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ORIGINAL ARTICLE

Influence of maternal infections on neonatal acute phase proteins and their interaction in the development of non-affective psychosis

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Although primary infections with *Toxoplasma gondii* or herpes viruses during pregnancy are established teratogens, chronic maternal infections with these pathogens are considered far less serious. However, such chronic infections have been associated with neuropsychiatric disorders in the offspring. The risks of non-affective psychoses, including schizophrenia, in offspring associated with these exposures during pregnancy have not been completely defined. We used data from neonatal dried blood samples from 199 cases of non-affective psychosis and 525 matched controls (born 1975–1985). We measure immunoglobulin G antibodies directed at *T. gondii*, cytomegalovirus and herpes simplex virus type-1 and -2, as well as levels of nine acute phase proteins (APPs). We assessed the interaction between maternal antibodies and neonatal APP in terms of risk of non-affective psychosis. Among controls, maternal exposure to *T. gondii* or cytomegalovirus, but not to the other herpes viruses, was associated with significantly higher levels of neonatal APPs. Among cases, none of the maternal exposures were associated with any significant change in APPs. We observed increased RR for non-affective psychosis associated with maternal infection with *T. gondii* (odds ratio 2.1, 95% confidence interval 1.1–4.0) or cytomegalovirus (1.7, 0.9–3.3) only among neonates with low APP levels. These findings suggest that chronic maternal infection with *T. gondii* or cytomegalovirus affect neonatal markers of innate immunity. Deficient fetal immune responses in combination with maternal chronic infections may contribute to subsequent risk for psychosis. A greater understanding of the maternal–fetal immunological interplay may ultimately lead to preventive strategies toward neuropsychiatric disorders.

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INTRODUCTION

Primary infections during pregnancy with infectious agents such as *Toxoplasma gondii* (*T. gondii*) or certain herpes viruses, common throughout the world, pose a serious, and fortunately rare, teratogenic threat to the developing fetus following placental transmission. It is becoming increasingly apparent that some chronic maternal infections (for example, helminths, protozoa and HIV) have persistent effects on the offspring's later immune responses, independent of placental transmission of the pathogen.[1] Although chronic, latent maternal infections with *T. gondii* or herpes virus are generally considered harmless to the fetus; one recent study reported delayed motor development in offspring of mothers with latent *T. gondii* infections.[2] These infections have also been associated with risk of non-affective psychoses, such as schizophrenia, in the offspring.[3–7] Taken together, these reports imply that some common chronic and clinically unapparent infections among pregnant women may be of greater public health concern than hitherto appreciated.

In a recent study, we reported that certain acute phase proteins (APP) were lower in neonatal dried blood spots (NDBSs) from individuals later diagnosed with non-affective psychosis compared with matched control individuals.[8] APPs are generally not transported across the placenta and thus provide a measure of the activity of the innate immune system in the neonate.[9]

Here, we hypothesize that neonates with low innate immune reactivity might be more susceptible to risks posed by chronic maternal infections. We use the previously reported data obtained from NDBS to investigate levels of APP in neonates in relation to maternal exposure to four microbial agents (*T. gondii*, cytomegalovirus (CMV), HSV-1 and -2). We then evaluate potential interactions between the maternal exposures and neonatal APP levels in terms of future psychosis risk.

MATERIALS AND METHODS

Study population

As previously described,[3,8] the study population was selected from individuals born in Sweden between 1975 and 1985. Participants had to be alive and residents in Sweden on 31 December 2003. The study was approved by the regional research ethics committee at Karolinska Institutet, Stockholm, Sweden.

Cases ascertainment of non-affective psychosis

Data on psychiatric illness were extracted from the National Patient Register, which includes all in-patient care in Sweden since 1987, and from the Stockholm psychiatric healthcare registry, which includes psychiatric out-patient care since 1997. To be included, cases had to be diagnosed in Stockholm with non-affective psychoses as in-patients 1987–2003 or as out-patients 1997–2003. Non-affective psychoses were defined as F20–29,

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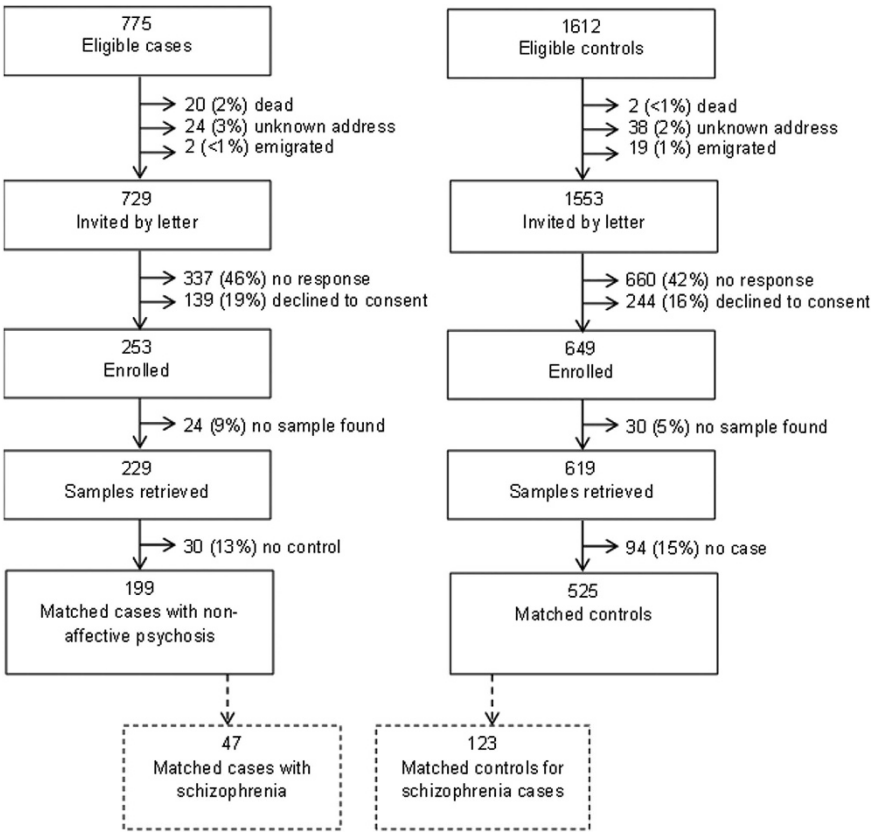

Figure 1. Participant flow, exclusions and losses.

and schizophrenia specifically as F20 according to the International Classification of Disease, Tenth edition, or their corresponding codes in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition and International Classification of Disease – 9, as described in detail previously.[3] Eligible subjects were invited to participate by letter. After complete description of the study to the subjects, written informed consent was obtained. Two hundred and fifty-three subjects consented and were enrolled, Figure 1.

Selection of controls

Comparison individuals were matched for sex, birth date and birth hospital, and selected from the Swedish Medical Birth Register, which includes pregnancy outcome data on all children born in Sweden since 1973. Individuals who had been treated as in-patients at a psychiatric clinic were excluded. Six hundred and forty-nine controls consented and were enrolled, Figure 1.

Blood spot analyses

Since 1975, blood has been collected on a filter from all newborns in Sweden and stored at 4 °C at a central biobank following neonatal screening for metabolic diseases. For this study, we used data obtained from NDBSs from 199 consenting cases and 525 consenting controls, matched at a ratio varying from 1:1 to 1:5, Figure 1.[3,8]

For elution of immunoglobulin (Ig)G, 3.2-mm discs were punched from each blood spot and incubated for 1 h in 200 µl phosphate-buffered saline. Anti-CMV *and -T. gondii* IgG were measured by assays from Vitro-Immun Labor Diagnostika GmbH (Oberursel, Germany) and anti-HSV-1 and -2 IgG by assays from Focus Diagnostics (Cypress, CA, USA). For APP concentration analyses, another 3.2-mm diameter disc was punched from each blood spot and immersed in 80 µl of phosphate-buffered saline containing 1% bovine serum albumin and 0.05% Tween. Eluates were analyzed for the concentration of nine APPs using a premixed, magnetic bead-based multiplex panel (Bio-Rad, Hercules, CA, USA), according to manufacturer instructions.[8] Concentrations of the APPs were imputed using the Bio-Plex 200 Suspension Array System (Bio-Rad) with Bio-Plex Manager 6.0 software (Hercules, CA, USA).

A full analysis of IgG data has been published in Blomstrom *et al*.[3] A full analysis of APP data has been published in Gardner *et al*.[8]

Statistical analyses

As previously described,[3] levels of IgG directed at infectious agents were analyzed as dichotomous variables corresponding to exposure status based on the expected age-weighted prevalences among pregnant women in Stockholm during the years 1975–1985: *T. gondii* 25%, CMV 75%, HSV-1 60% and HSV-2 25%.[10–13] The distributions among controls were used to find the absorbance cutoff value corresponding to these prevalences. The distribution of APP concentrations was skewed. Hence, the Mann–Whitney *U*-test was used to compare median levels of the nine APPs between exposed and unexposed individuals for each of the infectious agents, separately for controls and cases.

To estimate the effect of maternal exposure and neonatal APP levels on psychosis risk, conditional logistic regression was used to calculate odds ratios. Individuals were classified as either exposed or unexposed to a microbial agent (as above) and as having either low APP levels (those in the lowest tertile) or high APP levels (those in the middle and highest tertiles), again established using the distribution of each APP among controls. Unexposed individuals with high APP were used as a referent group.

We also used principal components analysis to create an APP score, collapsing information from the nine inter-correlated APP[8] into a single score for each person. The APP concentrations were log2-transformed prior to the calculation of the APP score due to the skewed distribution. The first principal component accounted for the greatest variance (55%) in the APP data and was used as the APP score. Each of the nine APPs loaded to a similar extent onto this score (0.49–0.89). Individuals were classified as having either a low APP score (having an APP score below the median) or a high APP score (APP score above the median).

In order to formally test for interaction, that is, departure from additivity, we quantified the relative excess risk due to interaction (RERI). Assuming that the matched odds ratio can be used alternately of the relative risk (RR), RERI was defined as: $RERI = RR_{11} - RR_{10} - RR_{01} + 1$. The reference category was defined as those unexposed to both risk factors, that is, $RR_{00} = 1$. $RERI = 0$ indicates no interaction.[14]

Analyses were made with the SAS software package, version 9.1 (SAS Institute, Cary, NC, USA), and IBM SPSS Statistics 22.0 (IBM, Armonk, NY, USA).

RESULTS

APP levels across maternal exposures among control neonates

As can be seen from Table 1, each of the nine different APPs and the APP score were significantly higher in NDBS from children born to mothers with serological evidence of *T. gondii* exposure as compared with NDBS from children born to unexposed mothers. Maternal CMV exposure was also associated with significant, but less pronounced, elevations in neonatal APP levels, with the exception of C-reactive protein, and with a significantly higher APP score, Table 1. Maternal exposure to HSV-1 or -2 was not associated with neonatal APP levels or the APP score (data not shown).

APP levels across maternal exposures among cases

Levels of the different APPs or APP scores among individuals who later developed non-affective psychosis or the more restricted diagnosis of schizophrenia did not significantly vary according to maternal exposure to *T. gondii* or CMV, Table 1. Similar to the controls, no significant differences in APP levels or scores were observed according to maternal exposure to HSV-1 or -2 among the cases (data not shown).

Risk interactions

Maternal *T. gondii* infection did not significantly affect the odds of developing non-affective psychosis among neonates with high APP levels, Figure 2. Low levels of serum amyloid P or procalcitonin were associated with psychosis risk among neonates regardless of maternal exposure to *T. gondii*. Neonates with maternal *T. gondii* exposure and low levels of α-2-macroglobulin, tissue-type plasminogen activator or fibrinogen had significantly increased odds of non-affective psychosis. When restricted to cases of schizophrenia only, our analysis showed a similar pattern, but the odds of developing schizophrenia increased substantially among neonates with low APP levels and maternal *T. gondii* exposure, for example, by 10-fold among those with low fibrinogen levels. Moreover, neonates with maternal *T. gondii* exposure and a low APP score had significantly increased odds of developing non-affective psychosis (odds ratio 2.1, 95% confidence interval 1.1–4.0) and schizophrenia, (3.6, 1.0–13.4).

Maternal IgG reactivity against CMV did not affect the odds of developing non-affective psychosis among neonates with high APP levels, Figure 3. Neonates with low levels of α-2-macroglobulin, SAP or tissue-type plasminogen activator and maternal CMV exposure had increased odds of non-affective psychosis. Low levels of procalcitonin increased the odds of non-affective psychosis regardless of maternal CMV exposure status. When the analysis was restricted to schizophrenia only as an outcome, maternal CMV exposure increased the odds of schizophrenia even among those with high levels of most APPs and a high APP score. Maternal CMV exposure and low neonatal levels of all APPs, except ferritin, were significantly associated with increased odds of schizophrenia. Again, being in the lower tertile of fibrinogen together with maternal CMV exposure increased the hazard ratio for schizophrenia by sixfold. Neonates with maternal exposure to CMV and a low APP score had significantly increased odds of developing non-affective psychosis (1.7, 0.9–3.3) and schizophrenia (6.0, 1.1–33.1).

A significant RERI between maternal exposures and APP levels on future psychosis risk was detected only for maternal *T. gondii* exposure in combination with low neonatal levels of fibrinogen, RERI 1.1 (95% confidence interval 0.0–2.2).

DISCUSSION

Increasing evidence suggest that some maternal chronic infections can influence the neonatal immune response and affect the child's later susceptibility to not only the specific agent that infected the mother but also to unrelated pathogens.[1] To date, most studies have focused on chronic infections prevalent during pregnancy in developing countries, such as helminths, HIV and protozoa, and have commonly used levels of cytokines or antibodies as end points. Compared with cytokines, levels of APPs are less prone to rapid fluctuations. Moreover, APPs are likely not transported across the placenta and thus provide information on the status of innate immunity in the neonate.[9] We here report that serological evidence of chronic maternal infection with *T. gondii* or CMV is associated with increased levels of several different APPs in neonatal blood. In contrast, maternal infections with HSV-1 or -2 had very little influence on APP levels in the neonate. Taken together, these observations suggest that some chronic maternal infections can influence the immune response in the neonate depending on the nature of the microorganism.[15]

The three herpes viruses and the parasite investigated in this study all establish chronic presumably life-long infections in humans and can infect the fetus following primary infection during pregnancy. The finding that serological evidence of maternal exposure to HSV-1 or -2 appeared to have little or no influence on neonatal levels of APP, whereas maternal CMV infection was associated with increased levels of APP in newborns, could hypothetically relate to mechanisms controlling latency and reactivation during pregnancy. Congenital infection may occur following reactivation of a latent CMV infection in mothers with pre-conceptual immunity,[16] whereas for herpes simplex viruses, maternal transmission appears to only occur following primary infections during late pregnancy.[17] Similar to CMV infection, reactivation of chronic maternal *T. gondii* infection has been reported to cause congenital infection.[18] Thus, our present observations may indicate that *T. gondii* and CMV infections reactivate and target fetal tissues eliciting an innate immune response that in combination with protective maternal IgG leads to successful control of the infection. Alternatively, maternal factors relating specifically to maintenance of latency of CMV and of the bradyzoite stage of *T. gondii* infection may influence APP levels in the fetus and neonate. For example, interferon-γ signaling is reported to be important for controlling chronic *T. gondii* infection as well as maintaining latent CMV infection,[19,20] and also acts selectively upon certain APP levels.[21] Although it is becoming increasingly clear that communication exists between maternal and fetal immune systems,[22] the mechanisms mediating this communication remain to be established.

Of potential relevance for the etiology of non-affective psychosis is whether these individuals exhibit responses to each of the different maternal exposures that differ from their comparison subjects. Interestingly, in the group of neonates who will later be diagnosed with non-affective psychoses, APP levels were similar across exposed and unexposed individuals. APP levels also appeared to be similar across unexposed cases and controls. Thus, rather than exhibiting lower levels *per se*, it seems as if the innate immune system in neonates who will develop psychosis are unable to 'respond' to specific maternal infections. This notion is in line with earlier studies reporting deficient innate immune activation among schizophrenia patients.[23]

The cause(s) of low levels of APP, or perhaps unresponsiveness in terms of APP levels, in the neonatal period are not known, but could be related to genetic factors determining their synthesis and metabolism. Although adult circulating APP levels are only weakly associated with genetic variation,[24–26] it is possible that such associations may be stronger among neonates. Recent studies point to a highly correlated T-cell response in mothers and their fetuses.[22] Thus, some of our observations may be explained by

Table 1. Mann–Whitney *U*-test, *P*-values of the difference in levels of acute phase proteins among neonates to exposed and unexposed mothers (median, 25th–75th percentile), controls and cases separately

APP	T. gondii								
	Controls			*Neonates who will develop non-affective psychosis, ICD-10 F20–29*			*Neonates who will develop schizophrenia, ICD-10 F20*		
	Unexposed (n = *403*)	*Exposed* (n = *122*)	P	*Unexposed* (n = *153*)	*Exposed* (n = *46*)	P	*Unexposed* (n = *30*)	*Exposed* (n = *16*)	P
a-2-Macroglobulin (ng ml^{-1})	357 (137–615)	594 (352–895)	***	340 (158–589)	420 (129–824)	NS	282 (101–508)	368 (128–606)	NS
Haptoglobulin (ng ml^{-1})	6.0 (2.6–21.1)	11.2 (3.3–36.4)	***	6.3 (2.5–15.7)	6.4 (2.3–22.4)	NS	6.2 (2.1–42.1)	6.6 (1.6–23.9)	NS
C-reactive protein (ng ml^{-1})	0.6 (0.2–1.8)	1.1 (0.5–2.4)	**	0.6 (0.2–1.3)	0.8 (0.2–2.2)	NS	0.5 (0.1–1.3)	0.3 (0.1–1.2)	NS
Serum amyloid P (ng ml^{-1})	10.3 (5.1–16.1)	13.8 (7.8–20.5)	***	8.8 (4.7–15.2)	11.0 (6.1–16.0)	NS	8.6 (4.2–13.3)	10.0 (5.1–12.5)	NS
Procalcitonin (pg ml^{-1})	2.1 (0.8–3.3)	3.3 (1.4–5.2)	***	1.9 (0.8–3.2)	2.6 (0.8–4.4)	NS	2.0 (0.3–2.6)	2.2 (0.2–4.4)	NS
Ferritin (pg ml^{-1})	1130 (301–2500)	2350 (665–4760)	***	1430 (331–2830)	1800 (260–4290)	NS	1080 (220–2580)	1250 (150–3920)	NS
tPA (pg ml^{-1})	3.6 (1.3–6.0)	4.8 (2.2–6.9)	*	3.1 (1.0–5.3)	2.2 (0.0–5.6)	NS	2.9 (0.8–4.9)	2.3 (0.0–4.4)	NS
Fibrinogen (ng ml^{-1})	6.8 (2.2–17.9)	14.9 (2.7–46.2)	**	7.6 (2.6–24.9)	3.6 (1.2–20.9)	NS	3.7 (2.7–26.5)	2.6 (0.4–13.0)	NS
Serum amyloid A (ng ml^{-1})	1.6 (0.7–3.5)	2.2 (1.0–5.0)	**	1.5 (0.7–2.9)	1.2 (0.4–2.4)	NS	1.7 (0.7–2.1)	1.2 (0.0–2.3)	NS
APP score	0.1 (−0.7 to −0.6)	0.6 (−0.8 to −1.1)	***	0.2 (−0.6 to −0.5)	0.1 (−0.6 to −0.8)	NS	0.1 (−0.8 to −0.5)	−0.2 (−1.1 to −0.4)	NS
APP	*CMV*								
	Controls			*Neonates who will develop non-affective psychosis, ICD-10 F20–29*			*Neonates who will develop schizophrenia, ICD-10 F20*		
	Unexposed (n = *135*)	*Exposed* (n = *390*)	P	*Unexposed* (n = *48*)	*Exposed* (n = *151*)	P	*Unexposed* (n = *8*)	*Exposed* (n = *38*)	P
a-2-Macroglobulin (ng ml^{-1})	348 (83.2–588)	431 (187–698)	**	340 (100–565)	355 (159–678)	NS	343 (128–521)	336 (101–551)	NS
Haptoglobulin (ng ml^{-1})	5.1 (2.3–17.5)	7.2 (2.8–27.8)	*	5.7 (2.2–22.3)	6.5 (2.8–16.1)	NS	1.9 (1.6–37.5)	7.1 (2.4–37.0)	NS
C-reactive protein (ng ml^{-1})	0.7 (0.2–2.0)	0.8 (0.2–1.9)	NS	0.8 (0.2–1.7)	0.6 (0.2–1.4)	NS	0.8 (0.1–0.9)	0.4 (0.1–1.2)	NS
Serum amyloid P (ng ml^{-1})	9.4 (4.3–16.5)	11.5 (6.1–18.0)	*	8.9 (5.8–14.3)	8.9 (4.8–17.0)	NS	7.9 (6.0–10.8)	9.0 (4.2–13.3)	NS
Procalcitonin (pg ml^{-1})	1.9 (4.3–16.5)	2.3 (0.9–3.8)	*	1.8 (0.8–3.2)	2.0 (0.8–3.5)	NS	2.3 (0.4–3.5)	1.9 (0.3–3.5)	NS
Ferritin (pg ml^{-1})	965 (191–2410)	1590 (439–3180)	**	1230 (259–2720)	1730 (335–3130)	NS	960 (250–2080)	1180 (120–2660)	NS
tPA (pg ml^{-1})	3.0 (0.9–5.8)	4.1 (2.0–6.4)	*	2.8 (1.0–4.8)	3.1 (0.5–5.6)	NS	2.4 (0.6–5.3)	2.9 (0.2–4.6)	NS
Fibrinogen (ng ml^{-1})	5.2 (2.0–17.0)	8.2 (2.4–27.3)	*	5.3 (2.5–16.0)	7.4 (2.1–26.2)	NS	3.5 (3.0–20.0)	3.4 (1.4–26.1)	NS
Serum amyloid A (ng ml^{-1})	1.4 (0.6–3.0)	1.8 (0.9–4.1)	*	1.2 (0.5–3.0)	1.6 (0.6–2.8)	NS	0.9 (0.2–2.4)	1.5 (0.6–2.1)	NS
APP score	0.1 (−1.1 to −0.6)	0.3 (−0.5 to −0.8)	*	0.1 (−0.5 to −0.6)	0.1 (−0.6 to −0.6)	NS	−0.3 (−0.6 to −0.5)	0.1 (−1.0 to −0.4)	NS

Abbreviations: APP, acute phase protein; ICD, International Classification of Disease; tPA, tissue-type plasminogen activator. *$P \leqslant 0.05$, **$P \leqslant 0.01$, ***$P \leqslant 0.001$. NS: no significant difference in levels of APP between unexposed and exposed neonates.

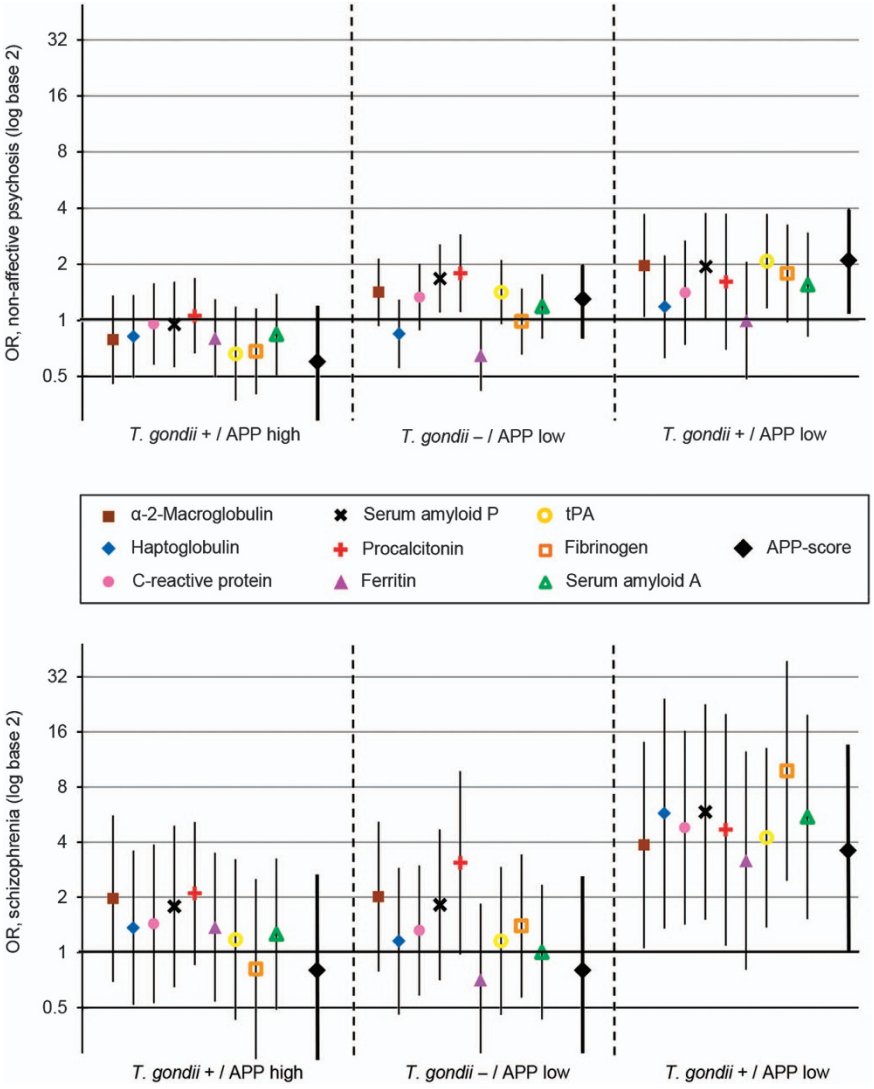

Figure 2. Odds ratios (ORs) and 95% confidence intervals of non-affective psychosis or schizophrenia according to maternal *T. gondii* exposure status and levels of each acute phase protein (APP) (lowest 1/3 tertile, and highest 2/3 tertile) and APP score (below median and above median). tPA, tissue-type plasminogen activator.

variation in how the maternal immune system handles chronic infections during pregnancy, potentially leading to a suboptimal fetal response and/or programming among cases. Indeed, elevated levels of CRP, interleukin-8 and tumor necrosis factor-α, potentially indicating a dysregulated immune response, have been found in sera from mothers of patients with schizophrenia.[27–29] In this context, it should be noted that genetic variation in the human leukocyte antigen region is related to not only the outcome of infections,[30] but also to schizophrenia risk.[31]

Our risk estimates indicate that maternal reactivity toward *T. gondii* or CMV along with low levels of APP increases psychosis risk, particularly risk of schizophrenia. This finding is consistent with our previous findings of a specific association between maternal *T. gondii* or CMV infection and schizophrenia.[3] Plausibly, maternal *T. gondii* or CMV infections become harmful to the fetus only if their innate immune defense, as represented by APP levels, remains low. Noteworthy is the 10-fold increased risk of developing schizophrenia associated with low fibrinogen levels and maternal *T. gondii* infection. A significant interaction between maternal *T. gondii* and low neonatal levels of fibrinogen in terms of psychosis risk was also detected by our RERI analysis. Although fibrinogen is reported to be involved in the virulence of *Streptococcus agalactiae*[32] and in the defense against *Yersinia pestis*,[33] its potential role in protecting the neonate from adverse effects of a maternal *T. gondii* or CMV infection is not known.

Regarding long-term implications, it can be hypothesized that a deficiency in the APP response not only renders the fetus more vulnerable to some maternal infections, but also increases their susceptibility and/or vulnerability to infections later in life. Indeed, epidemiological studies suggest that severe infections (that is, those requiring hospitalization) during both childhood and adulthood are more prevalent among psychosis patients.[34–36]

Strengths and limitations

A number of limitations of the present study should be noted. Examining correlations between maternal exposures and neonatal immune markers using matched controls from a case–control study as we have done in Table 1 may reduce the external validity of the study. The controls are healthier in terms of severe psychiatric illness and associated comorbidities compared with the general population. However, there is no reason to believe that this group differs from the general population in terms of immune response to maternal exposure status. As noted earlier, the number of participants was relatively small due to a fairly low

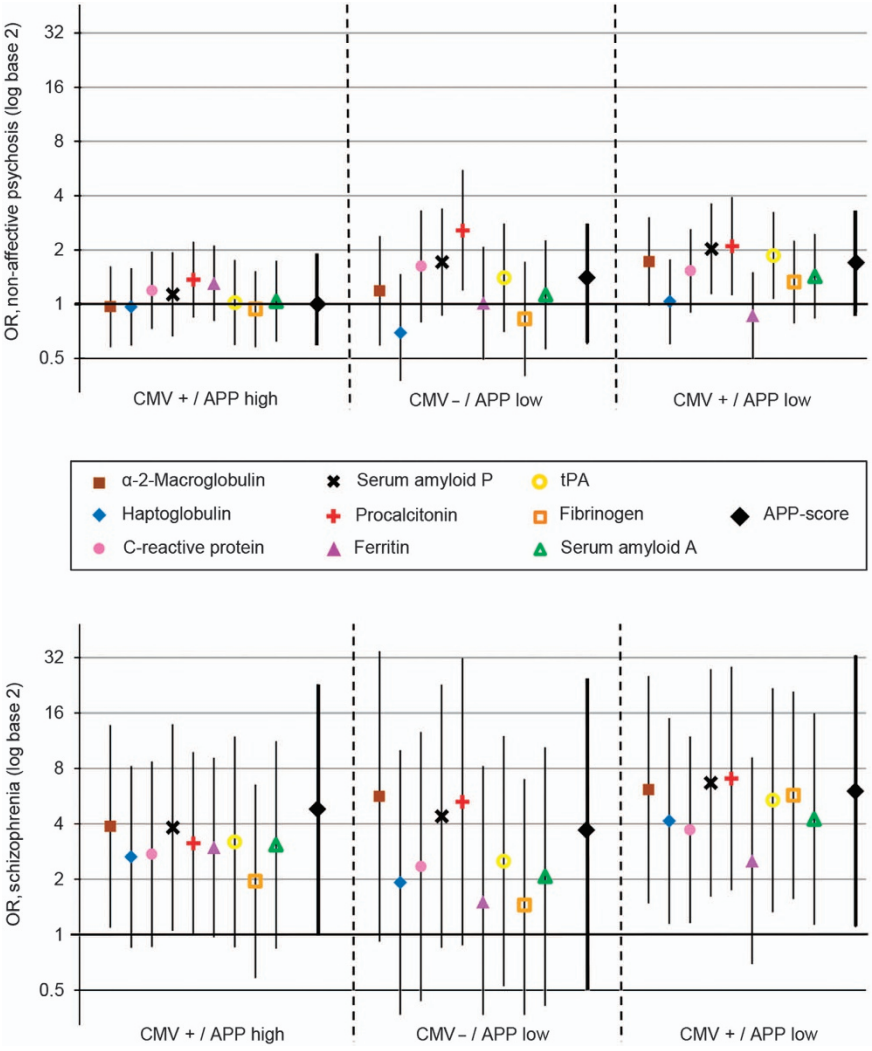

Figure 3. Odds ratios (OR) and 95% confidence intervals of non-affective psychosis or schizophrenia according to maternal cytomegalovirus (CMV) exposure status and levels of each acute phase protein (APP) (lowest 1/3 tertile, and highest 2/3 tertile) and APP score (below median and above median).

participation rate, although there was no indication of selection bias.[3] It should also be noted that the participants were up to 28 years of age at the time of recruitment. Thus, more cases of non-affective psychosis were likely to develop within the source population with increasing age, possibly including some of the control subjects included here.

It is not possible to know when the maternal IgG first developed due to the cross-sectional design. Although primary exposures during pregnancy could have occurred in a few cases, the IgGs measured here are most likely representing exposure prior to conception. Future studies should focus on exploring the associations identified here in longitudinal studies, including maternal sera obtained pre-conceptually or during earlier stages of pregnancy.

Another limitation is that we have not corrected for multiple comparisons. However, the consistent patterns in our observations, including the congruent results obtained using principal components analysis, are assuring that the associations are not likely type I errors. The APP score explains a relatively low proportion of the total variance in the APP data set (55%). As we reported previously,[8] the correlations among the nine APPs varied from 0.21 to 0.83, so this result is not entirely unexpected. Given the sometimes quite strong correlations between some of the APPs, we aimed to provide a description of the overall consistent pattern that was observed when examining the APPs individually.

CONCLUSIONS

At present, maternal immune activation and the immune deficiency hypothesis is under focus in schizophrenia research. Our study is the first to explore the combined effect by these two potential risk factors: maternal immune activity (in terms of maternal exposure to the four pathogens) and neonatal immune response (in terms of neonatal APP levels). Our data suggest that maternal exposure to *T. gondii* or CMV increases levels of APPs in neonates. Moreover, maternal reactivity toward *T. gondii* or CMV appears to confer an increased RR of psychosis, and a substantial increase in RR of schizophrenia, among neonates who do not show elevations in APP levels. In light of the high prevalences of *T. gondii* and CMV in large regions of the world, these infections could potentially contribute to a number of future cases among susceptible neonates. These exploratory findings can primarily be seen as hypotheses generating and need to be confirmed. If these associations are confirmed, this type of study can lead to a better

understanding of the risks associated with maternal infections and the development of strategies for the prevention of schizophrenia and related neuropsychiatric disorders.

CONFLICT OF INTEREST

Dr Yolken received grants from the Stanley Medical Research Institute during the conduct of the study. The remaining authors declare no conflict of interest.

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