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Research paper

Serum signature of antibodies to *Toxoplasma gondii*, rubella virus, and cytomegalovirus in females with bipolar disorder: A cross-sectional study

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ABSTRACT

Background and aim: Immunity alterations have been observed in bipolar disorder (BD). However, whether serum positivity of antibodies to *Toxoplasma gondii (T gondii)*, rubella, and cytomegalovirus (CMV) shared clinical relevance with BD, remains controversial. This study aimed to investigate this association.
Methods: Antibody seropositivity of IgM and IgG to *T gondii*, rubella virus, and CMV of females with BD and controls was extracted based on medical records from January 2018 to January 2023. Family history, type of BD, onset age, and psychotic symptom history were also collected.
Results: 585 individuals with BD and 800 healthy controls were involved. Individuals with BD revealed a lower positive rate of *T gondii* IgG in the 10–20 aged group (OR = 0.10), and a higher positive rate of rubella IgG in the 10–20 (OR = 5.44) and 20–30 aged group (OR = 3.15). BD with family history preferred a higher positive rate of *T gondii* IgG (OR = 24.00). Type-I BD owned a decreased positive rate of rubella IgG (OR = 0.37) and an elevated positive rate of CMV IgG (OR = 2.12) compared to type-II BD, while BD with early onset showed contrast results compared to BD without early onset (Rubella IgG, OR = 2.54; CMV IgG, OR = 0.26). BD with psychotic symptom history displayed a lower positive rate of rubella IgG (OR = 0.50).
Limitations: Absence of male evidence and control of socioeconomic status and environmental exposure.
Conclusions: Differential antibody seropositive rates of *T gondii*, rubella, and cytomegalovirus in BD were observed.

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1. Introduction

Bipolar disorder (BD) is a debilitating mental disorder featuring mood and energy fluctuation (Voelker, 2024). Substantial functional deficits, profound healthcare burden, and striking premature mortality make an urgent appeal for clarifying the etiology of BD (Polcwiartek et al., 2024; Roshanaei-Moghaddam and Katon, 2009). However, the pathophysiology of BD remains elusive to date. The standstill of genetic discoveries has led to a renewed interest in non-genetic risk factors and their interaction with predisposing genes (Gershon et al., 2011; Gordovez and McMahon, 2020; Herrera-Rivero et al., 2024; Seifuddin et al., 2012). So far, accumulated evidence has postulated immunity (e.g., inflammation) mechanism as an association bridging genetic factors with environmental factors in BD. Low-grade immune alterations, exemplified by pro-inflammatory cytokines, positive acute-phase proteins, complement factors, and levels of T cell-related activation markers, are independently or concurrently present during the disease course or in acute depressive or manic episodes (Anderson and Maes, 2015; Chancel et al., 2024; Coello et al., 2024; Jones et al., 2021; Misiak et al., 2020; Tseng et al., 2021; Zhou et al., 2023).

Among several environmental factors, exposure to pathogens is hypothesized to elicit inflammation activation and subsequently influence the development of BD (Koyuncu et al., 2013; Snijders et al., 2019). *Toxoplasma gondii (T gondii)*, rubella virus, and cytomegalovirus (CMV), known as severe infectious teratogens, are also neurotropic pathogens. They can pass through the blood-brain barrier and then reside in the brain tissue to drive a latent central infection, or depend on the peripheral mechanism to provoke the central inflammation alterations, theoretically (Barichello et al., 2016; Cain et al., 2019). Therefore, they possibly play a role in shaping the brain function and affecting the neuropsychiatric consequences of the host. This neurotropic-pathogen hypothesis is supported by the higher prevalence of chronic contagious diseases, which has been previously observed among individuals with BD (Benros et al., 2013), and infection of these neurotropic pathogens in the central nervous system might elicit changes in mental status, including mania, depression, and psychosis, which resembles the typical symptoms of BD (Caroff et al., 2001; Savitz and Yolken, 2023; Zheng and Savitz, 2023). Evidence from animals that were exposed to these pathogens also suggested the potential linkage between the infection and post-infection cognitive and behavioral impairment (Kannan and Pletnikov, 2012).

To date, explorations of the association between environmental infection and BD, have been reported in the United States, France, Germany, Italy, Brazil, Saudi Arabia, and Ethiopia (Afifi et al., 2018; Cossu et al., 2022; Dickerson et al., 2014; Frye et al., 2019; Galli et al., 2019; Hamdani et al., 2013, 2017; Houenou et al., 2014; Lycke et al., 1974; Prossin et al., 2013; Rizzo et al., 2013; Simanek et al., 2018; Stich et al., 2015; Tedla et al., 2011). However, the exact extent of risk, underlying mechanism, and the short- or long-term altered immunity trait (i.e., immunoglobulin M [IgM], and immunoglobulin G [IgG]) have not been established conclusively. Therefore, the goal of this study was to investigate whether IgM and IgG to common neurotropic pathogens, including *T gondii*, rubella virus, and CMV, are associated with BD in Chinese Han female serum samples. Specifically, given that immunity might explain only a proportion of individuals with BD, the analysis focused on the BD subgroup (i.e., family history, bipolar subtype, age at early onset, and psychotic symptom history) was also applied to fill the paucity of association.

2. Materials and methods

2.1. Participants and data acquisition

Data on female individuals with BD in TORCH screening were collected from the electronic medical system of the First Affiliated Hospital of Zhejiang University, Psychiatric Department.

Inclusion criteria:

1) Chinese Han females aged 10–80 years old;
2) a diagnosis of BD according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), with no restriction on the frequency of episode, subtype, and with or without baseline medication.

Exclusion criteria:

1) a lifetime history of other psychiatric disorders including schizophrenia, major depressive disorder, and post-traumatic stress disorder (co-occurring substance use disorder and other conditions that belong to the complication of BD were permitted);
2) seizures or epilepsy history (or family history of both);
3) current pregnancy or lactation.

Data on female controls without psychiatric disorders in TORCH screening were also collected from online medical records of the Women's Hospital of Zhejiang University. Data of participants were grouped by ages: 10 to 20 years old, 20 to 30 years old, 30 to 40 years old, and over 40 years old. The divisions contained the left boundary and excluded the right boundary.

Altogether, the seropositivity of *T gondii*, rubella virus, and CMV antibodies, including IgM and IgG of screened individuals with BD and controls were extracted. The antibody was examined using chemiluminescent enzyme immunoassays. Positivity standards were: *T gondii* IgM $>$ 1.0 Cut off index (COI), *T gondii* IgG $>$ 3.0 IU/ml, rubella virus IgM $>$ 1.0 COI, rubella virus IgG $>$ 10.0 IU/ml, CMV IgM $>$ 1.0 COI, CMV IgG $>$ 1.0 IU/ml. Data were gathered from January 1st, 2018, to January 1st, 2023. In particular, herpes simplex virus (HSV) IgM and IgG tests were conducted mainly using cervical secretion samples instead of serum in the Women's Hospital of Zhejiang University. Thus, due to the constricted number of serum positivity results in healthy control, we did not compare the HSV IgM and IgG serum-positive rates in this article.

This study was approved by:

1) the Clinical Research Ethics Committee of the First Affiliated Hospital of Zhejiang University School of Medicine (IIT20240570A);
2) the Clinical Research Ethics Committee of the Women's Hospital, Zhejiang University School of Medicine (20230042-R).

Given the anonymous, retrospective, and non-intervention nature of this study, informed consent was waived.

2.2. BD subgroup analysis

Due to the great heterogeneity in BD, surging interest has been paid to the narrower category of the disease (Bora, 2018; Scott et al., 2023). It was revealed that family history highly predicted a poor outcome (Baldessarini et al., 2012). Therefore, the BD history in third-degree relatives was collected. Early onset was defined as the primary episode that emerged at 19 years old or younger, and non-early onset was defined as the primary episode that occurred after 19 years old (Bellivier et al., 2014; Croarkin et al., 2017; Sleurs et al., 2024). As reported, BD with a psychotic history revealed a resemblance to schizophrenia rather than nonpsychotic type-I and type-II BD on a genetic basis (Markota et al., 2018; Ortiz-Orendain et al., 2023). Therefore, the existence of psychotic symptoms based on medical history and *DSM-5* was collected out of particular interest. Considering the heterogeneity of BD, family history, type of BD, onset age, and psychotic history were assessed for inpatients based on electronic medical records for subgroup analyses.

2.3. Statistical analysis

All statistical analyses were performed with GraphPad Prism version 9.5.0. For categorical variables, the Chi-square test, Fisher's exact test, or corrected Chi-square test was used when applicable. The continuous variable (i.e., age) was compared using the Mann-Whitney *U* test due to non-normal distribution. All statistical tests were two-tailed. The threshold of statistically significant difference was defined as $P < 0.05$.

3. Results

3.1. Demographic and clinical data

Altogether, 585 individuals with BD (mean [SD] age, 20.8 [8.4] years), with no restriction of frequency of episode, type, and baseline medication, were screened with serum antibodies positivity of *T gondii*, rubella virus, and CMV. Among cases, 57 (9.7 %) individuals had a family history of BD, 205 (35.0 %) individuals had no family history, and the rest individuals were not identified. For the type of BD, 409 (69.9 %) individuals were diagnosed with type-I BD, 157 (26.8 %) individuals were diagnosed with type-II BD, and the rest individuals (19, 3.2 %) were other specified or unspecified BD. Divided by the type of primary onset, 439 (75.0 %) individuals met the criteria for early-onset BD, whereas 146 (25.0 %) individuals met the criteria for non-early onset BD. Considering the history of psychotic symptoms, 114 (19.5 %) individuals had a psychotic history, and 471 (80.5 %) individuals did not report a history of psychotic episodes. As for healthy controls, the positive rate of serum *T gondii*, rubella virus, and CMV antibody data of 800 women (mean [SD] age, 29.1 [7.8] years) without mental disorder records were collected. A significant age difference was detected between these two groups (Mann-Whitney U test, $P < 0.0001$).

3.2. Serum pathogen antibody positive rates varied across age groups

Serum pathogen antibody-positive rates of BD and healthy controls were revealed in Fig. 1 and Table 1.

For *T gondii*, IgM positivity was observed in 2/353 (0.57 %) individuals with BD aged 10–20, 2/149 (1.34 %) individuals with BD aged 20–30, and 1/21 (4.76 %) individuals with BD aged 40+, while no IgM positivity was observed in healthy control. Although an increased trend existed in individuals with BD aged 20–30 ($P = 0.05$), no significant associations of IgM positivity were found between BD and healthy control. *T gondii* IgG antibodies were detected in 4/353 (1.13 %) individuals with BD aged 10–20, with a significant negative association observed ($P = 0.005$, OR = 0.10, 95 % CI = 0.03–0.37), while only an increased trend was indicated in individuals with BD aged 30–40 (P = 0.05, OR = 9.67, 95 % CI = 1.40–126.0), compared to related controls. No other significant associations were identified in *T gondii* IgG positivity.

For rubella IgM positivity, no significant associations were found in most age groups, except for a borderline significant negative association in the 10–20 age group for individuals with BD compared to related controls ($P = 0.08$, OR = 0.16, 95 % CI = 0.03–0.95). Rubella IgG antibodies were detected in a high proportion of individuals in all age groups, with the highest seropositivity observed in the 10–20 age group of individuals with BD (330/353, 93.48 %). Significant positive associations were found in the 10–20 ($P < 0.0001$, OR = 5.01, 95 % CI = 2.30–11.04) and 20–30 ($P = 0.002$, OR = 2.21, 95 % CI = 1.32–3.71) age groups of individuals with BD compared to its related healthy control.

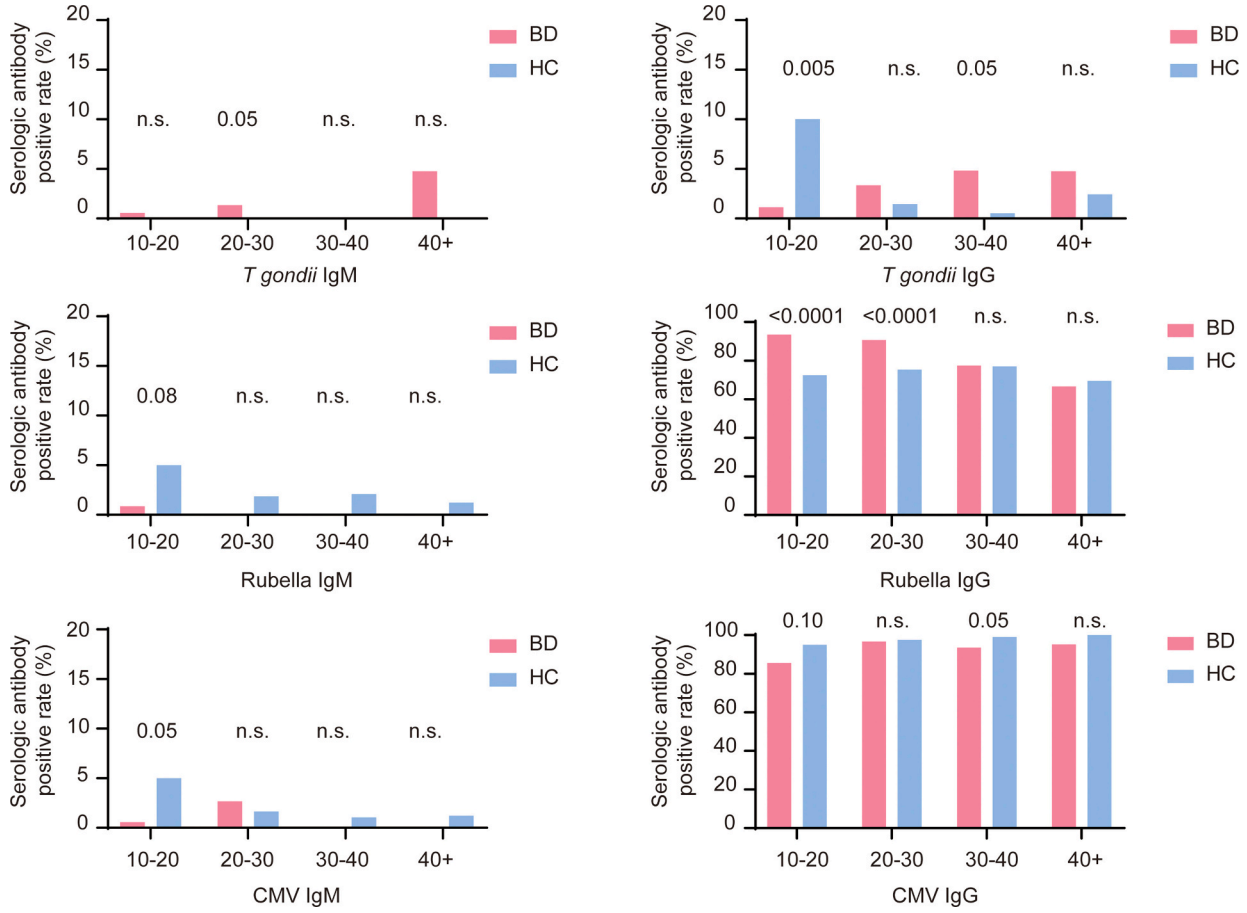

Fig. 1. Serum pathogen antibody positive rates varied across age groups.

Table 1
Analysis of each serologic antibody positive rate in BD and HC.

Age (Years)	BD positive/total	BD positive rate (%)	HC positive/total	HC positi2ve rate (%)	*P* value	OR	95 % CI
T gondii IgM							
10–20	2/353	0.57	0/40	0	1	lnf	>0.05
20–30	2/149	1.34	0/487	0	0.05	lnf	>1.52
30–40	0/62	0	0/191	0	1	–	–
40+	1/21	4.76	0/82	0	0.20	lnf	>0.43
T gondii IgG							
10–20	4/353	1.13	4/40	10.00	0.005	0.10	0.03–0.37
20–30	5/149	3.36	7/487	1.44	0.25	2.38	0.84–6.87
30–40	3/62	4.84	1/191	0.52	0.05	9.67	1.40–126.0
40+	1/21	4.76	2/82	2.44	0.50	2	0.13–17.72
Rubella IgM							
10–20	3/353	0.85	2/40	5.00	0.08	0.16	0.03–0.95
20–30	0/149	0	9/487	1.85	0.20	0	0–1.24
30–40	0/62	0	4/191	2.09	0.57	0	0–3.13
40+	0/21	0	1/82	1.22	1	0	0–35.14
Rubella IgG							
10–20	330/353	93.48	29/40	72.50	<0.0001	5.44	2.50–12.26
20–30	135/149	90.60	367/487	75.36	<0.0001	3.15	1.79–5.85
30–40	48/62	77.42	147/191	76.96	0.94	1.03	0.52–2.05
40+	14/21	66.67	57/82	69.51	0.8	0.88	0.32–2.27
CMV IgM							
10–20	2/353	0.57	2/40	5.00	0.05	0.11	0.02–0.71
20–30	4/149	2.68	8/487	1.64	0.64	1.65	0.55–5.79
30–40	0/62	0	2/191	1.05	1	0	0–6.68
40+	0/21	0	1/82	1.22	1	0	0–35.14
CMV IgG							
10–20	302/353	85.55	38/40	95.00	0.10	0.38	0.10–1.42
20–30	144/149	96.64	475/487	97.54	0.76	0.73	0.26–1.90
30–40	58/62	93.55	189/191	98.95	0.05	0.15	0.03–0.68
40+	20/21	95.24	82/82	100	0.2	0	0–2.31

BD, bipolar disorder; HC, healthy control; *T gondii*, *Toxoplasma gondii*; CMV, cytomegalovirus.

For CMV, IgM positivity was observed in 2/353 (0.57 %) individuals with BD aged 10–20 and 4/149 (2.68 %) individuals with BD aged 20–30. However, no seropositive cases were observed in the 30–40 and 40+ age groups. Despite a borderline significant negative association in the 10–20 age group for individuals with BD (P = 0.05, OR = 0.11, 95 % CI = 0.02–0.71), no significant associations of CMV IgM positivity were found in most age groups. Although the decreased trend existed in individuals with BD aged 10–20 (*P* = 0.10, OR = 0.38, 95 % CI = 0.10–1.42) and individuals with BD aged 30–40 (P = 0.05, OR = 0.15, 95 % CI = 0.03–0.68), no significant associations of IgM positivity were found between BD and healthy control.

3.3. Differential serum pathogen antibody positivity in stratified BD population

BD subgroup analysis results were displayed in Tables 2–5.

3.3.1. Family history was associated with T gondii IgG in individuals with BD

For the family history of BD in Table 2, it was observed that the positive rate of *T gondii* IgG was higher in the BD subgroup with family history than BD subgroup without family history (*P* = 0.0002, OR = 24.00, 95 % CI: 3.74–276.5). No significant association was found in other positive rates.

3.3.2. Type-I BD was associated with CMV IgG, while type-II BD was associated with rubella IgG

Of clinical bipolar subtypes in Table 3, a significant decrease in the positive rate of rubella IgG in type-I BD compared to type-II BD was found (*P* = 0.009, OR = 0.37, 95 % CI: 0.17–0.82). Additionally, the type-I BD subgroup revealed a higher positive rate of CMV IgG than the type-II BD subgroup (*P* = 0.006, OR = 2.12, 95 % CI: 1.25–3.61).

3.3.3. BD with early onset was associated with rubella IgG, while BD without early onset was associated with CMV IgG

For age at onset in Table 4, it was found that the early onset subgroup

Table 2
Analysis of each serologic antibody positive rate stratified by family history.

	BD with family history	BD without family history	*P* value	OR	95 % CI
T gondii IgM	0/57 (0)	0/205 (0)	1	–	–
T gondii IgG	6/57 (10.53 %)	1/205 (0.49 %)	0.0002	24.00	3.74–276.5
Rubella IgM	1/57 (1.75 %)	1/205 (0.49 %)	0.39	3.64	0.19–69.48
Rubella IgG	47/57 (82.46 %)	184/205 (89.76 %)	0.13	0.54	0.24–1.20
CMV IgM	0/57 (0)	2/205 (0.98 %)	1	0	0–7.80
CMV IgG	53/57 (92.98 %)	190/205 (92.68 %)	0.94	1.05	0.35–3.00

BD, bipolar disorder; HC, healthy control; *T gondii*, *Toxoplasma gondii*; CMV, cytomegalovirus.

Table 3
Analysis of each serologic antibody positive rate stratified by bipolar subtype.

	type-I BD	type-II BD	*P* value	OR	95 % CI
T gondii IgM	4/409 (0.98 %)	1/157 (0.64 %)	0.91	1.54	0.25–18.97
T gondii IgG	9/409 (2.20 %)	2/157 (1.27 %)	0.71	1.74	0.45–8.12
Rubella IgM	2/409 (0.49 %)	1/157 (0.64 %)	1	0.77	0.09–11.18
Rubella IgG	361/409 (88.26 %)	150/157 (95.54 %)	0.009	0.37	0.17–0.82
CMV IgM	4/409 (0.98 %)	1/157 (0.64 %)	0.91	1.54	0.25–18.97
CMV IgG	374/409 (91.44 %)	131/157 (83.44 %)	0.006	2.12	1.25–3.61

BD, bipolar disorder; HC, healthy control; *T gondii*, *Toxoplasma gondii*; CMV, cytomegalovirus.

revealed a higher positive rate of rubella IgG than BD without the early onset subgroup ($P = 0.0008$, OR = 2.54, 95 % CI: 1.46–4.44). Furthermore, the positive rate of CMV IgG was lower in BD with the early onset subgroup, compared to BD without the early onset subgroup ($P = 0.0009$, OR = 0.26, 95 % CI: 0.11–0.65).

3.3.4. BD with psychotic history revealed decreased rubella IgG

In the psychotic symptom history facet in Table 5, BD with the psychotic history subgroup displayed a lower positive rate of rubella IgG ($P = 0.02$, OR = 0.50, 95 % CI: 0.27–0.90), compared to BD without the psychotic symptom history subgroup.

4. Discussion

The results showed that individuals with BD revealed a lower positive rate of *T gondii* IgG in the 10–20 aged group (OR = 0.10), and a higher positive rate of rubella IgG in the 10–20 (OR = 5.44) and 20–30 aged group (OR = 3.15). In subgroup analyses, BD with family history was associated with the elevated seroprevalence of *T gondii* IgG (OR = 24.00). Furthermore, type-I BD owned a decreased positive rate of rubella IgG (OR = 0.37) and an elevated positive rate of CMV IgG (OR = 2.12) compared to type-II BD, while BD with early onset showed contrast results compared to BD without early onset (Rubella IgG, OR = 2.54; CMV IgG, OR = 0.26). BD with psychotic symptom history displayed a lower positive rate of rubella IgG (OR = 0.50). The likelihood of being seropositive for individuals with BD-specific traits did not differ in IgM comparison, indicating active infection might not be associated with BD-specific traits.

Since the antibody titers can be accumulated by pathogen exposure and be withdrawn over time, and considerable factors can affect this process, the dynamic antibody in body remains subtle. However, it is suggested that IgM generally reflects the active disease or recent infection, and IgG reflects chronic exposure and immune response development. Hopefully, the relatively homogeneous large sample and detailed clinical disease subtype could provide feasible new insights into the pathophysiologic mechanisms of BD.

T gondii is a widespread neurotropic protozoan parasite affecting approximately one-third of people worldwide, with evidence supporting its influence on the behaviors of the host (Webster, 2001). Existing evidence suggested that acute, chronic, and maternal infection of *T gondii* predisposed to schizophrenia (Monroe et al., 2015; Sutterland et al., 2015; Torrey et al., 2007, 2012). However, such association in BD is still controversial (Snijders et al., 2019). Some researchers observed that *T gondii* infections potentially promoted the acute episode of disease or manifested as persistent risk factors (Afifi et al., 2018; Cossu et al., 2022; de Barros et al., 2017; Dickerson et al., 2014; Tedla et al., 2011), while others documented that the lower frequency of *T gondii* infection in BD (Frye et al., 2019; Galli et al., 2019; Şirin et al., 2021). In this study, a borderline increased seroprevalence of *T gondii* IgM existed in the 10–20 aged individuals with BD, but decreased seroprevalence of *T gondii* IgG was revealed in the 10–20 aged individuals with BD. It suggested that acute infections of *T gondii* might be associated with the development of some 10–20 aged individuals with BD, and the long-term antibody response to *T gondii* of the 10–20 aged individuals with BD tended to be weakened, which might cause the susceptibility to *T gondii*. Furthermore, a higher positive rate of IgG only in BD with family history, indicating that the individuals with a vulnerable genetic background of BD were more associated with chronic *T gondii* exposure. However, how *T gondii* interacts with genetic factors remains to be elucidated (Oliveira et al., 2016), which should be addressed in future research through a gene-environment interaction perspective.

It was reported that women with *T gondii* infection showed an increased risk of self-directed violence (Pedersen et al., 2012). Strikingly, it was confirmed that the suicide risk of individuals with BD was

Table 4
Analysis of each serologic antibody positive rate stratified by age at onset.

	BD with early onset	BD without early onset	*P* value	OR	95 % CI
T gondii IgM	2/439 (0.46 %)	3/146 (2.05 %)	0.19	0.22	0.04–1.08
T gondii IgG	7/439 (1.59 %)	6/146 (4.11 %)	0.14	0.38	0.14–1.16
Rubella IgM	3/439 (0.68 %)	0/146 (0)	0.58	Inf	>0.29
Rubella IgG	406/439 (92.48 %)	121/146 (82.88 %)	0.0008	2.54	1.46–4.44
CMV IgM	4/439 (0.91 %)	2/146 (1.37 %)	1	0.66	0.15–3.51
CMV IgG	383/439 (87.24 %)	141/146 (96.58 %)	0.0009	0.26	0.11–0.65

BD, bipolar disorder; HC, healthy control; *T gondii*, *Toxoplasma gondii*; CMV, cytomegalovirus.

Table 5
Analysis of each serologic antibody positive rate stratified by psychotic symptom history.

	BD with psychotic history	BD without psychotic history	*P* value	OR	95 % CI
T gondii IgM	1/114 (0.88 %)	4/471 (0.85 %)	1	1.04	0.08–6.31
T gondii IgG	1/114 (0.88 %)	12/471 (2.55 %)	0.46	0.34	0.03–2.18
Rubella IgM	0/114 (0)	3/471 (0.64 %)	1	0	0–4.78
Rubella IgG	96/114 (84.21 %)	431/471 (91.51 %)	0.02	0.50	0.27–0.90
CMV IgM	0/114 (0 %)	6/471 (1.27 %)	0.49	0	0–2.92
CMV IgG	99/114 (86.84 %)	425/471 (90.23 %)	0.29	0.71	0.38–1.37

BD, bipolar disorder; HC, healthy control; *T gondii*, *Toxoplasma gondii*; CMV, cytomegalovirus.

about 20–30 times higher than the general population, representing the highest risk of successful suicide and the most frequent suicidal behavior among all psychiatric disorders (Beyer and Weisler, 2016; Brown et al., 2000; Nordentoft et al., 2011; Pompili et al., 2013; Schaffer et al., 2015). Nowadays, *T gondii* is found to participate in the etiopathogenesis of BD through at least three candidate mechanisms. First, *T gondii* could influence the pathways of some neurotransmitters that are implicated in BD brain abnormalities, especially dopamine. Second, it could provoke brain inflammation by direct stimulation of inflammatory cytokines in the brain. Third, it could rely on immune dysregulation to influence the development of BD (de Barros et al., 2017). Thus, whether *T gondii* infection contributes to the suicide behavior of individuals with BD, as well as its underlying mechanisms, remained to be explored.

Rubella is the sole member of the genus Rubivirus in the family of Togaviridae, and its infection is always systematic. Nowadays, rubella-containing vaccine is highly effective and safe, thus, the transmission of rubella is well interrupted due to vaccination (Winter and Moss, 2022). Cohort studies demonstrated that early gestational rubella exposure might represent increased vulnerability for schizophrenia spectrum disorders (Brown et al., 2001). One study suggested schizophrenia susceptibility genes are directly implicated in the life cycles of pathogens including rubella (Carter, 2009). Meanwhile, previous findings indicated that congenital rubella had been associated with an elevated incidence of affective disorder (mainly including major depression disorder and mood disorder not otherwise specified) (Brown et al., 2001). However, its association with BD has been scarcely explored, both in epidemiology and pathophysiology. In this study, a higher positive rate of rubella IgG were detected in individuals with BD. Moreover, it is also observed that the increased positive rate of IgG antibody in type-II BD, BD with early onset, and BD without psychotic symptom history subgroup, when compared to the respective BD controls. Thus, which factor distinctly mediated this subtle difference remains a deep investigation.

CMV is a common neurotrophic herpesvirus that can be reactivated by inflammation and is involved in neurological disease (Zheng et al., 2023). Of note, individuals with BD were discovered with a significant negative correlation between CMV lgG titers and right hippocampal volume, indicating hippocampal abnormalities (Houenou et al., 2014). Currently, it was also reported that seropositivity of CMV IgG significantly increased the odds of BD diagnosis (OR = 2.45) and suicide behavior in the psychiatric samples (OR = 2.09), which was potentially attributed to high neuroinflammation based on the gene expression of postmortem brain samples in dorsal lateral prefrontal cortex (OR = 4.41, an effect driven by both schizophrenia and BD samples), in a small sample sized research (Zheng et al., 2023). This positive association between BD and CMV IgG was also found in some research (Frye et al., 2019; Lycke et al., 1974; Prossin et al., 2013; Rizzo et al., 2013; Tedla et al., 2011), whereas some findings and a meta-analysis indicated insignificance with a decreasing trend (Dickerson et al., 2014; Houenou et al., 2014; Oliveira et al., 2016). Since CMV is a highly transmissible virus, the high seropositivity rates across all age groups confirmed the widespread exposure to CMV, and individuals developed long-lasting IgG antibodies to CMV. Our results showed evidence of the decreased trend in seroprevalence of CMV IgG for individuals with BD aged 30–40 compared to its related healthy control. The difference might be due to female samples, the specific race, and the age group in the study. Further preclinical research is expected to delineate the CMV-related neuroanatomic alterations.

Remarkably, preliminary explorations of CMV influence on mental disorders indicated a sex-dependent manner. Under the condition of BD, a report indicated that female individuals with CMV seropositivity revealed no difference in intelligence quotient with CMV seronegative individuals, while a significantly higher intelligence quotient was found in male seropositive individuals with BD (Andreou et al., 2021b). A significant CMV-by-sex interaction was also detected in its influence on dentate gyrus (DG) volume of BD, as CMV-positive male individuals had smaller volumes than CMV-negative male individuals, whereas no CMV-DG association was found in female individuals (Andreou et al., 2021a). Thus, future study is required for the potential cognition influence of CMV in BD and caution should be paid when interpreting the sex-mixed epidemical results. Moreover, sub-analysis results revealed that type-I BD and non-early onset subgroups owned higher positive rates of CMV IgG. It was consistent with previous studies (Frye et al., 2019; Prossin et al., 2013). The CMV IgG was significantly correlated with impulsivity (Prossin et al., 2013), which might explain the higher positive rates of CMV IgG for type-I BD in a behavioral sense. Meanwhile, BD with non-early onset might be more correlated with environmental exposure instead of genetic background (Croarkin et al., 2017), which possibly caused the elevated CMV.

These common pathogens always go unnoticed, with symptoms ranging from asymptomatic in the most common cases, to severe in rare cases. People exposed to various stressors are usually faced with a higher risk of psychiatric disorders such as BD, and the reactivation of these accompanying pathogens (Yolken and Torrey, 1995). It is increasingly recognized that inflammation is implicated in the etiology of psychiatric disorders. Moreover, the inflammation alterations also predispose to the reactivation of different kinds of pathogens and vice versa (Chan et al., 2023; Friedrich, 2014; Pape et al., 2019). Therefore, whether these pathogens share a common risk factor like stress, or rely on the inflammatory mechanism to directly or mutually potentiate or protect the process of BD remains to be elucidated. Promisingly, more findings elucidating pathogen-related brain structure and function changes in BD will be carried out, which might provide immune target suggestions for future drug development.

4.1. Limitations

The preliminary limitations lie in the absence of male evidence due to the inaccessibility of male health control results and without controlling socioeconomic status and environmental factors such as the presence of cats in households, early life trauma exposure, living conditions, education years, smoking history, drinking history, and medication situation (e.g., psychotropic drug). In addition, it also lacks psychometric parameters on clinical symptoms to evaluate the potential correlation with a positive rate of antibody. In major depressive disorder, it has been postulated that certain immune markers were related to the distinct clinical symptoms (Perry et al., 2021). Likewise, BD also showed the potential link between antibody titer and clinical behavior (e.g., clinical severity, disease duration time, current mood state, cognitive function, and suicide attempt) (Misiak et al., 2020; Tseng et al., 2021), which warrants explorations in the future. As we only provided the correlation results, the causal relationship remained unclear.

5. Conclusion

The current study represented the association between infection of different pathogens including *T gondii*, rubella virus, and CMV exemplified by the positive rate of IgM or IgG with BD in Chinese females. In the results, BD revealed a lower positive rate of *T gondii* IgG in the 10–20 aged group and a higher positive rate of rubella IgG in the 10–20 and 20–30 aged groups. Furthermore, the relationship in BD with distinct traits (family history, bipolar type, age at onset, and psychotic symptom history) was also identified. In the subgroup analyses for individuals with BD, *T gondii* IgG was associated with family history, rubella IgG was associated with type-II BD, BD with early onset and BD without psychotic symptom history, and CMV IgG was associated with type-I BD and BD without early onset. Further investigation is required to elucidate how these pathogen infections cooperate with inflammation or other mechanism that contributes to the development of BD.

Abbreviations

BD	bipolar disorder
T gondii	*Toxoplasma gondii*
CMV	cytomegalovirus
IgG	immunoglobulin G
IgM	immunoglobulin M
DSM-5	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SD	standardized difference
OR	odds ratio
DG	dentate gyrus

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CRediT authorship contribution statement

Xiaonan Guo: Writing – review & editing, Writing – original draft, Methodology, Investigation, Formal analysis. **Yiqing Chen:** Validation, Methodology, Data curation. **Huimin Huang:** Validation, Methodology, Data curation. **Yifeng Liu:** Writing – review & editing, Data curation. **Lingzhuo Kong:** Writing – review & editing. **Lizichen Chen:** Validation, Methodology, Formal analysis. **Hailong Lyu:** Data curation. **Tongsheng Gao:** Data curation. **Jianbo Lai:** Writing – review & editing, Supervision. **Dan Zhang:** Writing – review & editing, Supervision. **Shaohua Hu:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

The authors have no competing interests to declare that are relevant to the content of this article.

Data availability

The data is available from the corresponding author on reasonable request.

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Ethics statement

This study was approved by the Clinical Research Ethics Committee of the First Affiliated Hospital, Zhejiang University School of Medicine and Women's Hospital, Zhejiang University School of Medicine.

Consent for publication

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Declaration of Generative AI and AI-assisted technologies in the writing process

No AI and AI-assisted technologies were used in the writing process or statistical analyses.

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