Is schizophrenia related to birthdate? This article presents data and possible confounding variables.

Statistical Sleuthing During Epidemics: Maternal Influenza and Schizophrenia

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Beginnings

Schizophrenia is among the most debilitating of mental illnesses (NARSAD 2003). Although relatively rare, affecting less than 1% of the population, this form of psychosis is the focus of a great deal of study due to its etiological complexity and its devastating social, economic, and personal effects. The National Institute of Mental Health estimates that schizophrenia is responsible for 2.3 million lost years of healthy life in America (NIMH 2001) and there is a huge economic cost burden associated with the disease [$7 billion dollars for treatment annually in the U.S., by one estimate (Bromet 1995)].

Schizophrenics typically experience frightening hallucinations or bizarre and persistent delusions, sometimes in conjunction with paranoia. Many have disorganized thought and speech patterns and have absent or diminished outward emotional expression. While recent advances in psychopharmacology offer relief of some symptoms, schizophrenia remains an incurable, lifelong illness and most patients remain impaired to a large degree.
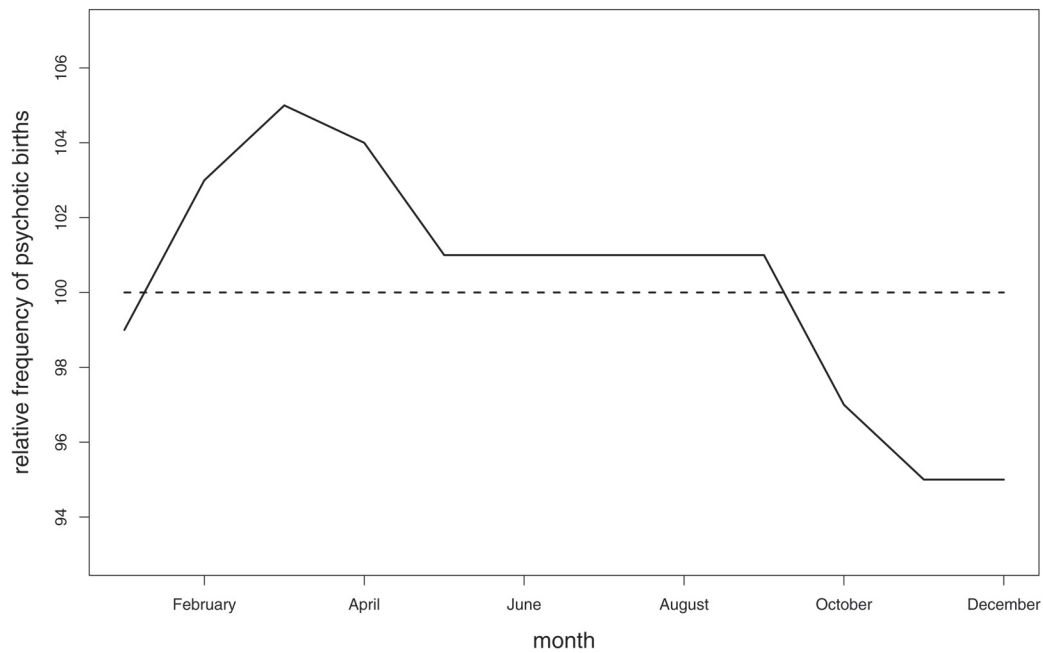
Figure 1. Distribution of relative frequency of births for Swiss psychotic patients (n=3100, values are relative to 100, dashed line), reprinted from data presented in *Schweizer Archiv fuer Neurologie und Psychiatrie*.
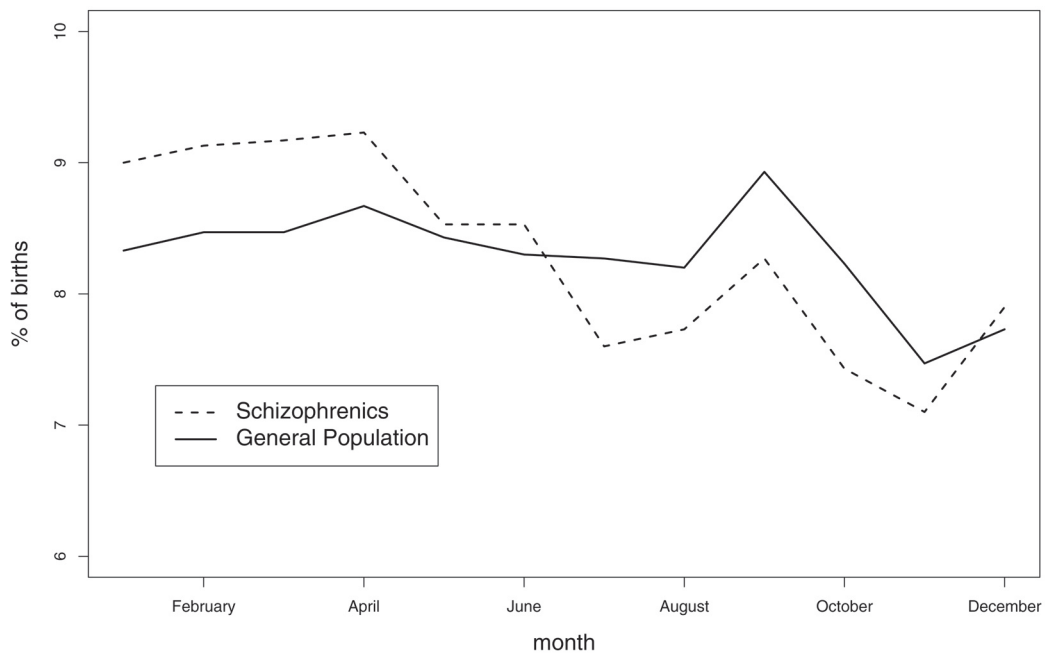
Figure 2. Season-of-birth-rate differences in schizophrenics vs. population from a Norwegian sample, reprinted with permission from the *British Journal of Psychiatry*.

Researchers have long sought to understand the underlying causes of schizophrenia in the hope of finding a means of prevention. One intriguing hint as to the etiology of the disease was first described by Tramer (1929), who noted that psychotic patients were more often born in the late winter or spring. From his sample of 3,100 Swiss psychotic patients, approximately 10% were born in March, while fewer than 7% were born in May. Since birth rates vary by month, he standardized these rates to that of a comparison population, and calculated the relative frequency of psychotic births by month. Figure 1 displays the relative birth month distribution (where 100 corresponds to the expected count in the population).

Tramer found an excess number of births in February through April, and an under abundance in October through January. While the origins of the hypothesis are unclear, perhaps staff at a mental institution noticed some increase in the number of birthday celebrations for patients in the late winter.

While these seasonal effects are modest (most studies which report seasonal effects cite an excess of winter births of 5-15%), they are consistent across samples, continents, and even hemispheres (Bradbury and Miller 1985). For example, Ødegård (1974) found similar results in a sample of approximately 20,000 Norwegian schizophrenics, who were compared to control data from birth records for the population as a whole (see Figure 2).

This "season of birth" effect led to a number of hypotheses regarding exposures during pregnancy or childbirth. One hypothesis linked maternal influenza (which is more common in winter) during pregnancy and later development of schizophrenia in offspring (Mednick and Machon 1988; Brown and Susser 2002). Determining whether this association exists and its potential magnitude is complicated by a number of factors. These include the relatively low incidence of schizophrenia, the age of onset, problems with the measurement of exposure as well as reliable diagnosis of the disease. We consider a number of methodological and statistical issues in the design and conduct of studies that attempt to better understand the associations between maternal influenza and schizophrenia.

We begin with a natural experiment which provided data relating to this question. In 1957 an epidemic of A2 influenza (Asian flu) started in Northern China and, with the help of international air travel, spread around the world. A huge number of people were infected, in some places up to 30% of the urban population (Kendell and Kemp 1989). During one month at the peak of the epidemic, it was estimated that workers used an additional 400,000 sick days in England (O'Callaghan et al. 1991). Large numbers of cases were noted in a number of countries (e.g., Scandinavia and the United Kingdom) that have a history of meticulous tracking of health data, including elaborate surveillance of epidemics and the existence of comprehensive registries for cases of schizophrenia and other forms
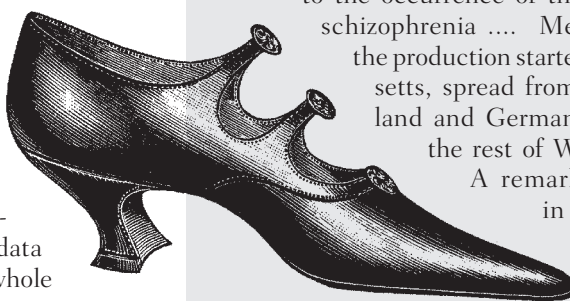
of psychosis. Information from these countries was used by researchers in the late 1980s and 1990s to investigate links between the timing of the epidemic and births of people who would later develop schizophrenia.

One such study was conducted in 1988 using data from Helsinki, Finland (Mednick and Machon 1988). Researchers compared the proportion of schizophrenic patients in a psychiatric population who were in gestation at the peak of the 1957 epidemic (November 1957–August 1958) to the proportion of schizophrenic patients in the same psychiatric population who were in gestation in the six years prior to the epidemic.

There were significantly more schizophrenics than expected who were exposed to the epidemic during their
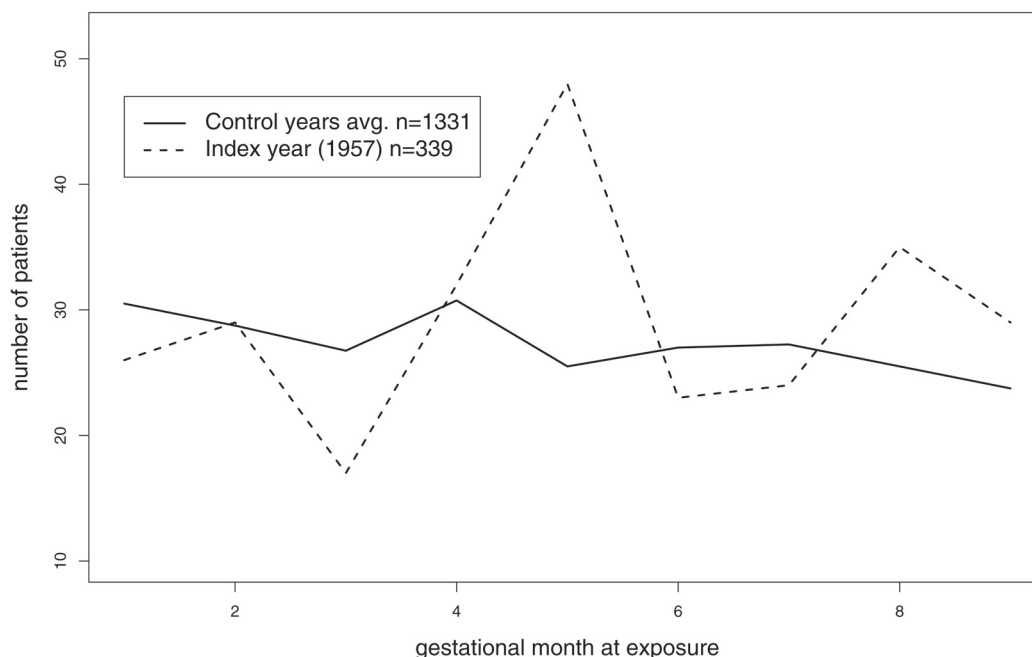
Figure 3. Number of schizophrenics born during influenza epidemic or control years (by month of gestational exposure), reprinted with permission from *The Lancet*, May 25, 1991.

second trimester. They reported a relative risk (RR) of 1.66 [95% confidence interval (CI)=1.18,2.34]; i.e., subjects who were exposed to the epidemic in the second trimester had two-thirds higher chance of developing schizophrenia than those born from 1951 to August 1957 (when there was not an influenza epidemic).

Initial studies attempting to replicate these results looked promising, in particular a study by O' Callaghan et al. (1991) using data from Scotland. In this investigation, the birth months of schizophrenics (*n*=339) who were in gestation during the 1957 epidemic were compared to those born in the previous two and subsequent two years (*n*=1331). This study reported a significantly different distribution of births by month of schizophrenics exposed to the 1957 influenza epidemic compared with the reference years (χ^2_{11}=23.22, *p*=0.016). Figure 3 displays their results, in particular, the spike during the fifth month of gestation.

Other investigations of this association have been inconsistent at best. In the 16 years since Mednick and colleagues published their results, intense debate has raged. Evidence for everything from the most vulnerable time in pregnancy (second trimester? fifth month?) to which gender shows a larger effect is conflicting. Contradictory results have been reported when the association was studied independently for the same epidemic in Japan (Kunugi et al. 1995, Mino and Oshima 2000), in the Southern

hemisphere (McGrath and Pemb1994) and with secondary analyses, such as in Scotland where researchers reanalyzing data with slightly different assumptions and methods yielded different conclusions (Adams and Kendell 1993; Kendell and Kemp 1989).

Statistical Challenges

These disparate results are not entirely surprising given the statistical challenges inherent in this line of research. In the next sections we consider some of these issues.

Prospective Studies

Because schizophrenia is a rare disease (generally affecting only 1% of a population), prospective studies that enroll subjects and follow them over time need to be quite large to ensure sufficient cases occur to study associations with exposures. In addition, because the typical age of onset for schizophrenia is in the late teen years (for males) or early adulthood (for females), and because a prospective study enrolls subjects during (or, ideally, before) pregnancy, such a design requires extremely patient investigators and participants. A study would need to be on a very large scale (with at least tens of thousands of subjects) and be run for several decades to have a good chance of finding a significant relationship with an exposure measured during pregnancy.

Sometimes researchers get lucky, and an existing study may provide data that can help answer questions of interest. By coincidence, a longitudinal study (the Perinatal Mortality Survey and the National Child Development Study) was undertaken which enrolled all children born in England and Wales during the week of March 3–9, 1958. These children happened to be in their second trimester of gestation during the peak of the 1957/1958 influenza epidemic. In the study, maternal reports of influenza and other medical problems relating to the pregnancy were recorded at the time of delivery.

Crow and Done (1992) reported that of the 16,268 subjects in the study, 11% reported influenza during pregnancy, (231 in the first trimester, 945 during the second trimester, and 675 in the third trimester). There were only zero, three, and four cases of schizophrenia respectively in the three groups (and only one, eight, and nine cases using a broader definition including all psychoses), and no significant association was found (observed RR comparing second trimester to no exposure for schizophrenia was 0.9, 95% CI 0.3–2.9, while for psychoses the RR was 1.6, 95% CI 0.8–3.33). However, this may be due to a lack of power, even though they had a relatively large number of subjects. Takei and Murray (1994) estimated that the study had only 30% power to detect a relative risk of 1.88.

Non-differential Measurement Error

In many of these studies maternal influenza was defined as "exposure to an influenza epidemic." In other words, rather than considering individual cases of influenza during pregnancy (a difficult logistic task), influenza exposure is defined as pregnancy during a local influenza epidemic. This indirect method likely mismeasures exposure for some subjects.

Measurement error can make a profound difference in the significance and magnitude of findings (Thomas et al.1993). We illustrate this by considering a study of 10,000 subjects, 1% of which have schizophrenia, and 10% are truly exposed to influenza. Using the relative risk similar to that seen by Mednick and colleagues, we can construct the hypothetical 2 x 2 cross-classification seen in Table 1.

Cell (a) represents the number of subjects with both the exposure and the disease (n=15). The relative risk is calculated as

$$\frac{\text{Risk}_{\text{exposed}}}{\text{Risk}_{\text{unexposed}}} = \frac{a/(a+b)}{c/(c+d)} = \frac{\frac{15}{15+985}}{\frac{85}{85+8915}} = 1.588$$

$$\frac{\text{Risk}_{\text{exposed}}}{\text{Risk}_{\text{unexposed}}} = \frac{(.9a+.1c)/(.9a+.9b+.1c+.1d)}{(.9c+.1a)/(.9c+.1a+.9d+.1b)} = \frac{\frac{22}{22+1778}}{\frac{78}{78+8122}} = 1.28$$

even though only 10% of subjects were misclassified.

Several researchers noted that subjects in the study by Crow and Done (1992) reported lower than expected rates of exposure to influenza during the epidemic, and speculated that this was due to their reliance on reports of expo-

Table 1—Hypothetical cross-classification by exposure (true) and disease status (TRUE RR=1.588)

true exposure	schizophrenia yes	no	
yes	15 (a)	985 (b)	1000 (a+b)
no	85 (c)	8915 (d)	9000 (c+d)
	100	9900	10000

Table 2—Hypothetical cross-classification by exposure (observed) and disease status (OBSERVED RR=1.28)

observed exposure	schizophrenia yes	no	
yes	.9a+.1c	.9b+.1d	
no	.9c+.1a	.9d+.1b	
	a+c	b+d	

sure collected by midwives at delivery (using the report from the mother and chart review), which could lead to misclassification of exposure. In a sample taken from a population of women presenting for prenatal care at a hospital in Copenhagen, Voldsgaard et al. (2002) found that such reports are not always accurate. The researchers assessed influenza at the 25th week of gestation, and again one or two days after birth, and found that mothers tended to underreport infections. Perhaps nondifferential measurement error attenuated the results of Crow and Done (1992).

Case Control Studies and Differential Measurement Error

As a result of the limitations of prospective studies (need for huge samples, accurate recording of exposures, and patience) investigators have studied the association between maternal influenza and schizophrenia using retrospective

Table 3—Hypothetical cross-classification by exposure (true) and disease status (TRUE RR=1.0)

really exposed	schizophrenia yes	no	
yes	10 (e)	990 (f)	1000
no	90 (g)	8910 (h)	9000
	100	9900	10000

Table 4—Hypothetical cross-classification by exposure (observed) and disease status (OBSERVED RR=2.3)

observed exposed	schizophrenia yes	no	
yes	.7e+.3g (34)	.9f+.1h (1782)	
no	.7g+.3e (66)	.9h+.1f (8118)	
	e+g (100)	f+h (9900)	

data. These case-control studies might select schizophrenics from national registries and psychiatric hospitals, and then seek to ascertain their exposure status. This type of research comes with its own set of challenges.

One of the drawbacks of retrospective reporting of exposure is the potential for recall bias. Mothers of schizophrenics asked to recall complications during pregnancy could potentially over or underreport symptoms of influenza or other complications, though other types of differential misclassification may be operating. As an example, one investigation of another prospective cohort study (National Collaborative Perinatal Project) found that mothers of schizophrenics actually underreport complications during pregnancy compared to the accuracy of reports by normal controls (Buka and Goldstein 2000).

Differential measurement error can also bias results, and not always toward the null. Consider a setting with the same marginal distributions for exposure and disease as before, but

where there is no association between these factors. Table 3 displays the cross-classification, where the relative risk is

$$\frac{10/1000}{90/9000} = 1$$.

Suppose that instead of observing the true classification, we observe exposure correctly for mothers of schizophrenics 70% of the time, while mothers of nonschizophrenics report exposure correctly 90% of the time. This yields the situation found in Table 4 and an observed relative risk of 2.3 (though this is purely an artifact of the misclassification).

Case Identification

In addition to measuring exposure, researchers also need to accurately identify cases of schizophrenia. Criteria for determining a diagnosis of schizophrenia has changed over the years and frequently differ between countries. At times, psychiatrists in the United States included length of illness when making a diagnosis, in contrast to practice in many European countries. In the 1970s, the U.S.-U.K. Diagnostic project (Cooper 1972) found systematic differences in diagnoses; of 118 subjects diagnosed as schizophrenic by psychiatrists in New York, only 50 (42%) were diagnosed as schizophrenic by the research team. While these diagnostic differences appear to have narrowed in recent decades, many of the studies we have discussed use diagnoses recorded during this period. In any case, the issue of diagnosing schizophrenia consistently and reliably remains a challenge.

An additional problem involves loss to follow up. Crow and Done (1992) retrieved diagnoses using a search through the Mental Health Enquiry system for individuals born during the study week, excluding patients born abroad. However, this database would not include subjects who moved out of the United Kingdom, or were not included for some other reason in this registry. Misclassification and missing data could both lead to misclassification of disease and introduce biases in measures of association between exposure and disease.

Multiple Comparisons

If multiple tests of hypotheses are calculated, each with a Type I error of α (typically 0.05) then to ensure that the overall Type I error rate for the study remains at α, it is necessary to perform some correction (such as a Bonferroni adjustment). Without this (or a similar) adjustment, researchers who conduct a number of tests will reject the null hypothesis when it is true at more than the specified rate. As one example of this, consider Table 4 of Adams and Kendell (1993), which displays a matrix of $13*14=182$ t-statistics (providing comparisons of data from three samples, two of which are stratified by broad and narrow criteria, as well as male, female or both, for each of 14 months). Fifteen of these t-statistics are flagged as being statistically significant at $p < 0.05$, though the true error rate is likely much higher. When multiple tests are used to explore relationships (such as to pick month of exposure with the largest association for a particular gender and

particular criteria for diagnosis), p values should be interpreted with restraint.

Attributable Risk

We close by considering how important this research is in understanding the etiology of schizophrenia and preventing future cases. It is generally agreed upon that if maternal influenza is associated with an increase in adult schizophrenia, this effect is not large. Sham et al (1992) estimated that only 1–2% of schizophrenic births are explained by the number of influenza deaths, while Barr and Mednick (1990) found that the proportion of variation (R^2) accounted for by influenza was only 4.0%. We can also consider the population attributable risk percent (Hennekens and Buring 1987), defined as:

$$PAR\% = \frac{P_e(RR-1)}{P_e(RR-1)+1} * 100.$$

If we assume that 10% of the population (pregnant women) are exposed to influenza, and the true RR is 2 (both larger than seen in many of the existing studies), then an estimate of PAR% is $1/11*100=9.1\%$.

In a recent paper analyzing data from the Child Health and Development Study (a large cohort study conducted from 1959 through 1966), researchers used a single assay of maternal serum to estimate the timing of influenza infection during pregnancy and the association of influenza with schizophrenia. They estimated the PAR as 14% (Brown et al. 2004). If the true exposure rate and RR are in this range, then completely eliminating exposure to influenza during pregnancy would only prevent one-seventh to one-tenth of schizophrenia cases.

Discussion

The use of randomized trials to assess whether there is an association between maternal influenza and schizophrenia would be clearly unethical. As a result, observational studies need to be utilized. The issues of exposure misclassification, difficulties in case identification, lack of power, as well as other concerns (such as multiple comparisons inflating the Type I error rate) complicate the interpretation of the research results, and do not fully resolve whether or not influenza causes schizophrenia. Animal studies have provided some additional justification for a biological pathway from influenza to brain disruption (Gilmore et al. 2004). Some research suggests that obstetrical complications at birth may be a more potent risk factor for the disorder (Zornberg et al. 2000). If there is an association between maternal influenza and schizophrenia, it is likely of relatively small magnitude [in comparison to genetic risk factors, for which relative risks of 10 or more have been reported (Stefan et al. 2002)].

While public health interventions to decrease maternal influenza may be helpful in decreasing the incidence of schizophrenia, this is a challenging task in its own right.

Perhaps the most useful aspect of this line of research is to spur hypotheses for neuroscientists interested in normal and abnormal fetal brain development.

The prior research points out the value of secondary analyses of large community-based prospective cohort studies to augment and complement results seen from retrospective (case-control) studies. These prospective studies are quite expensive and difficult to implement, but they can provide priceless information. The National Children's Study (NCS 2003) was recently undertaken to examine the effects of environment (broadly defined) on the health and development of 100,000 United States children. This study has the potential to help future researchers untangle complicated relationships.

We have considered methodological and statistical issues that complicate study of the association between a common exposure and a debilitating disease. As Crow and Done (1992) noted, this is a *literature rich in complex statistical methods, inconsistencies, and contradictions* (page 392). Given the limitations of study designs in this setting, careful work by statisticians, epidemiologists, and clinical researchers is needed to draw correct inferences.

Acknowledgments

References

Adams, W., Kendell, R. E., Hare, E. H. & Munk-Jorgenson, P. (1993). Epidemiological evidence that maternal influenza contributes to the aetiology of schizophrenia: An analysis of Scottish, English and Danish data, *British Journal of Psychiatry* **163**: 522-34.

Barr, C. E., Mednick, S. A. & Munk-Jorgenson, P. (1990). Exposure to influenza epidemics during gestation and adult schizophrenia: a 40 year study, *Archives of General Psychiatry* **47**: 869-74.

Bradbury, T. N. & Miller, G. A. (1985). Season of birth in schizophrenia: A review of evidence, methodology, and etiology, *Psychological Bulletin* **98**: 569-94.

Bromet, E., Dew, M. A. & Eaton, W. (1995). Epidemiology of psychosis with special reference to schizophrenia, *Textbook in Psychiatric Epidemiology*, John Wiley & Sons, pp. 283-300.

Brown, A. S., Begg, M. D., Gravenstein, S., Schaefer, C. A., Wyatt, R. J., Bresnahan, M., Babulas, V. P. & Susser, E. S. (2004). Serologic evidence of prenatal influenza in the etiology of schizophrenia, *Archives of General Psychiatry* **61**: 774-780.

Brown, A. S. & Susser, E. S. (2002). In utero infection and adult schizophrenia, *Mental retardation and developmental disabilities research reviews* **8**: 51-57.

Buka, S. L., Goldstein, J. M., Seidman, L. J. & Tsuang, M. T. (2000). Maternal recall of pregnancy history: Accuracy and bias in schizophrenia research, *Schizophrenia Bulletin* **26**: 335-45.

Cooper, J. E. (1972). *Psychiatric diagnosis in New York and London: A comparative study of mental hospital admissions*, Oxford University Press.

Crow, T. J. & Done, D. J. (1992). Prenatal exposure to influenza does not cause schizophrenia, *British Journal of Psychiatry* **161**: 390-3.

Gilmore, J. H., Jarskog, L. F., Vadlamudi, S. & Lauder, J. M. (2004). Prenatal infection and risk for schizophrenia: IL-Iβ, IL-6, and TNFα inhibit cortical neuron dendrite development, *Neuropsychopharmacology* **29**: 1221-1229.

Hennekens, C. H. & Buring, J. E. (1987). *Epidemiology in Medicine*, Little, Brown.

Kendell, R. E. & Kemp, I. W. (1989). Maternal influenza in the etiology of schizophrenia, *Archives of General Psychiatry* **46**: 878-82.

Kunugi, H., Nanko, S., Takei, N., Saito, K., Hayashi, N. & Kazamatsuri, H. (1995). Schizophrenia following in utero exposure to the 1957 influenza epidemic in Japan, *American Journal of Psychiatry* **152**: 450-2.

McGrath, J. J., Pemberton, M. R., Welham, J. L. & Murray, R. M. (1994). Schizophrenia and the influenza epidemics of 1954, 1957, and 1959: A southern hemisphere study, *Schizophrenia Research* **14**: 1-8.

Mednick, S. A., Machon, R. A., Huttunen, M. O. & Bonett, D. (1988). Adult schizophrenia following prenatal exposure to an influenza epidemic, *Archives of General Psychiatry* **45**: 189-92.

Mino, Y. & Oshima, I. (2000). No relationship between schizophrenic birth and influenza epidemic in Japan, *Journal of Psychiatric Research* 34: 133-138.

NARSAD (2003). *Understanding Schizophrenia*, National Alliance for Research on Schizophrenia and Depression.

O'Callaghan, E., Sham, P., Takei, N., Glover, G. & Murray, R. M. (1991). Schizophrenia after prenatal exposure to 1957 A2 influenza epidemic, *Lancet* **337**: 1248-50.

Ødegård, Ø. (1974). Season of birth in the general population and in patients with mental disorder in Norway, *British Journal of Psychiatry* **125**: 397-405.

Sham, P. C., O'Callaghan, E., Takei, N., Murray, G. K., Hare, E. H. & Murray, R. M. (1992). Schizophrenia following pre-natal exposure to influenza epidemics between 1939 and 1960, *British Journal of Psychiatry* **160**: 461-6.

Stefan, M., Travis, M. & Murray, R. M. (2002). *An Atlas of Schizophrenia*, Parthenon Publishing.

Takei, N. & Murray, R. M. (1994). Prenatal influenza and schizophrenia, *British Journal of Psychiatry* **165**: 833-4.

Thomas, D., Stram, D. & Dwyer, J. (1993). Exposure measurement error: influence on exposure-disease relationships and methods of correction, *Annual Reviews of Public Health* **14**: 69-93.

Tramer, M. (1929). Ueber die biologische bedeutung des geburtsmonates insbesondere fuer die psychoseerkrankung, *Schweiser Archiv fuer Neurologie und Psychiatrie* **24**: 17-24.

US Department of Health and Human Services (2001). *The Impact of Mental Illness on Society (NIH Publication 01-4586)*, National Institutes of Health.

US Department of Health and Human Services (2003). *The National Children's Study (NIH Publication 03-5187)*, National Institutes of Health.

Voldsgaard, P., Schiffman, J., Mednick, S., Rodgers, B., Christensen, H., Bredkjaer, S. & Schulsinger, F. (1996). Accuracy of retrospective reports of infections during pregnancy, *International Journal of Methods in Psychiatric Research* **11**: 184-6.

Zornberg, G. L., Buka, S. L. & Tsuang, M. T. (2000). At issue: the problem of obstetrical complications and schizophrenia, *Schizophrenia Bulletin* **26**: 249-256.