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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.

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infection. Consequently, a substantial number of mothers with a positive serology in the Brown et al. and Canetta et al. investigations may have been infected *before* pregnancy.

3.2. Meta-analysis schizophrenia, selected studies

We selected eight ecological studies from Europe (Mednick et al., 1988; Kendell and Kemp, 1989; O'Callaghan et al., 1991; Selten and Slaets, 1994; Erlenmeyer-Kimling et al., 1994), America (Torrey et al., 1991) and Australia (McGrath et al., 1994; Morgan et al., 1997), which had been used in a previous meta-analysis (Selten et al., 2010). These investigations compared the risk among subjects born any time in the 9 months after the pandemic (i.e., index period) with that among those born during corresponding periods of time in the previous and/or subsequent year (i.e., control period).

We excluded three ecological studies from Japan, because they examined the possible impact of exposure during the second trimester, not the first (Kunugi et al., 1995; Izumoto et al., 1999; Mino et al., 2000b).

Two follow-up studies of individuals born to mothers who reported having had influenza during the first trimester of pregnancy were also excluded, because none of these children developed schizophrenia. This renders the calculation of a relative risk impossible. The first investigation concerned 231 first-trimester exposed subjects (Crow et al., 1991) and the second 20 such subjects (Cannon et al., 1996).

3.3. Meta-analysis of studies on risk for schizophrenia

The effect sizes of eight studies relating to the 1957 pandemic have been listed in Table 1. Albeit statistically non-significant, the relative risks were all somewhat lower than 1.0, indicating a trend towards a protective effect of being in utero during the first trimester of prenatal life, at the time of the pandemic. When we combined the effects within a fixed-effects model, the mean, weighted RR was estimated at 0.91 (95% CI 0.85–0.98). A fixed-effects model was warranted as no significant differences between the separate studies emerged (test for heterogeneity: $p = 0.840$) (Table 2). The Brown et al. (2004) study, however, had a positive effect and adding this outlier to the eight "1957 studies" yielded a significant test for heterogeneity ($p = 0.015$) (Table 2). When we mitigated the influence of the Brown et al. study using a random-effects model, a pooled RR of 0.90 was found, minimally different from the estimate based on eight "1957 studies". By increasing the weight given to the Brown et al. study (30 times, 100 times, 500 times), the influence of the study increased, but the heterogeneity of the model became also more pronounced. When we took this into account by applying a random-effects model, the mean weighted RR reached a maximum of only 1.10 (non-significant), even when we allocated a weight of 500 to the Brown et al. study. Using a fixed-effects model, ignoring the heterogeneity, a substantial effect could only be established by allotting a weight of 500 to the Brown et al. study (RR = 3.34; 95% CI 3.20–3.48). See Fig. 1.

3.4. Meta-analysis bipolar disorder, selected studies

Seven relevant studies were retrieved. A large multiple-year study from Denmark reported that there was no effect of the rates of influenza during the in utero period on the risk for BD, but it did not show the data (Mortensen et al., 2003). We asked for information, but learnt that this was not readily available.

We retained six studies, from Finland, Ireland, the UK, the USA ($N = 2$), and Japan. Each study used a different method. A study from Finland (Machón et al., 1997) compared the proportion of individuals diagnosed with BD among individuals born during the 9 months after the 1957 pandemic to that for individuals born in control periods; for this meta-analysis we used the results of a re-analysis based on numbers of live births (Selten and Morgan, 2010), the results of which were similar to those presented by the authors. A study from Ireland examined the risk of mania among individuals born to mothers who reported having had influenza during pregnancy (Cannon et al., 1996). A prospective birth cohort study from the UK examined whether offspring born to mothers who had reported influenza during pregnancy were at an increased risk of having developed hypomania by early adulthood (Anderson et al., 2016). The diagnosis was based on self-report, the criteria were somewhat broader than the DSM-5 criteria in that the required duration of hypomania was 3 days, not 4. We combined the results for individuals with and without additional psychotic experiences.

A nested case-control study from the USA examined the prevalence of a clinical diagnosis of influenza among mothers of cases of BD and mothers of controls (Parboosing et al., 2013). A second study, using the same cohort, compared the serology in these mothers (Canetta et al., 2014). (Remarkably, the authors did not report on the prevalence of a clinical diagnosis of influenza among mothers of cases of schizophrenia).

Finally, a study from Japan examined whether *second-trimester* exposure to any of three influenza epidemics, in 1957/58, 1962 and 1965, increased the risk of BD (Mino et al., 2000a). The index patients had been born five months after these epidemics and control patients had been born in the corresponding months one or two years earlier or later. The proportions of patients born during the months possibly associated with exposure were compared with those of patients born in the corresponding months of the comparison years. This is a less desirable statistical method, but it was impossible to conduct a re-analysis. Results for possible second-trimester exposure were also reported by Selten and Morgan (2010), Parboosing et al. (2013) and Canetta et al. (2014).

Thus, we examined the effects of possible exposure during the 9-month prenatal period and of exposure during the second trimester. Since the studies by Parboosing and Canetta concerned the same cohort, in each meta-analysis we used the effect of only one study. In view of

Table 2
Results of meta-analysis of (a) eight ecological studies on schizophrenia risk for subjects in utero in first trimester of prenatal life during 1957 pandemic of influenza and (b) one study on this risk with serologic evidence of maternal first-trimester exposure (Brown et al., 2004). Results shown with and without the Brown study, and with different weights for the Brown study.

	Weight of Brown study	Mean weighted RR		Test for heterogeneity		
		RR	95% CI	Q	df	*p*-Value
Eight ecological studies, fixed effects model		0.91	0.85–0.98	3.5	7	0.840
Eight ecological studies and Brown study, fixed-effects model	1	0.92	0.86–0.98	18.9	8	0.015
Eight ecological studies and Brown study, random-effects model	1	0.90	0.78–1.05	16.0	8	0.043
Eight ecological studies and Brown study, fixed-effects model	30	1.09	1.03–1.17	426.4	8	<0.001
Eight ecological studies and Brown study, random-effects model	30	1.10	0.62–1.95	7.3	8	0.503
Eight ecological studies and Brown study, fixed-effects model	100	1.50	1.41–1.59	1176.2	8	<0.001
Eight ecological studies and Brown study, random-effects model	100	1.10	0.49–2.48	3.5	8	0.896
Eight ecological studies and Brown study, fixed-effects model	500	3.34	3.20–3.48	3008.8	8	<0.001
Eight ecological studies and Brown study, random-effects model	500	1.10	0.39–3.09	2.2	8	0.975

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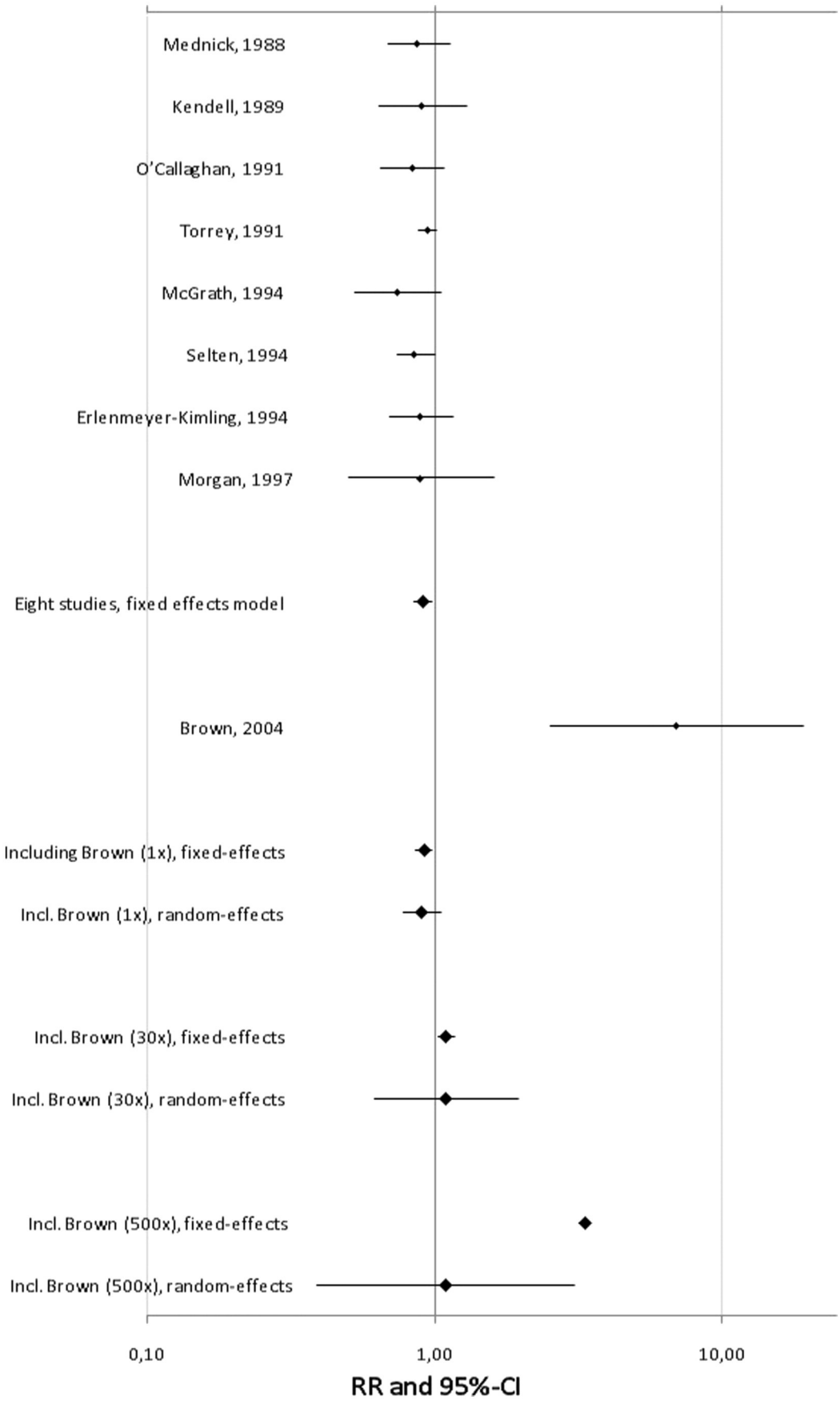

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Table 3
Results of studies on risk of bipolar disorder among individuals possibly exposed to influenza during 9-month period of prenatal life and results of meta-analysis.

First author and publication year	Study type	Cases in index group	Cases in control group	Denominator of index group	Denominator of control group	Odds ratio	95% CI
Cannon, 1996	Clinical[b]	2	2	236	285	1.21	0.17–8.64
Machón, first trimester 1997[a]	Ecological	0	11	3287	20,484	n.a.	
Machón, Second trimester 1997[a]	Ecological	3	7	3533	20,768	2.52	0.65–9.75
Machón, third trimester 1997[a]	Ecological	2	8	3417	18,890	1.38	0.29–6.51
Machón, three trimesters[a]	Ecological	5	26	10,237	60,142	1.13	0.43–2.94
Parboosing, 2013[d]	Clinical[c]	8	84	19	703	4.21	1.60–11.05
Canetta, 2014[d]	Serological	23	62	40	130	1.26	0.65–2.44
Anderson, 2016	Clinical[b]	32	95	285	11,704	1.44	0.94–2.19

Studies used in meta-analysis	Mean weighted OR		Test for heterogeneity		
	OR	95% CI	Q	df	*p*-Value
Cannon, Machón (3 trimesters combined), Canetta, Anderson; fixed effects model	1.34	0.78–2.29	0.26	3	0.96
Cannon, Machón (3 trimesters combined), Parboosing, Anderson; fixed effects model	1.59	0.89–2.83	4.68	3	0.19

[a] Results derived from Selten and Morgan (2010).
[b] Mother reported having had influenza during pregnancy.
[c] Clinician noted in file that mother had influenza during pregnancy.
[d] Parboosing, 2013 and Canetta, 2014 are two reports about same cohort. Consequently, the effects were used alternately in meta-analysis.

the uncertainty of the timing of exposure in Japan regarding the period 1957/58, we analysed the results with and without the 1957/58 data.

3.5. Meta-analysis of studies on risk for bipolar disorder

Five studies, presented in Table 3, yielded five effects of possible exposure at any time during the *9-month prenatal period* (Cannon et al., 1996; Machón et al., 1997 [results derived from Selten and Morgan, 2010]; Parboosing et al., 2013; Canetta et al., 2014; Anderson et al., 2016). Since the Canetta et al. and Parboosing et al. studies concern the same cohort, two separate meta-analyses were run, including either the first or the second investigation. An association between possible exposure to influenza and risk of BD or a significant heterogeneity between studies could not be established in these analyses. However, when we included the Parboosing et al. study, a trend towards an unfavourable effect of possible exposure at any time during the 9-month prenatal period was observed (OR = 1.59; 95% CI 0.89–2.83). See Fig. 2.

As for the influence of possible *second-trimester* exposure, five studies (Mino et al., 2000a; Selten and Morgan, 2010; Parboosing et al., 2013; Canetta et al., 2014; Anderson et al., 2016) yielded 10 effects, presented in Supplementary Table 1. Again, either the Canetta et al. or the Parboosing et al. study was included in a meta-analysis. No important differences were found between the two models. They showed neither a significant association between possible exposure to influenza and risk of BD nor a significant heterogeneity between studies. When we repeated the analysis without the effects of the epidemics in Japan in 1957/1958, the results were similar. When we included the Canetta study (not the Parboosing study), the mean weighted OR of BD for individuals exposed during the second trimester was 1.35 (95% CI 0.84–2.17). With the Parboosing study (not the Canetta study), the mean weighted OR was 1.51 (95% CI 0.90–2.53).

4. Discussion

4.1. Main findings

The first aim of the study was to assess the validity of the methods used in the serological studies. The results showed that they carried a high risk of misclassification of timing of exposure, because antibodies may remain positive for months or years after infection. The aim of the first meta-analysis, relating to schizophrenia, was to compare the weight of the serological study to that of previous ecological studies. The result showed that the serological study carried hardly any weight. The aim of the second meta-analysis was to examine whether the combined results of ecological, clinical and serological studies point to a relationship between maternal influenza and risk of BD in general. The result did not support such a relationship, but was not of sufficient precision to exclude it.

4.2. A possible source of confusion

The first report in this area addressed the impact of the 1957 pandemic of A2 influenza on individuals born in Uusima County, Greater Helsinki, Finland (Mednick et al., 1988). For this purpose the researchers compared the proportions of hospitalized patients diagnosed with schizophrenia, by period of birth. The results showed a higher proportion of such diagnoses among those born in the period mid-February to mid-May 1958 (4–6 months after the pandemic) than among those born in control periods (34.6% vs. 20.8%) and the researchers interpreted this as a second-trimester effect of maternal influenza. However, if one applies a population-based approach and divides the number of individuals hospitalized for schizophrenia by the number of live births in Uusima County, one obtains a non-significant *decreased risk* for second-trimester exposed individuals (relative risk [RR]: 0.85; 95% confidence interval [CI] 0.68–1.07) (Selten et al., 2010). Attempts to replicate the alleged second-trimester effect were negative (Selten et al., 2010).

4.3. Validity of serological and ecological studies

The serological studies used a strain-specific antibody titre of 1:20 or greater as a *proxy* for influenza exposure. The ecological studies with reference to the 1957 pandemic used the month of birth as a *proxy* for influenza exposure. Given infection rates among pregnant women of 40–50% (Clarke et al., 1958; Ferguson et al., 2005; Glass et al., 2006) and in view of the fact that some children were born prematurely, the positive predictive value of this method can be estimated at roughly

Fig. 1. Relative Risks (and 95% confidence intervals) for subjects included in eight ecological studies of risk for schizophrenia associated with exposure to 1957 influenza pandemic during first trimester of prenatal life, as well as relative risk (and 95% confidence interval) for first-trimester exposed subjects derived from Brown et al., 2004. Arch. Gen. Psychiatry 54, 322–328). Studies are identified by first author and year of publication. Figure also shows mean weighted relative risks, by weight attributed to Brown et al. study, and by model (fixed-effects vs. Random-effects).

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40%. The negative predictive value of being born in a control month can be estimated at 90%, because the risk of infection in non-pandemic years has been estimated at 5–11% (Griffiths et al., 1980; Irving et al., 2000). Given the large amount of knowledge on the timing of the 1957 pandemic, there can be little doubt about the simultaneous presence of a pregnancy and a pandemic. Consequently, the ecological approach is not entirely devoid of validity.

In sum, both the serological and ecological investigations used *proxies* for influenza exposure. Advantages of the serological studies were the assessments at the individual level and the psychiatric diagnosis based on a diagnostic interview. Advantages of the ecological investigations are the greater numbers of participants, the minimal risk of selection bias due to the use of national registers and the smaller risk of misclassification of the timing of exposure. In our opinion, therefore,

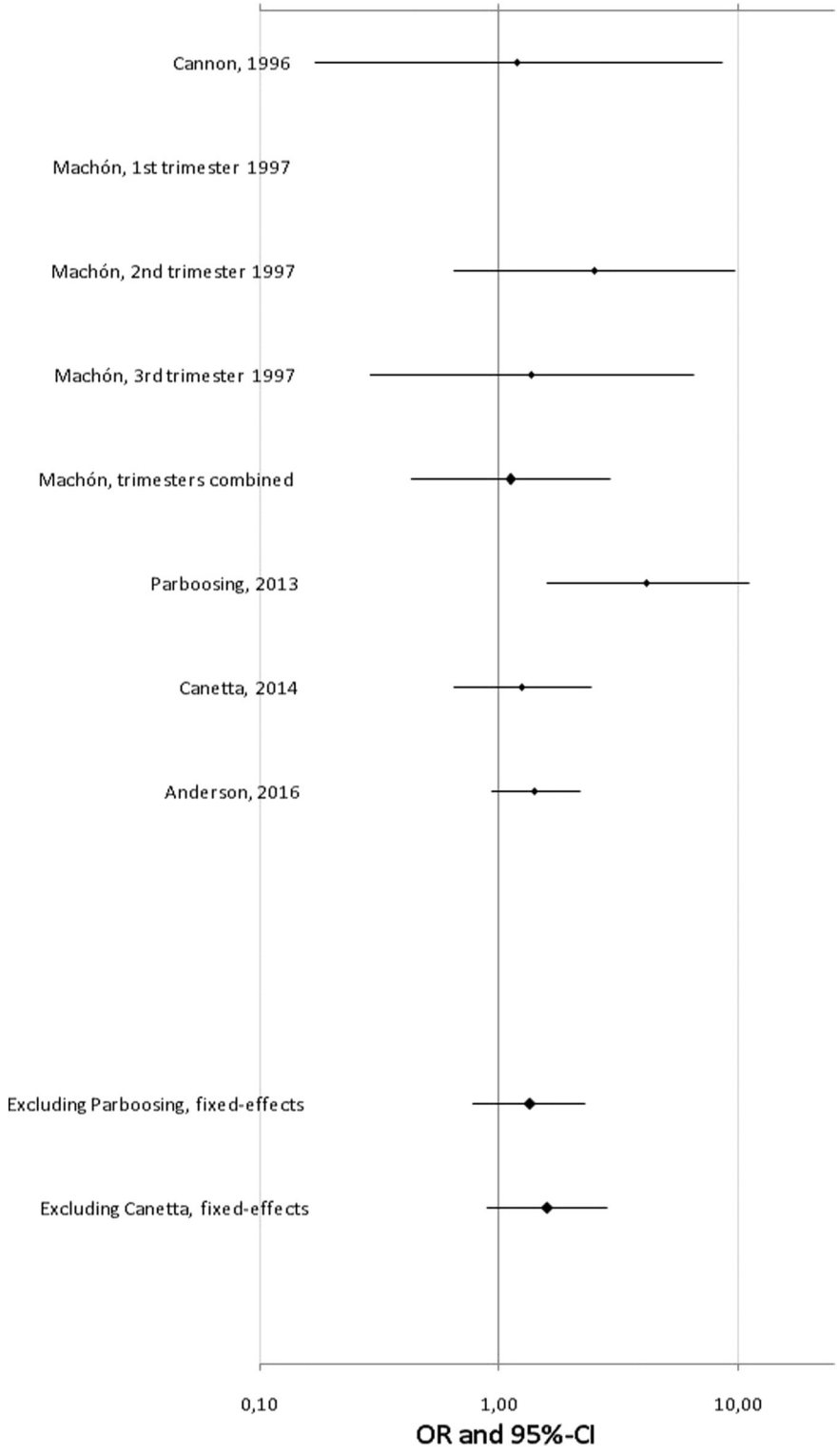

Fig. 2. Odds ratios (and 95% confidence intervals) of risk for bipolar disorder associated with (possible) maternal exposure to influenza during pregnancy. Studies are identified by first author and year of publication. Figure also shows mean weighted odds ratio.

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the ecological investigations are not inferior to their serological counterparts and deserve to be called natural experiments.

4.4. Interaction with family history or maternal mental disorder?

Two studies reported an interaction between maternal infection during pregnancy and family history of psychosis or maternal psychiatric disorder. Clarke et al. (2009) found no effect of maternal pyelonephritis during pregnancy on the risk for psychotic disorder in the child. However, there was a significant effect on children born to mothers with a family history of psychosis. Likewise, Blomström et al. (2016) found that maternal infection during pregnancy per se did not increase the risk for the offspring, while maternal infection during pregnancy and maternal psychiatric disorder acted synergistically in offspring psychosis development. However, as the authors of both studies acknowledge, a number of other factors than maternal infections can explain the reported associations. Evidence for an interaction between familial liability and prenatal exposure to influenza has not yet been shown.

4.5. Strengths and limitations

Major strengths of the ecological studies with respect to schizophrenia are the size of the data-sets and the quality of the registers used. The usefulness of these registers for research has been amply demonstrated (Susser et al., 1996; Millar et al., 2005). A limitation of the meta-analysis of schizophrenia risk is the combination of retrospective cohort studies with a single case-control study (Brown et al., 2004). However, since Brown et al. performed serological tests to ascertain exposure to influenza, we deemed it appropriate to treat the effect of their study as if it were derived from a prospective cohort study. It is true, this procedure is not perfect, but it is in the advantage of the Brown et al. study and makes our conclusion stronger, not weaker.

A limitation of the meta-analysis on risk of BD is the pooling of effects from studies which differed widely in methodology. However, we wanted to evaluate all of the available evidence. It was not possible to include the largest study of all, which examined the relationship between influenza activity and risk for BD in 2.1 million Danes (Mortensen et al., 2003). However, as the result of this study was negative, inclusion would have resulted in a lower mean, weighted OR.

It was not meaningful to conduct a separate meta-analysis of studies on the risk for BD with psychotic features, because there were only two studies (Canetta et al., 2014; Anderson et al., 2016). Of note, the OR of hypomania with psychotic experiences for subjects exposed to gestational influenza in the Anderson et al. study was much smaller than that reported by Canetta et al. and statistically not significant (OR = 1.50; 95% CI: 070–3.22).

Finally, our study concerns influenza during pregnancy, not other infections during pregnancy or infections in childhood or youth.

4.6. Conclusion

Given the results of this meta-analysis and the methodological shortcomings of the serological assessments (risk of misclassification of timing of exposure), we conclude that the evidence for maternal influenza during pregnancy as a risk factor for schizophrenia or BD in the child is insufficient.

Supplementary data to this article can be found online at http://dx.doi.org/10.1016/j.schres.2016.11.006.

Contributors

Selten had the research idea. Termorshuizen helped with its development and conducted the statistical analysis. Selten wrote the first and subsequent drafts of the paper, with important intellectual input from Termorshuizen. Both authors have approved the final version of the manuscript.

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Conflict of interest

The authors report no conflict of interest.

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