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Maternal complement C1q and increased odds for psychosis in adult offspring

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Abstract

The presence of maternal antibodies to food and infectious antigens may confer an increased risk of developing schizophrenia and psychosis in adult offspring. Complement factor C1q is an immune molecule with multiple functions including clearance of antigen-antibody complexes from circulation and mediation of synaptic pruning during fetal brain development. To determine if maternal C1q was associated with offspring schizophrenia and psychosis, we evaluated 55 matched case-control maternal serum pairs from the National Collaborative Perinatal Project. Sample pairs were composed of mothers whose offspring developed psychoses as adults and those whose offspring were free from psychiatric disease. Matching criteria for offspring included birth date, delivery hospital, race and gender, with further matching based on mother's age. IgG markers of C1q, bovine milk casein, egg ovalbumin and wheat gluten were measured with enzyme-linked immunosorbent assays. C1q levels were compared to food antigen IgG and to previously generated data for C-reactive protein, adenovirus, herpes simplex viruses, influenza viruses, measles virus and *Toxoplasma gondii*. C1q was significantly elevated in case mothers with odds ratios of 2.66–6.31 (conditional logistic regressions, $p \leq 0.008$–0.05). In case mothers only, C1q was significantly correlated with antibodies to both food and infectious antigens: gluten ($R^2=0.26$, $p \leq 0.004$), herpes simplex virus type 2 ($R^2=0.21$, $p \leq 0.02$), adenovirus ($R^2=0.25$,

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Contributors

Drs. Severance, Cannon, Buka and Yolken designed the study. All authors collected and/or analyzed data. Dr. Severance wrote the first draft of the manuscript. All authors approved the final manuscript.

Conflict of Interest

Robert Yolken is a member of the Stanley Medical Research Institute Board of Directors and Scientific Advisory Board. The terms of this arrangement are being managed by the Johns Hopkins University in accordance with its conflict of interest policies. None of the other authors report any potential conflicts of interest.

p≤0.006). In conclusion, exposure to maternal C1q activity during pregnancy may be a risk factor for the development of schizophrenia and psychosis in offspring. Prenatal measurement of maternal C1q may be an important and convergent screening tool to identify potentially deleterious immune activation from multiple sources.

Keywords

Innate immune activation; inflammation; maternal exposure; maternal-fetal interface; synapses

1. Introduction

The pathogeneses of schizophrenia and other complex neuropsychiatric disorders are likely rooted in aberrant neurodevelopment (Lewis and Levitt, 2002; Piper et al., 2012; Rapoport et al., 2012). Environmental disturbances during pregnancy may interact adversely in genetically predisposed offspring to compromise neuronal circuitry. Maternal immune activation has become a strong candidate as a process that might impact perinatal brain function (Bauman et al., 2014; Brown and Derkits, 2010; Canetta et al., 2014; Garbett et al., 2012; Meyer, 2013; Shi et al., 2009). Birth cohort studies have identified a number of infectious disease and food antigens and corresponding antibodies that when elevated in the mother during pregnancy are implicated as risk factors for the development of schizophrenia and other psychotic disorders in offspring; these antigens include cytomegalovirus, herpes simplex virus type 2, influenza, rubella, *Toxoplasma gondii*, and wheat glutens (Blomstrom et al., 2012; Brown et al., 2004a; Brown et al., 2000a; Brown et al., 2004b; Buka et al., 2008; Ellman et al., 2009; Karlsson et al., 2012; Mortensen et al., 2010; Pedersen et al., 2011; Xiao et al., 2009).

The presence of immune complexes composed of antibodies bound to infectious and non-infectious antigens triggers the activation of the innate immune system's classic complement pathway. Complement factor C1q is the molecule of first response that recognizes and binds to these immunoglobulin-antigen complexes (Walport, 2001a, b). C1q was also one of the first immune molecules discovered to have effects on synapse development and function in the brain by mechanisms that are not part of standard immune pathways (Benoit and Tenner, 2011; Bialas and Stevens, 2013; Boulanger, 2009; Fourgeaud and Boulanger, 2007; Stephan et al., 2013; Stevens et al., 2007). In our studies of schizophrenia, we have linked elevated C1q to the presence of IgG antibodies directed against milk caseins and wheat glutens (Severance et al., 2012b), and to inflammatory gut processes in experimental animal models (Severance et al., 2012c). Numerous other accounts also report complement system physiological and genetic aberrations in schizophrenia (Arakelyan et al., 2011; Boyajyan et al., 2008; Havik et al., 2011; Mailian et al., 2005; Mayilyan et al., 2008; Vetlugina et al., 1984; Zakharyan et al., 2011).

Previous studies of serum samples from the National Collaborative Perinatal Project (NCPP) revealed significant associations of maternal antibodies to herpes simplex virus type 2, influenza and *T. gondii* with the development of schizophrenia and other psychoses in offspring (Buka et al., 2008; Ellman et al., 2009; Xiao et al., 2009). In the present study of

the NCPP, we postulate that the downstream activation of the innate immune pathway, and specifically activation of C1q during neurodevelopment, may be as important in the etiology of schizophrenia as the specificity of a particular antigen, for example, as food-derived or infectious in origin. If maternal antibody abundance impacts the development of schizophrenia and psychosis in offspring, we would expect that circulating levels of C1q are also elevated to respond to an increased antibody-antigen presence, irrespective of the source or type of antigen. Furthermore, because C1q is active in synaptic pruning processes in the developing perinatal brain (Boulanger, 2009; Fourgeaud and Boulanger, 2007; Stevens et al., 2007), exposure of the fetus to maternally-derived C1q during a critical period of synaptic pruning might, therefore, be an important risk factor for the future development of brain-associated diseases.

Here, our primary goal was to examine changes in C1q activity in maternal serum samples from the Philadelphia cohort of the NCPP. C1q-associated IgG from 55 pregnant women whose children developed schizophrenia and affective psychoses as adults were compared to 55 matched control mothers whose adult offspring did not have a psychiatric illness. C1q-related antibodies were then further evaluated for associations with newly generated data of antibodies to food antigens and with previously generated infectious disease IgG and C-reactive protein measures. Correlations of C1q levels with antibodies from multiple antigen sources would support the prenatal screening of maternal C1q as a more broad measure of maternal antibody overabundance during pregnancy. This C1q-based biomarker strategy would help to identify early those mothers whose offspring might be at-risk for the development of psychoses and schizophrenia.

2. Materials and methods

2.1 Study population

Our study focused on the Philadelphia cohort of the National Collaborative Perinatal Project (NCPP), a large, prospective examination of prenatal care practices at multiple sites across the U.S. (Buka et al., 2008; Cannon et al., 2000; Cannon et al., 2008; Ellman et al., 2009; Xiao et al., 2009). Blood samples were collected from mothers at the time of offspring birth from 1959 to 1966 and were stored at the National Institutes of Health repository. Study participants were informed of the study procedures, although during this time, standard research practice did not require formal informed consent. For the present study, approval for conducting ethical research and use of human subjects was granted by the Institutional Review Board at the Johns Hopkins School of Medicine. All samples were de-identified prior to receipt to protect the privacy of study participants.

To select individuals for the Philadelphia cohort, the Penn Longitudinal Database was searched to identify adult NCPP participants (offspring) with psychiatric diagnoses of psychiatric disorders (Cannon et al., 2000; Cannon et al., 2008; Ellman et al., 2009). Diagnoses of schizophrenia and other psychotic disorders were verified by medical records, as previously described (Buka et al., 2008; Cannon et al., 2000; Cannon et al., 2008; Ellman et al., 2009). Offspring controls were free from psychiatric disorders as adults and initially matched in a nested case-control design where three control individuals were selected for every identified case individual. Matching criteria for offspring included geographic region,

date of birth, birth hospital, race, gender and parental history of mental illness. In our previous studies, we found age-associated patterns of C1q-food antibody immune complexes (Severance et al., 2012b); therefore, for the current study, we further restricted the control group based on maternal age. For each identified 1:3 case-control match, we chose the one of three maternal controls who was closest in age to the case mother, with the additional limitation that the age difference could not exceed three years. Mean ages (years±standard error of the mean) were 23.02±0.72 for control mothers and 23.20±0.74 for case mothers. Furthermore, 88% of the individuals in the Philadelphia cohort were African American (Ellman et al., 2009). Therefore, to further strengthen overall matching, we excluded offspring who were Caucasians from the current study, which resulted in the exclusion of an additional five study pairs. Thus, our study was composed of 55 very closely matched pairs of case and control mothers. The composition of diagnoses among offspring from the case group was as follows: n=38/55 (69.1%) schizophrenia and n=17/55 (30.9%) affective psychoses.

2.2 Laboratory procedures

The enzyme-linked immmunosorbent assays (ELISAs) to detect C1q-, bovine casein-, and wheat gluten-related IgG have been previously described (Severance et al., 2012a; Severance et al., 2012b). The ELISA to measure C1q activation will detect C1q-associated immune complexes as well as IgG directed against the C1q molecule. To measure IgG to ovalbumin, we bound 100ng of protein (Sigma, St. Louis, MO, U.S.A) to the solid phase according to the same protocol. Data for IgG directed against the infectious disease antigens adenovirus (ADV), herpes simplex virus type 1 (HSV-1), herpes simplex virus type 2 (HSV-2), influenza-A and -B viruses, measles virus and *Toxoplasma gondii*, and C-reactive protein (CRP) ELISAs were previously generated as part of ongoing studies, and ELISA kits were purchased from IBL America (Minneapolis, MN, U.S.A.), IBL International GmbH (Hamburg, Germany) and Focus Diagnostics (Cypress, CA, U.S.A.).

2.3 Statistical analyses

Plates were control mean-normalized as previously described to minimize plate-to-plate variation (Severance et al., 2010). Differences in quantitative levels of each marker between case and control mothers were first identified with one-tailed t-tests and multiple comparisons addressed with a Bonferroni correction for each class of marker. Seropositivity was assigned for each significant marker based on cutoffs corresponding to 75%, 90% and 95% of control values. Odds ratios (ORs) were calculated using conditional logistic regressions for matched data. We evaluated a number of different ORs generated based on 75%, 90% and 95% control seropositivities. Socioeconomic status was included as a covariate in these matched comparisons; matched sets were already controlled for geographic region, date of offspring birth, offspring race, offspring gender and mother's age as indicated above. Significant correlations of C1q with food and infectious disease antigens and C-reactive protein were identified with multiple linear regressions with C1q as the dependent variable in all analyses. Covariates included in these non-matched regressions were socioeconomic status, birth month and mother's age. STATA version 12 was used for all statistical analyses.

3. Results

Mean levels of C1q IgG were significantly greater in mothers whose offspring developed psychoses as adults compared to control mothers (t-test, control 1.00±0.04 vs case 1.19±0.06, p≤0.004; Table 1). The significant elevation in maternal C1q IgG persisted when offspring diagnoses of psychoses were stratified to schizophrenia (n=38 pairs, 1.18±0.07, p≤0.009) and affective disorders (n=17 pairs, 1.20±0.10, p≤0.009). Also significantly elevated in case mothers were levels of IgG directed against the infectious disease agents, ADV, HSV-2, influenza-B virus, and *T. gondii*, but only HSV-2 and *T. gondii* remained significant after Bonferroni correction (t-test, p≤0.006–0.007). No case-control differences in quantitative levels were detected for the food antigens, bovine milk casein, wheat gluten or egg ovalbumin, or for the infectious disease antigens, HSV-1, influenza-A virus, and measles virus. CRP levels were also not significantly different between case mothers and control mothers.

Dichotomous seropositivity variables were assigned based on a range of cut-off values, and levels of C1q above the 75th and 95th percentiles conferred significant ORs for association with offspring development of psychoses (ORs=2.66–6.31, p≤0.008–0.05, conditional logistic regression for matched pairs; Table 2). Antibodies to the infectious disease antigens, HSV-2, influenza-B virus, and *T. gondii* defined in this way were also significantly associated with offspring development of psychoses (ORs=2.82–7.75, p≤0.002–0.04).

C1q activation was significantly correlated with certain, but not all of the antigens tested (multiple linear regressions corrected for mother's age, socioeconomic status and birth month; Table 3). In case mothers only, C1q was significantly correlated with the food antigen, wheat gluten, and the infectious disease antigens, ADV and HSV-2 (R^2=0.21–0.26, p≤0.004–0.02). C1q was not significantly correlated with C-reactive protein, bovine milk casein, egg ovalbumin, HSV-1, influenza-A or-B virus, measles virus or *T. gondii*.

4. Discussion

C1q is the initiator molecule of the classic complement pathway, and it has multiple physiological functions including the binding to and clearing of antibody-antigen immune complexes, the interaction with cell surface receptors to promote phagocytosis and local inflammatory response, the attachment to acute phase reactants such as CRP and pentraxin to initiate pathway activation, and the recognition and removal of apoptotic or damaged cells (Sontheimer et al., 2005; Walport, 2001a, b). Of interest to the study of psychiatric disorders, complement C1q and the major histocompatibility complex 1 (MHC1) were some of the first peripherally-acting immune molecules identified to have primary effects on synapse development in the brain (Boulanger, 2009; Fourgeaud and Boulanger, 2007; Huh et al., 2000; Shatz, 2009; Stevens et al., 2007). In experimental mouse models, maternal immune activation was recently found to increase MHC1 levels on the surface of cortical neurons in offspring resulting in alterations of the synaptic densities (Elmer et al., 2013). Here, we identified maternal C1q activation in humans as a potentially important risk factor for the development of schizophrenia and psychosis in offspring. C1q was significantly elevated and associated with antibodies to gluten, HSV-2 and adenovirus in those mothers

whose children developed psychoses as adults, as compared to control mothers. The significant association of C1q with IgG from both infectious and non-infectious antigens in case mothers favors the interpretation of an overall increased rate of immune complex formation in maternal case samples irrespective of the antigen source. These results also suggest that C1q, as an early indicator of innate immune system activation, is an informative target to supplement analyses of single antigen associations with psychotic diseases. The specific mechanisms by which maternal C1q might impact the developing brain are not known, but our results present several possibilities regarding how fetal C1q might be dysregulated as a result of processes that occur maternally.

One objective of our study was to evaluate the association of C1q with both infectious and non-infectious antigens, because C1q activation irrespective of source might represent an important physiological junction by which multiple risk factors for psychoses (infection, inflammation, food sensitivity) could be related. We found significant, positive correlations of C1q with adenovirus, HSV-2 and gluten antibodies. The presence of maternal antibodies to HSV-2 is a replicated risk factor for the development of psychosis in offspring (Buka et al., 2008; Mortensen et al., 2010), and here we show for the first time that this antibody elevation is associated with C1q. Likewise, maternal exposure to respiratory infections has previously been associated with schizophrenia, although adenoviruses were not specifically assessed in this study (Brown et al., 2000b). Interestingly, maternal exposure to *T. gondii*, a well-characterized risk factor for the development of schizophrenia in offspring, was not associated with C1q in this dataset, although it was elevated in case mothers independently from C1q. Similarly, antibodies to influenza-B virus were increased in maternal case samples, yet no correlations were observed with C1q. This lack of correlation may reflect an absence of active infection and could be a possible indication that a different mechanism of pathogenicity and immune system evasion may be in place by certain parasites and viruses. With respect to food antigens, we found a significant association of maternal anti-gluten IgG with maternal C1q. This finding is supported by results from Karlsson et al (2012) who reported that maternal anti-gluten antibodies confers a risk of nonaffective psychosis to offspring (Karlsson et al., 2012). Although our maternal gluten antibody association was not independent from C1q, the diagnostic compositions of our cohorts were not the same, and differences in geography, generations and culture between Philadelphia and Sweden likely influence dietary preferences and thus the immune response to food-derived proteins.

The elevated maternal IgG to a variety of antigens in case mothers may indicate an overall excess of maternal IgG. Maternal IgG antibodies start to transfer to the fetus by 13 weeks gestation and are as abundant as maternal levels at time of birth (Malek et al., 1996; Simister, 2003). Overabundant maternal IgG in the fetal environment thus might be one means by which fetal C1q could be activated. Alternatively, our assay design cannot discount the possibility that we are measuring autoantibodies directed at the C1q molecule in the mothers. Thus, fetal C1q dysfunction could be manifested as a deficiency brought about by inactivation of fetal C1q by maternally-generated C1q autoantibodies. The presence of maternal autoantibodies and development of complex neuropsychiatric disorders has precedence, especially in autism spectrum disorders where maternal autoantibodies have been found to recognize brain proteins critical to the neurodevelopmental process

(Braunschweig et al., 2013; Brimberg et al., 2013). These scenarios share a common end result that any fetal C1q dysregulation during critical periods of C1q-mediated synaptic pruning will presumably permanently alter synaptic connections in the developing brain either through over- or under-pruning.

The complement system including C1q is also involved in pro-inflammatory processes associated with initial placental development (Bulla et al., 2012). Maternal levels of a marker of general inflammation, CRP, while not significantly elevated in case samples in our cohort, was associated with schizophrenia in offspring in a large Finnish cohort (n=777 case-control pairs; odds ratio=1.31) (Canetta et al., 2014). Our sample size was modest compared to this large study and, therefore, likely did not provide enough power to detect the subtle increases in odds ratios that are detectable in analyses of large cohorts.

The extent that our results can be interpreted is limited by the sample size of our cohort, in spite of the rigorous matching criteria applied. Of note, our replication of disease-associated maternal HSV-2, influenza-B virus and *T. gondii* IgG can be considered a methodological control that supports the power of our study (Blomstrom et al., 2012; Brown et al., 2004a; Buka et al., 2008; Ellman et al., 2009; Mortensen et al., 2010; Pedersen et al., 2011; Xiao et al., 2009). Another limitation of our study is the use of serum from mothers of healthy controls instead of controls who might have a non-psychiatric central nervous system (CNS) disorder. The best control would be a disorder of known etiology and a minimal likelihood of being impacted by C1q activation, a combination that might be difficult to achieve as the role of C1q during development and processes responsible for its activation in the brain are still being characterized. Trisomy and spina bifida might be appropriate comparison control conditions. Our study is also limited by its cross-sectional design. Therefore, it is not possible to extrapolate the current results to predict the triggers and resulting duration of C1q activation in the present study. Because C1q activity is associated with a variety of physiological states, its activation may be an acute response to infectious pathogens, for example, or it may take the form of a chronic stimulation due to continued exposure to dietary antigens or autoimmune condition.

In conclusion, we are only just beginning to disentangle the complex functions of components of the immune system and their role in the pathophysiology of psychiatric disorders. Our findings suggest that maternal C1q activity during the perinatal period may be one such risk factor and may represent a pathogenic mechanism by which fetal exposure to certain antigens or antibodies including autoantibodies might impact neurodevelopment. Maternal C1q activity may be the result of exposure to food-derived antigenic proteins such as wheat glutens and to infectious disease agents such as adenovirus and HSV-2. Much more mechanistic and translational data are needed to fully understand the consequences on fetal brain connections of aberrant activation of the complement pathway. Our findings are an important step in identifying biological processes that might link multiple types of immune-based hypotheses (infectious agents, food sensitivities, autoimmunity) and focus future studies aimed to understand the consequences of this convergence on the development of psychotic diseases. Our results have longer-term clinical implications as well. Maternal serum C1q is a measurable biomarker that could be easily incorporated into prenatal screening strategies and has the advantage of being an early indicator of innate immune

system activation due to multiple sources. Detection of its elevation in pregnant women would allow the identification of potentially at-risk mothers, for whom additional clinical care and testing could be implemented.

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Abbreviations

ADV	Adenovirus
CLR	Conditional logistic regression
CRP	C-reactive protein
ELISA	Enzyme-linked immunosorbent assays
HSV-1	Herpes simplex virus type 1
HSV-2	Herpes simplex virus type 2
IgG	Immunoglobulin G
OR	Odds ratio
SE	Standard error

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Table 1

Quantitative levels of study markers

	Control (n=55) Mean±SE[a]	Case (n=55) Mean±SE	t	p-value
Immune/Inflammation				
C1q[b]	**1.00±0.04**	**1.19±0.06**	**2.70**	**0.004**[c]
C-reactive protein	1.00±0.09	0.90±0.10	−0.79	0.78
Food antigens				
Bovine casein	1.00±0.12	0.98±0.11	−0.15	0.56
Egg ovalbumin	1.00±0.08	0.99±0.09	−0.09	0.54
Wheat gluten	1.00±0.07	1.14±0.11	1.06	0.15
Infectious antigens				
Adenovirus	**1.00±0.06**	**1.17±0.07**	**1.80**	**0.04**
Herpes simplex virus 1	1.00±0.07	0.98±0.06	−0.22	0.59
Herpes simplex virus 2	**1.00±0.16**	**1.66±0.20**	**2.53**	**0.006**[c]
Influenza-A virus	1.00±0.04	1.01±0.05	0.17	0.43
Influenza-B virus	**1.00±0.05**	**1.15±0.06**	**2.05**	**0.02**
Measles virus	1.00±0.06	1.12±0.06	1.41	0.08
T. gondii	**1.00±0.09**	**1.40±0.13**	**2.51**	**0.007**[c]

[a] Mean±SE refers to mean absorbances±standard error. Each immunoassay plate was meannormalized based on control values to minimize plate-to-plate variation.

[b] Bolded entries indicate statistically significant differences at $p \leq 0.05$.

[c] Differences remain significant following Bonferroni correction.

Table 2

Odds ratios of marker associations with psychosis development

	Control (n=55)	Case (n=55)	Odds ratio	CLR[a] p-value	Confidence interval
Immune/inflammation	No. Seropositive above cut-off (%)				
C1q[b]					
75th percentile	**13 (23.6)**	**23 (41.8)**	**2.66**	**0.05**	**1.06–6.68**
90th percentile	6 (10.9)	15 (27.3)	2.56	0.07	0.98–6.71
95th percentile	**2 (3.6)**	**13 (23.6)**	**6.31**	**0.008**	**1.42–28.18**
Infectious antigens					
Adenovirus					
75th percentile	13 (23.6)	20 (36.4)	1.98	0.19	0.79–4.95
90th percentile	6 (10.9)	6 (10.9)	1.02	0.58	0.32–3.23
95th percentile	2 (3.6)	3 (5.5)	1.50	0.53	0.25–9.14
Herpes simplex virus 2					
75th percentile	**13 (23.6)**	**27 (49.1)**	**7.75**	**0.002**	**1.75–34.34**
90th percentile	6 (10.9)	7 (12.7)	1.12	0.57	0.33–3.74
95th percentile	2 (3.6)	5 (9.1)	2.18	0.37	0.41–11.67
Influenza-B virus					
75th percentile	**14 (25.5)**	**25 (45.5)**	**2.82**	**0.03**	**1.14–6.97**
90th percentile	**5 (9.1)**	**13 (23.6)**	**4.01**	**0.04**	**1.08–14.89**
95th percentile	2 (3.6)	5 (9.1)	5.69	0.14	0.56–58.04
T. gondii					
75th percentile	**13 (23.6)**	**26 (47.3)**	**2.86**	**0.02**	**1.20–6.84**
90th percentile	**5 (9.1)**	**17 (30.9)**	**3.48**	**0.02**	**1.26–9.62**
95th percentile	3 (5.5)	10 (18.2)	3.53	0.07	0.94–13.19

[a] CLR refers to conditional logistic regression

[b] Bolded entries indicate statistically significant associations of seropositivity with psychosis development in offspring at p≤0.05.

Table 3

Correlations of C1q with an inflammation marker and with antibodies to food and infectious antigens.

	Control (n=55)				Case (n=55)			
	R^2	**Coefficient**	**Confidence interval**	**p-value**	**R^2**	**Coefficient**	**Confidence interval**	**p-value**
Immune/inflammation[a]								
C-reactive protein	0.04	−0.06	−0.17–0.05	0.77	0.03	−0.04	−0.23–0.14	0.86
Food antigens								
Bovine casein	0.05	0.06	−0.03–0.14	0.64	0.02	0.003	−0.15–0.16	0.89
Egg ovalbumin	0.05	0.08	−0.05–0.21	0.67	0.04	0.09	−0.10–0.28	0.73
Wheat gluten[b]	0.10	0.15	0.02–0.28	0.23	**0.26**	**0.29**	**0.14–0.43**	**0.004**
Infectious antigens								
Adenovirus	0.04	0.09	−0.08–0.25	0.76	**0.25**	**0.43**	**0.21–0.65**	**0.006**
Herpes simplex virus 1	0.10	0.16	0.01–0.31	0.25	0.03	−0.11	−0.39–0.17	0.78
Herpes simplex virus 2	0.06	0.05	−0.01–0.12	0.53	**0.21**	**0.14**	**0.06–0.22**	**0.02**
Influenza-A virus	0.03	0.13	−0.14–0.40	0.79	0.04	0.15	−0.17–0.48	0.73
Influenza-B virus	0.12	0.26	0.05–0.46	0.12	0.08	0.28	−0.02–0.59	0.34
Measles virus	0.05	0.11	−0.06–0.29	0.65	0.03	0.07	−0.20–0.34	0.85
T. gondii	0.02	0.03	−0.08–0.14	0.90	0.03	0.04	−0.09–0.17	0.82

[a] For all comparisons, C1q was the dependent variable and the other markers were the independent variables

[b] Bolded entries indicate statistically significant correlations at $p \leq 0.05$