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The serological evidence for maternal influenza as risk factor for psychosis in offspring is insufficient: critical review and meta-analysis

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ABSTRACT

Maternal influenza during pregnancy has been suggested to increase the psychosis risk for the offspring. This hypothesis has been tested using "ecological" studies, which examined the risk for individuals born after epidemics, and "serological" studies, based on serological evidence. A study of the latter type obtained an increased schizophrenia risk for individuals exposed during the first trimester. A second study found a relationship between influenza at any time during gestation and risk for bipolar disorder with psychotic features. The aims of this paper are to assess the validity of the serological studies and to evaluate the combined results of ecological and serological investigations using meta-analysis.

The serological studies turned out to be of limited validity, because they utilized a single serum specimen. Since influenza antibodies can remain positive for years after infection, many mothers of cases may have been infected *before* pregnancy. For an adequate timing of exposure one needs an acute and a convalescent specimen, obtained 10–20 days later.

Meta-analysis with respect to schizophrenia: we pooled the results of the single serological investigation and 8 ecological studies related to the 1957 pandemic (with negative results) and found that the first investigation carried hardly any weight. Bipolar disorder: we pooled the results of the serological investigation and three other studies and obtained a mean, weighted odds ratio of 1.34 (95% CI 0.78–2.29) for individuals possibly exposed during prenatal life. The evidence for gestational influenza as psychosis risk factor is insufficient.

1. Introduction

Maternal influenza during pregnancy is a controversial risk factor for psychosis. Investigations in the 1980s and 1990s have tested the hypothesis of a relationship between peaks of influenza activity and the risk of psychosis among children born in the nine subsequent months. Since the presence of exposure to the virus was uncertain at the level of the individual, these studies have been designated "ecological". A meta-analysis of the most relevant studies of this type, which addressed the impact of the 1957 pandemic of A2 influenza, was negative. Not a single study found a significant first- or second-trimester effect (Selten et al., 2010).

Three investigations in the 21st century, however, have used maternal sera to test the hypothesis. Brown et al. (2004) performed a follow-up of a birth cohort, identified those who had developed major mental disorder and compared the archived maternal sera of cases and controls. The results showed an increased risk of schizophrenia for those exposed during the first trimester of prenatal life (odds ratio [OR] = 7.7; 95% CI 0.7–75.3), but not for those exposed during the second or third trimester.

A second investigation of the same cohort addressed the risk for bipolar disorder (BD) (Canetta et al., 2014). Serological evidence of exposure to influenza during any trimester of prenatal life did not increase the risk. An analysis for BD with psychotic features, however, showed that exposure at any time during the whole 9-month period increased the risk significantly (OR = 5.0; 95% CI 1.4–18.4), but not exposure during any particular trimester.

Finally, a study of maternal sera obtained at delivery found no significant association between evidence of recent infection with influenza and risk of psychotic disorder for the child (Ellman et al., 2009).

The question, now, is what to believe? The proponents of the serological studies argue that the negative results of the ecological studies were due to misclassification, because many individuals were incorrectly classified as exposed (Brown and Derkits, 2010). However, it is difficult to imagine how a pandemic with infection rates of 40–50% (Clarke et al., 1958; Ferguson et al., 2005; Glass et al., 2006) does not produce an even slightly increased risk. The purpose of our paper, therefore, is threefold.

First, we examined whether the serological studies are indeed more valid than the ecological ones. Do antibody titres of 1:20 or greater, the

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values used in both serological studies with positive findings (Brown et al., 2004; Canetta et al., 2014), indicate that the subjects under investigation were exposed to influenza virus during pregnancy?

Secondly, we evaluated the combined results of serological and ecological investigations with respect to schizophrenia using meta-analytic methods. For this purpose we pooled the result of the serological study with those of eight ecological studies of the 1957 pandemic and estimated the net first-trimester effect.

Thirdly, we conducted a meta-analysis of studies on the relationship between maternal influenza and risk for BD in offspring. If maternal influenza is indeed associated with a five-fold increased risk of BD with psychotic features, as Canetta et al. (2014) suggest, it is reasonable to expect that this meta-analysis yields an association between maternal influenza and risk for BD in general, because it has been estimated that approximately 61% of manic patients exhibit psychotic symptoms (Goodwin and Jamison, 2007).

2. Materials and methods

2.1. Validity of serological studies

In order to evaluate the validity of the serological methods used, we consulted textbooks on infectious diseases. Since we imagined that high antibody titres obtained during the first trimester of pregnancy could reflect exposure to influenza before pregnancy, we searched the literature for studies on the persistence of antibodies after infection.

2.2. Data sources meta-analysis

Schizophrenia: The meta-analysis of the relationship between the 1957 pandemic and subsequent risk for schizophrenia was based on publications in the period until March 2008. A Medline search for new publications in the period March 2008–August 2016, using the key words influenza, pandemic, psychosis, schizophrenia and paranoid, was negative.

BD: We performed a Medline search (1960–August 2016) using the key words influenza, bipolar disorder, affective disorder, mood disorder. In order to be included a study had to report an odds ratio (OR) or relative risk (RR), or provide sufficient information to allow the calculation of an OR or RR.

2.3. Data extraction meta-analysis

Schizophrenia: See the previous meta-analysis (Selten et al., 2010). For each separate ecological cohort a RR and 95% CI were estimated. For the purpose of the present study the variance of each ln(RR) was calculated according to the formula $(1 / a + 1 / c)$, in which a is the number of pre-schizophrenic births in the index period and c is the number of such births in the control period. By not taking into account the denominators, the variance was a little overestimated and each study became somewhat less influential.

The Brown et al. (2004) study was a case-control study, not a cohort study, and yielded an OR of 7.0 (95% CI 0.7–75.3). For the purpose of this meta-analysis we considered the OR as a good approximation of the RR, as if the data had originated from a cohort study. To estimate the variance of the lnRR, we used the crude numbers of pre-schizophrenic births (5 exposed and 15 non-exposed) for the above formula $(1 / a + 1 / c)$, the net result of which is that the study became somewhat more influential. The 95% CI used for the meta-analysis, 2.5–19.2, indicates a significant first-trimester effect. For an overview, see Table 1.

BD: Since the results of one study (Mino et al., 2000a) could not be transformed into a RR, ORs were used as effect estimates. Both authors independently extracted the data and calculated the ORs. Discrepancies were resolved by discussion.

2.4. Data synthesis

The analyses were carried out using the fixed-effects and random-effects models with MetaWin 2.0 statistical software (Rosenberg et al., 2000). Firstly, a homogeneity statistic, Q, was calculated to test whether the studies could be considered to share one common population effect size. When this was not possible, a random-effect model was used. Such a model, before it estimates the overall effect estimate and its variance, weighs each study both by the variance of its individual effect size and by the between study variance. Thus, the influence of studies with an outlier as effect estimate is mitigated.

3. Results

3.1. Validity of serological studies

According to textbooks on infectious diseases, serologic tests with respect to influenza should be based on paired serum specimens, consisting of an acute serum specimen and a convalescent serum specimen, obtained 10 to 20 days later. A four-fold rise in strain-specific antibody titre, usually based on a hemagglutination inhibition assay, is considered diagnostic (De Gascun et al., 2010; Treanor, 2010).

Since Brown et al. and Canetta et al. disposed of only a single specimen for each mother, they tried to develop a method for determining influenza infection status during pregnancy with the use of a single antibody titre. After testing 51 specimens obtained from non-cases and non-controls, they concluded that a strain-specific antibody titre of 1:20 was an adequate *proxy* for influenza exposure. However, the accepted threshold in such circumstances is a titre of 1:40 (Potter and Oxford, 1979; Dowse et al., 2011; http://ecdc.europa.eu/en/healthtopics/seasonal_influenza/vaccines/Pages/influenza_vaccination.aspx). The use of lower values is likely to result in the inclusion of individuals who have not been infected recently. According to several papers, antibodies to influenza may remain positive for months or years after infection (Foy et al., 1973; Smith and Davies, 1976; Grilli et al., 1986; Petrie et al., 2015). In general, after vaccination the levels of antibodies reach a higher peak and subside more rapidly than after a natural

Table 1
Results of eight ecological studies on schizophrenia risk for subjects in utero in first trimester of prenatal life during 1957 influenza pandemic and of one study on this risk with serologic evidence of maternal first-trimester exposure (Brown et al., 2004).

First author and publication year	Study type	Cases in index group	Cases in control group	Denominator of index group	Denominator of control group	RR	95% CI
Mednick, 1988	Ecological	70	494	3288	20,495	0.88	0.69–1.13
Kendell, 1989	Ecological	46	106	28,967	60,743	0.91	0.64–1.29
O'Callaghan, 1991	Ecological	72	344	20,437	82,020	0.84	0.65–1.08
Torrey, 1991	Ecological	1089	2293	285,793	571,586	0.95	0.88–1.02
McGrath, 1994	Ecological	34	464	8669	88,561	0.75	0.53–1.06
Selten, 1994	Ecological	210	1005	59,083	243,636	0.86	0.74–1.00
Erlenmeyer-Kimling, 1994	Ecological	72	348	17,594	76,832	0.90	0.70–1.16
Morgan, 1997	Ecological	16	37	4080	8492	0.90	0.50–1.62
Brown, 2004[a]	Serology	5	15	n.a.	n.a.	7.00	2.54–19.26

[a] Case-control study. In order to conduct a meta-analysis, the effect (odds ratio = 7.0; 95% CI 0.7–75.3) had to be transformed into a relative risk. For the purpose of the meta-analysis we used a relative risk of 7.0 (95% CI 2.54–19.26). See text.