previous reports noted an association between *H. pylori* and HSP in both children [40] and adults [41]. *H. pylori* eradication therapy improved BD symptoms, with higher cagA positivity in BD patients [42]. We found a nominal association between *T. gondii* and the onset of RA, extending beyond previous cross-sectional studies from Egypt and China that reported higher seroprevalence of *T. gondii* in prevalent RA patients [43, 44].

We have identified several novel findings, including a new positive

nominal association between JCV and prevalent psoriasis. Infections such as HIV, HPV, and SARS-CoV2 can trigger skin inflammation by disrupting the host's antiviral immune response [45]. The presence of JCV DNA in psoriatic lesions suggests a potential role in keratinocyte dysregulation and immune recruitment, processes that may amplify cutaneous inflammation, particularly under immunosuppressive conditions such as biologic therapy, where viral reactivation could influence both psoriasis progression and neurological risk [46,47]. Additionally, the novel positive nominal association between HPV-18 and incident RF/RHD in males warrants further investigation. Although not related to RHD, HPV has been associated with increased cardiovascular mortality in females [48]. Furthermore, nominal associations between *C. trachomatis* and the incidence of psoriasis highlight the *Chlamydiae* family's role in autoimmune skin conditions. A case-control study reported a higher prevalence of subclinical *C. psittaci* infection in psoriasis patients, measured by the bacterial DNA in the peripheral blood [49].

Inverse associations between antibodies to infection and autoimmune diseases suggest that infections may modulate the immune system, reduce pro-inflammatory processes, or reflect an altered immune state. Infections could promote immune tolerance through anti-inflammatory cytokines like IL-10 and TGF- β [50,51], enhancing regulatory T cell activity, potentially protecting against autoimmunity [3, 52]. Additionally, repeated pathogen exposure could enhance trained immunity, reducing inappropriate activation against self-antigens [3]. The hygiene hypothesis suggests reduced exposure to infections in early life can impair immune tolerance development, increasing autoimmune disease risk by impairing the immune system's ability to distinguish between harmful and harmless stimuli [53]. While these inverse associations may suggest mechanisms such as immune training or altered immunity, alternative explanations — including unmeasured confounding factors (e.g., vaccination) or survivor bias — should also be

considered [54]. We observed inverse nominal associations between *H. pylori* and the prevalent CD and ulcerative colitis in males, the results of which were consistent with prior case-control or cross-sectional studies [55–59]. Conversely, our findings on the inverse association between HSV-1 and prevalent RF/RHD in males, and prevalent MS in males and females combined do not align with earlier studies. This discrepancy could stem from differences in study design (prospective, not case-control) or from the use of different types of biospecimens (tissue, not blood) [60,61]. In addition, differences in infection prevalence across latitudes may also contribute to variations in observed associations between populations [62]. We identified inverse associations between HHV-7 and prevalent RA, as well as *T. gondii* and prevalent CD, contrasting with studies using questionnaire-based diagnoses or lacking control groups [63,64]. We observed an inverse association between *C. trachomatis* and prevalent psoriasis in females but a positive association with incident psoriasis, suggesting its role may vary over time or between different stages of the disease. Additionally, we found associations between HHV-6B and incident vasculitis (both sexes), and HHV-6 and incident Graves' disease (females). These associations were also reported in a case report describing a woman with HHV-6A and concurrent HHV-6B skin infection, presenting with idiopathic cutaneous leukocytoclastic vasculitis linked to HHV-6 reactivation [65]. Studies have not found an association between HHV-6B and Graves' disease but reported a positive link between HHV-6 and Hashimoto's thyroiditis, another autoimmune thyroid disorder [66]. A higher prevalence of HHV-6 in thyroid samples from Hashimoto's thyroiditis patients, suggests the virus may contribute to the disorder by inducing HLA class II expression on thyrocytes and triggering abnormal immune responses [66].

Immunity varies by sex, and autoimmune diseases disproportionately affect females [67–69]. This variance is attributed to several factors, including sex chromosomes [70,71], sex hormones [71,72], and behavioral differences [67]. Sex hormones such as estrogen can promote B-cell activation and antibody production and enhance T helper cell responses, particularly Th2 polarization. These effects facilitate increased autoantibody generation and may contribute to the stronger positive associations with autoimmune diseases observed in females [73]. These factors enhance the immune robustness in females, which may inadvertently lead to self-reactivity, suggesting that infections could more likely precipitate autoimmune reactions in females than in males [72]. Despite its importance, many studies lack sex-specific estimates for the infection-autoimmune disease association. Our sex-stratified analyses of various infections and autoimmune diseases including HSV-1 and prevalent RF/RHD, JCV and prevalent RA, HPV-18 and incident RA, and *T. gondii* and incident RA, demonstrate clear sex differences in associations, typically showing positive associations in females and inverse in males. These findings underscore the importance of sex-specific research in developing tailored strategies for autoimmune diseases.

This study has several strengths. First, it leverages data from the UK Biobank, a large population-based cohort, allowing for robust statistical analyses and generalizability to broader populations. Second, the rigorous data collection and standardized protocols enhance the reliability and reproducibility of the findings. Third, the prospective design of the study minimizes recall bias and enables temporal assessment of exposures and outcomes. Lastly, the availability of serological data on various infectious agents, along with comprehensive clinical information, provides a unique opportunity to investigate associations with autoimmune diseases at an unprecedented scale.

4.1. Limitations

Our study has several limitations. First, the use of baseline seropositivity data reflects past exposure to infectious agents rather than active infections, indicating an immune response with detectable antibodies. The one-time measurement cannot capture seroreversion, limiting the

accuracy of assessing past exposures [74], although its rarity minimizes its impact on our findings [75]. Second, we did not consider the effects of vaccinations or treatments, which could impact the observed associations. Third, despite using a large cohort, small sample sizes in some analyses due to the rarity of autoimmune diseases and varying prevalence of infections like EBV (over 90 %) versus scarcity of others like HIV, resulted in insufficient statistical power for some analyses. Fourth, given that only a few associations remained significant after Bonferroni correction, nominal ($p < 0.05$) findings should be interpreted with caution, as they may reflect false positives or overestimation of weaker associations. Fifth, the use of ICD-based diagnoses may introduce potential misclassification, as coding errors or variations in clinical documentation can affect the accuracy of case identification and consequently influence observed associations. Lastly, our study does not account for broader aspects of autoimmune ecology, including environmental exposures, genetic predisposition, and immune system regulation, which may influence infection–autoimmunity associations [76]. Nonetheless, our study reveals potential links between these infections and autoimmune diseases, and the consistent results across sensitivity analyses suggest these associations are meaningful.

5. Conclusions

In this large population-based cohort, to our knowledge, we are the first to examine the association between antibodies to infections and multiple autoimmune diseases, highlighting potential links that warrant further investigation. Unlike studies on single infectious agents and single autoimmune disease, our analysis provides comprehensive evidence across a broader range of infections and autoimmune conditions, evaluating prevalence and incidence and sex-specific associations. This approach identifies key associations between infections and autoimmune outcomes and provides a foundation for future mechanistic studies to better understand these relationships. Future research should explore the mechanisms, causal pathways, and immunological responses to refine prevention and treatment strategies for infection-related autoimmune conditions. Specifically, high-priority areas include longitudinal studies with repeated serology and experimental models to validate associations such as HPV-18 and RA, as well as investigations into the prevalence of latent autoimmunity, defined as the presence of autoantibodies without clinical symptoms, and its relationship with infectious serology.

CRedit authorship contribution statement

Choa Yun: Writing – original draft, Visualization, Methodology, Investigation, Formal analysis, Data curation. **Dongwon Yoon:** Writing – review & editing. **Sun-Young Jung:** Writing – review & editing. **Moonsuk Kim:** Writing – review & editing. **May A. Beydoun:** Writing – review & editing, Data curation. **Lenore Launer:** Writing – review & editing. **Minkyong Song:** Writing – review & editing, Supervision, Investigation, Funding acquisition, Data curation, Conceptualization.

Patient and public involvement

As we used de-identified data in our analyses, the need to obtain informed consent was waived. No patients were involved in establishing the research question or outcome measures or in developing plans for recruitment, design, or implementation of the study. No patients were asked for advice on interpretation or documentation of results. There are no plans to disseminate the research results to study participants or the relevant patient community.

Ethics approval

The UK Biobank project was ethically approved by the Northwest Multi-Centre Research Ethics Committee. It was also endorsed by the UK

Biobank access management team (application #77963) and the Institutional Review Board of the National Institutes of Health.

Transparency statement

The lead authors affirm that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities

We have no plans to disseminate the results of the research to study participants or the relevant patient community. As anonymized data were used in this study, the authors had no direct contact information of the study participants to disseminate the results of the research.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jtauto.2025.100315>.

Data availability

The authors do not have permission to share data.

References

- [1] Y. Shoenfeld, N. Agmon-Levin, N.R. Rose, *Infection and Autoimmunity*, Elsevier, 2004.
- [2] M. Rojas, P. Restrepo-Jiménez, D.M. Monsalve, Y. Pacheco, Y. Acosta-Ampudia, C. Ramírez-Santana, et al., Molecular mimicry and autoimmunity, *J. Autoimmun.* 95 (2018) 100–123.
- [3] A.A. Al-Qahtani, F.S. Alhamlan, A.A. Al-Qahtani, Pro-inflammatory and anti-inflammatory interleukins in infectious diseases: a comprehensive review, *Trop. Med. Infect. Dis.* 9 (2024) 13.
- [4] D. Johnson, W. Jiang, Infectious diseases, autoantibodies, and autoimmunity, *J. Autoimmun.* 137 (2023) 102962.
- [5] J.R. Carapetis, A. Beaton, M.W. Cunningham, L. Guilherme, G. Karthikeyan, B. M. Mayosi, et al., Acute rheumatic fever and rheumatic heart disease, *Nat. Rev. Dis. Primers* 2 (2016) 1–24.
- [6] O.-D. Ortega-Hernandez, E.M. Martínez-Cáceres, S. Presas-Rodríguez, C. Ramo-Tello, Epstein-Barr virus and multiple sclerosis: a convoluted interaction and the opportunity to unravel predictive biomarkers, *Int. J. Mol. Sci.* 24 (2023) 7407.
- [7] M.T. McClain, L.D. Heinlen, G.J. Dennis, J. Roebuck, J.B. Harley, J.A. James, Early events in lupus humoral autoimmunity suggest initiation through molecular mimicry, *Nat. Med.* 11 (2005) 85–89.
- [8] G. Houen, N.H. Trier, Epstein-Barr virus and systemic autoimmune diseases, *Front. Immunol.* 11 (2021) 587380.
- [9] K. Bjornevik, M. Cortese, B.C. Healy, J. Kuhle, M.J. Mina, Y. Leng, et al., Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, *Science* 375 (2022) 296–301.
- [10] K. Bjornevik, C. Münz, J.I. Cohen, A. Ascherio, Epstein-Barr virus as a leading cause of multiple sclerosis: mechanisms and implications, *Nat. Rev. Neurol.* 19 (2023) 160–171.
- [11] F. Tesch, F. Ehm, A. Vivirito, D. Wende, M. Batram, F. Loser, et al., Incident autoimmune diseases in association with SARS-CoV-2 infection: a matched cohort study, *Clin. Rheumatol.* 42 (2023) 2905–2914.
- [12] N. McCarthy, J. Giesecke, Incidence of Guillain-Barré syndrome following infection with *Campylobacter jejuni*, *Am. J. Epidemiol.* 153 (2001) 610–614.
- [13] C. Sudlow, J. Gallacher, N. Allen, V. Beral, P. Burton, J. Danesh, et al., UK biobank: an open access resource for identifying the causes of a wide range of complex diseases of middle and old age, *PLoS Med.* 12 (2015) e1001779.
- [14] A.J. Mentzer, N. Brenner, N. Allen, T.J. Littlejohns, A.Y. Chong, A. Cortes, et al., Identification of host–pathogen-disease relationships using a scalable multiplex serology platform in UK Biobank, *Nat. Commun.* 13 (2022) 1818.
- [15] Autoimmune Registry.
- [16] M.-m. He, C.-H. Lo, K. Wang, G. Polychronidis, L. Wang, R. Zhong, et al., Immune-mediated diseases associated with cancer risks, *JAMA Oncol.* 8 (2022) 209–219.
- [17] N. Conrad, S. Misra, J.Y. Verbakel, G. Verbeke, G. Molenberghs, P.N. Taylor, et al., Incidence, prevalence, and co-occurrence of autoimmune disorders over time and by age, sex, and socioeconomic status: a population-based cohort study of 22 million individuals in the UK, *Lancet* 401 (2023) 1878–1890.
- [18] M.J. Tilly, S. Geurts, F. Zhu, M.M. Bos, M.A. Ikram, M.P. de Maat, et al., Autoimmune diseases and new-onset atrial fibrillation: a UK Biobank study, *Europace* 25 (2023) 804–811.
- [19] L.J. Jensen, S.N. Jensen, P.W. McGonagill, T.S. Griffith, A.K. Mangalam, V. P. Badovinac, Autoimmunity increases susceptibility to and mortality from sepsis, *Immunohorizons* 5 (2021) 844–854.
- [20] H. Meier, F. Miller, G. Dinse, C. Weinberg, C. Cho, C. Parks, *Helicobacter pylori* seropositivity is associated with antinuclear antibodies in US adults, *NHANES 1999–2000*, *Epidemiol. Infect.* 148 (2020) e20.
- [21] V. Pordeus, M. Szyper-Kravitz, R. Levy, N. Vaz, Y. Shoenfeld, Infections and autoimmunity: a panorama, *Clin. Rev. Allergy Immunol.* 34 (2008) 283–299.
- [22] M.A. Habibi, F. Nezhad Shamohammadi, T. Rajaei, H. Namdari, M.R. Pashaei, H. Farajifard, et al., Immunopathogenesis of viral infections in neurological autoimmune disease, *BMC Neurol.* 23 (2023) 201.
- [23] P. Brodin, Immune-microbe interactions early in life: a determinant of health and disease long term, *Science* 376 (2022) 945–950.
- [24] C.C. Qiu, R. Caricchio, S. Gallucci, Triggers of autoimmunity: the role of bacterial infections in the extracellular exposure of lupus nuclear autoantigens, *Front. Immunol.* 10 (2019) 2608.
- [25] U. Christen, M.G. von Herrath, Infections and autoimmunity—good or bad? *J. Immunol.* 174 (2005) 7481–7486.
- [26] K.S.G. de Sa, J. Silva, R. Bayarri-Olmos, R. Brinda, R.A.R. Constable, P.A.C. Diaz, et al., A causal link between autoantibodies and neurological symptoms in long COVID, *medRxiv* (2024).
- [27] M.F. Cusick, J.E. Libbey, R.S. Fujinami, Molecular mimicry as a mechanism of autoimmune disease, *Clin. Rev. Allergy Immunol.* 42 (2012) 102–111.
- [28] T. Kamradt, N.A. Mitchison, Tolerance and autoimmunity, *N. Engl. J. Med.* 344 (2001) 655–664.
- [29] X. Meng, J.A. Layhadi, S.T. Keane, N.J. Cartwright, S.R. Durham, M.H. Shamji, Immunological mechanisms of tolerance: central, peripheral and the role of T and B cells, *Asia Pac. Allergy* 13 (2023) 175–186.
- [30] M. Versini, P.-Y. Jeandel, T. Bashi, G. Bizzaro, M. Blank, Y. Shoenfeld, Unraveling the hygiene hypothesis of helminthes and autoimmunity: origins, pathophysiology, and clinical applications, *BMC Med.* 13 (2015) 1–16.
- [31] T.B. Smallwood, P.R. Giacomini, A. Loukas, J.P. Mulvenna, R.J. Clark, J.J. Miles, Helminth immunomodulation in autoimmune disease, *Front. Immunol.* 8 (2017) 453.
- [32] N. Mahroum, A. Watad, Y. Shoenfeld, *Infection and Autoimmunity*, Academic Press, 2024.
- [33] B. Sundaresan, F. Shirafkan, K. Ripberger, K. Rattay, The role of viral infections in the onset of autoimmune diseases, *Viruses* 15 (2023) 782.
- [34] K.W. Wucherpfennig, Mechanisms for the induction of autoimmunity by infectious agents, *J. Clin. Invest.* 108 (2001) 1097–1104.
- [35] S. Sabouri, M.A. Benkahla, W.B. Kiosses, T. Rodriguez-Calvo, J. Zapardiel-Gonzalo, E. Castillo, et al., Human herpesvirus-6 is present at higher levels in the pancreatic tissues of donors with type 1 diabetes, *J. Autoimmun.* 107 (2020) 102378.
- [36] C. Yue, C. Zhang, C. Ying, H. Jiang, Diabetes associated with HPV infection in women aged over 50 years: a cross-sectional study from China's largest academic woman's hospital, *Front. Endocrinol.* 13 (2022) 92963.
- [37] Y.-T. Liu, H.-K. Tsou, J.-Y. Chiou, Y.-H. Wang, M.-C. Chou, J.-C.-C. Wei, Association of human papillomavirus infection with risk for rheumatoid arthritis: a population-based cohort study, *Ann. Rheum. Dis.* 78 (2019) 1734–1736.
- [38] M. Fehrer, T. Vogl, Molecular mimicry in the pathogenesis of autoimmune rheumatic diseases, *J. Trans. Autoimmun.* (2025) 100269.
- [39] B.L. Herndon, V. Vlach, M. Dew, S.K. Willise, *Helicobacter pylori*-related immunoglobulins in sarcoidosis, *J. Invest. Med.* 52 (2004) 137–143.

- [40] L.-J. Xiong, Y. Tong, Z.-L. Wang, M. Mao, Is *Helicobacter pylori* infection associated with Henoch-Schönlein purpura in Chinese children? a meta-analysis, *World J. Pediatr.* 8 (2012) 301–308.
- [41] M. Mohamed, M. Shariff, A. Al Hillan, R. Al Haj, C. Kaunzinger, M. Hossain, et al., A rare case of *Helicobacter pylori* infection complicated by henoch-schönlein purpura in an adult patient, *J. Med. Cases* 11 (2020) 160.
- [42] B. Wedi, A. Kapp, *Helicobacter pylori* infection in skin diseases: a critical appraisal, *Am. J. Clin. Dermatol.* 3 (2002) 273–282.
- [43] W.A. Aboukamar, S. Habib, S. Tharwat, M.K. Nassar, M.A. Elzoheiry, R. Atef, et al., Association between toxoplasmosis and autoimmune rheumatic diseases in Egyptian patients, *Reumatol. Clínica* 19 (2023) 488–494.
- [44] A.-L. Tian, Y.-L. Gu, N. Zhou, W. Cong, G.-X. Li, H.M. Elsheikha, et al., Seroprevalence of *Toxoplasma gondii* infection in arthritis patients in eastern China, *Infect. Dis. Poverty* 6 (2017) 1–7.
- [45] S. Liu, M. He, J. Jiang, X. Duan, B. Chai, J. Zhang, et al., Triggers for the onset and recurrence of psoriasis: a review and update, *Cell Commun. Signal.* 22 (2024) 108.
- [46] U. Moens, M. Ludvigsen, M. Van Ghelue, Human polyomaviruses in skin diseases, *Pathol. Res. Int.* 2011 (2011) 123491.
- [47] C. Nardis, E. Anzivino, A. Bellizzi, D.M. Rodio, O. De Pittà, F. Chiarini, et al., Reactivation of human polyomavirus JC in patients affected by psoriasis vulgaris and psoriatic arthritis and treated with biological drugs: preliminary results, *J. Cell. Physiol.* 227 (2012) 3796–3802.
- [48] H.S. Cheong, Y. Chang, Y. Kim, M.-J. Kwon, Y. Cho, B. Kim, et al., Human papillomavirus infection and cardiovascular mortality: a cohort study, *Eur. Heart J.* 45 (2024) 1072–1082.
- [49] G. Stinco, M. Fabris, E. Pasini, E. Pontarini, M. Patriarca, F. Piccirillo, et al., Detection of DNA of *Chlamydia psittaci* in subjects with psoriasis: a casual or a causal link? *Br. J. Dermatol.* 167 (2012) 926–928.
- [50] K.N. Couper, D.G. Blount, E.M. Riley, IL-10: the master regulator of immunity to infection, *J. Immunol.* 180 (2008) 5771–5777.
- [51] M.K. Levings, R. Bacchetta, U. Schulz, M.G. Roncarolo, The role of IL-10 and TGF- β in the differentiation and effector function of T regulatory cells, *Int. Arch. Allergy Immunol.* 129 (2002) 263–276.
- [52] M. Strzelec, J. Detka, P. Mieszczyk, M.K. Sobocińska, M. Majka, Immunomodulation—a general review of the current state-of-the-art and new therapeutic strategies for targeting the immune system, *Front. Immunol.* 14 (2023) 1127704.
- [53] J.-F. Bach, The effect of infections on susceptibility to autoimmune and allergic diseases, *N. Engl. J. Med.* 347 (2002) 911–920.
- [54] R. Krishnan, P.M. Stuart, Developments in vaccination for herpes simplex virus, *Front. Microbiol.* 12 (2021) 798927.
- [55] M. Yue, Q. Chen, X. Zhou, L. Li, C. Lu, Is *Helicobacter pylori* infection associated with celiac disease? A meta-analysis, *Turk. J. Gastroenterol.* 33 (2022) 205.
- [56] B. Lebowitz, M.J. Blaser, J.F. Ludvigsson, P.H. Green, A. Rundle, A. Sonnenberg, et al., Decreased risk of celiac disease in patients with *Helicobacter pylori* colonization, *Am. J. Epidemiol.* 178 (2013) 1721–1730.
- [57] A. Uyanikoglu, H. Dursun, N. Yenice, Is there any association between celiac disease and *Helicobacter pylori*? *Euroasian J. Hepatogastroenterol.* 6 (2016) 103.
- [58] I. Ali, Q. Abdo, M. Shayma'a, A. Shawabkeh, Association between ulcerative colitis and *Helicobacter pylori* infection: a case-control study, *Heliyon* 8 (2022).
- [59] K. Papamichael, P. Konstantopoulos, G.J. Mantzaris, *Helicobacter pylori* infection and inflammatory bowel disease: is there a link? *World J. Gastroenterol.* WJG 20 (2014) 6374.
- [60] P. Ferrante, R. Mancuso, E. Pagani, F.R. Guerini, M.G. Calvo, M. Saresella, et al., Molecular evidences for a role of HSV-1 in multiple sclerosis clinical acute attack, *J. Neurovirol.* 6 (2000) S109.
- [61] Y. Li, Z. Pan, Y. Ji, H. Zhang, L. Archard, Herpes simplex virus type 1 infection in rheumatic valvar disease, *Heart* 91 (2005) 87–88.
- [62] V. Pordeus, O. Barzilai, Y. Sherer, R.R. Luiz, M. Blank, N. Bizzaro, et al., A latitudinal gradient study of common anti-infectious agent antibody prevalence in Italy and Colombia, *Isr. Med. Assoc. J.* 10 (2008) 65.
- [63] A. Kadiša, Z. Nora-Krūkle, S. Kozireva, S. Svirskis, P. Studers, V. Groma, et al., Effect of human herpesviruses 6 and 7 infection on the clinical course of rheumatoid arthritis/Cilvēka Herpesvīrusa 6 Un 7 Infekcijas Ietekme Uz Reimatoīdā Artrītu Klinisko Gaitu, in: Proceedings of the Latvian Academy of Sciences Section B Natural, Exact, and Applied Sciences, 2016, pp. 165–174.
- [64] M. Rostami-Nejad, S.H. Hejazi, M. Bahadoran, N. Pestehchian, M. A. Pourhosseingholi, A.H. Safa, et al., Prevalence of toxoplasma gondii and the level of IL8 in patients with Celiac disease, *Koomesh* 18 (2016) 79–85.
- [65] A. Calvario, C. Foti, M. Scarasciulli, P. Romita, E. Eliassen, A. Marzullo, et al., Leukocytoclastic vasculitis associated with HHV6-A/CIHHV6-A and HHV6-B coinfection in an immunocompetent woman. Endocrine, metabolic & immune disorders-drug targets (formerly current drug targets-immune, *Endocr. Metabol. Disord.* 19 (2019) 221–225.
- [66] F. Broccoli, L. Fusetti, L. Ceccherini-Nelli, Possible role of human herpesvirus 6 as a trigger of autoimmune disease, *Sci. World J.* 2013 (2013) 867389.
- [67] S.L. Klein, K.L. Flanagan, Sex differences in immune responses, *Nat. Rev. Immunol.* 16 (2016) 626–638.
- [68] D.L. Jacobson, S.J. Gange, N.R. Rose, N.M. Graham, Epidemiology and estimated population burden of selected autoimmune diseases in the United States, *Clin. Immunol. Immunopathol.* 84 (1997) 223–243.
- [69] C.C. Whitacre, Sex differences in autoimmune disease, *Nat. Immunol.* 2 (2001) 777–780.
- [70] D. Fairweather, D.J. Beetler, E.J. McCabe, S.M. Lieberman, Mechanisms underlying sex differences in autoimmunity, *J. Clin. Invest.* 134 (2024).
- [71] E. Ortona, M. Pierdominici, A. Maselli, C. Veroni, F. Aloisi, Y. Shoenfeld, Sex-based differences in autoimmune diseases, *Annali dell'Istituto superiore di sanità* 52 (2016) 205–212.
- [72] R. Voskuhl, Sex differences in autoimmune diseases, *Biol. Sex Differ.* 2 (2011) 1–21.
- [73] A.V. Rubtsov, K. Rubtsova, J.W. Kappler, P. Marrack, Genetic and hormonal factors in female-biased autoimmunity, *Autoimmun. Rev.* 9 (2010) 494–498.
- [74] E. Connick, Incomplete Antibody Evolution and Seroreversion after Treatment of Primary HIV Type 1 Infection: what Is the Clinical Significance? The University of Chicago Press, 2005, pp. 874–875.
- [75] M.J. Roy, J.J. Damato, D.S. Burke, Absence of true seroreversion of HIV-1 antibody in seroreactive individuals, *JAMA* 269 (1993) 2876–2879.
- [76] J.-M. Anaya, C. Ramirez-Santana, M.A. Alzate, N. Molano-Gonzalez, A. Rojas-Villarraga, The autoimmune ecology, *Front. Immunol.* 7 (2016) 139.