OBSTETRIC COMPLICATIONS AND FUNCTIONAL PSYCHOSIS

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Declaration

I, Pauline Mary McConville, declare that I have composed this thesis, that it contains my own work and that it has not been submitted for any other degree or professional qualification. The work commenced when I was employed as a clinical lecturer at the University of Aberdeen and continued into my current employment as a consultant psychiatrist with NHS Lothian.

Signed:

Date: 7th August 2007

Abstract

Studies of obstetric complications (OCs) in schizophrenia and other psychoses continue to provide evidence that environmental factors in the earliest phases of life and during crucial periods of brain development are implicated in the aetiology of these conditions. However, evidence from such studies has led to a multitude of findings which conflict and which, thus far, have eluded any conclusive pattern. Questions remain about the methods used to study potential associations between OCs and psychosis, the specificity of any effect for schizophrenia and the potential aetiological role of OCs in the later development of illness.

Chapter 1 reviews the history of the interest in OCs, the findings of studies in schizophrenia, affective psychosis and other psychotic conditions, the methodologies used to assess potential relationships between OCs and later illness, and the limitations of these methods. Studies examining OCs in different subgroups of illness and the correlations between OCs and other features of illness are reviewed in Chapter 2, as are the implications of this evidence for current theories of the aetiology of schizophrenia and bipolar disorder. The main body of the work is a study of the rates of obstetric complications in 492 patients meeting ICD-9 criteria for schizophrenia, affective disorder and other functional psychosis, compared to their 797 non-psychotic siblings and to 2,460 normal controls. The aims and methods of the study are described in Chapter 3, which details the registers and databases used, the sampling and matching methods, the pregnancy, delivery and neonatal variables analysed and the statistical methods used to examine the data. The main results, for each of the three diagnostic groups, are presented in Chapter 4 and indicate significant confounding between obstetric complications, maternal marital status and social class. No single obstetric complication remained associated with schizophrenia once these factors had been controlled for. Bleeding in pregnancy was associated with an

increased risk of affective disorder compared to controls. A low Apgar score at 5 minutes was associated with an increased risk of affective disorder and of other functional psychosis compared to controls. Low social class and maternal marital status were also associated with the risk of affective disorder. Induction of labour or elective caesarean section was associated with an increased risk of other functional psychosis compared to their non-psychotic siblings.

Secondary analyses of the effect of season of birth, age of onset of illness and family history are presented in Chapter 5. Schizophrenic patients were more likely to have been born in winter than their siblings, but winter-born schizophrenics had similar rates of OCs to those born at other times. An induced labour or elective caesarean section was associated with an increased risk of schizophrenia of earlier onset and of familial schizophrenia. Being born to a primiparous mother was associated with an increased risk of affective disorder of early onset and of non-familial affective disorder. Bleeding in pregnancy was also associated with an increased risk of non-familial affective disorder. Chapter 6 summarises the main findings, explores possible reasons for the findings and critiques the study's strengths and limitations. In Chapter 7, the findings are compared to those of other studies and conclusions are drawn about the importance of obstetric complications in the aetiology of psychotic disorders, with particular emphasis on schizophrenia, and suggestions are made for further research.

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4. Main results

List of tables and figures

Glossary of terms

95% C.I.	95% Confidence interval
AMNDB	Aberdeen maternity and neonatal data bank
BMI	Body Mass Index = (weight (kg) / height $(m)^2$)
BPMS	British Perinatal Mortality Survey
c/s	Caesarean section
CT	Computerised tomography
DLPFC	Dorso-lateral prefrontal cortex
DZ	Dizygotic
fMRI	Functional magnetic resonance imaging
GAS	Global assessment scale
GPCR	Grampian psychiatric case register
HSBS	Height standardised birth weight score. Birthweight controlled for sex, gestation, parity and maternal height.
ICD	International classification of disease
IDDM	Insulin-dependent diabetes mellitus
IGF	Insulin-like growth factor
IQ	Intelligence quotient
IUGR	Intra-uterine growth retardation, usually SGA
IVH	Intraventricular haemorrhage
LBW	Low birth weight. Defined by WHO as <2500g
LDC	Labour or delivery complication

LMP	Last menstrual period
MPA	Minor physical anomaly
MRI	Magnetic resonance imaging
MZ	Monozygotic
NC	Neonatal complication
NOS	Not otherwise specified
NRG1	Neuregulin 1
OC	Obstetric complication
OPCRIT	Operational Criteria Checklist for Psychotic Illness
PI	Ponderal index. Defined as weight (in g) x 100/ length (in cm)
PBC	Pregnancy or birth complication
PC	Pregnancy complication
SBS	Standardised birth weight score. Birth weight standardised for sex, gestation and parity
SES	Socio-economic status
SGA	Small for gestational age. Usually defined as birth weight below the 10^{th} percentile for gestational age.
VBR	Ventricular-brain ratio

Chapter 1:

Are obstetric complications associated with psychosis?

1.1 Introduction

The idea that mental disorder could be caused by damage to the developing brain around the time of birth is far from new. Kraepelin (1919) proposed that some cases of dementia praecox might be due to cerebral infection in early life, but scientific examination of this hypothesis began only in 1934 and started to become more systematic only in the 1970s (Rosanoff, 1934b). Since that time, and particularly over the past twenty years, there have been numerous studies of the influences of what have been termed obstetric complications (OCs) and the development of psychiatric illness, mainly schizophrenia. The ongoing interest in this area reflects the desire to expose a clear example of an environmental risk factor for serious mental illness, theoretically necessary to explain the well replicated less than 100% concordance of monozygotic (MZ) twins for such illnesses (Rosanoff, 1934b; Pollin & Stabenau, 1968; Shields, 1978). It is also possible that if obstetric complications were confirmed as risk factors for schizophrenia, preventative strategies could be developed, especially if individuals at higher risk, in whom avoidance of additional environmental hazard would be most important, can be confidently identified.

The literature on obstetric complications is extensive, wide-ranging and diverse in both its methods and its results. This chapter reviews how the methods of investigation in this area have developed, the main findings in comparisons of patients with schizophrenia, affective psychosis or other functional psychosis to various control groups and the strengths and weaknesses of methods used. The following chapter considers how OCs may be related to these conditions by examining findings in specific subgroups of patients and concludes with a summary of our understanding thus far.

1.2 What are obstetric complications?

Before any further consideration of the research into obstetric complications, it is necessary first to clarify what is meant by this, and similar, terms. The term obstetric complication (OC) was widely in use among obstetricians before it entered the psychiatric literature and lacks a standardised definition, but refers to a wide range of deviations from normal pregnancy, delivery and early neonatal life. Some conditions, such as diseases of pregnancy known to adversely affect fetal outcome are accepted as obstetric complications (OCs), but others, such as interventions during delivery, reflect current obstetric practice and may be undertaken in order to improve fetal outcome where another underlying complication exists. In an attempt to clarify which obstetric variables may be important in this area, OCs have been divided into pregnancy complications (PCs), which occur between conception and the onset of labour, labour and delivery complications (LDCs) which occur during the three stages of labour, and neonatal complications (NCs) occurring from birth for an unspecified period, usually until the infant is discharged from hospital (McNeil & Kaij, 1978). In some analyses PCs and LDCs have been combined into a category of pregnancy and birth complications (PBCs) (Sacker *et al,* 1996). Multiple complications in each category have been examined, largely because many studies have used maternal health records or databases, and have been shaped by the variables routinely recorded, rather than guided by specific hypotheses. PCs have included hypertension, pre-eclampsia, vaginal bleeding, gestational diabetes and minor illnesses of pregnancy. LDCs have included induction of labour, prolonged labour, non-cephalic presentation, forceps and other instrumental deliveries and caesarean section (c/s) which may increase the risk of hypoxic-ischaemia or mechanical injury (Cantor-Graae *et al,* 2000). NCs have included premature birth, low birth weight, length and related measures such as ponderal index (PI), as well as assessments of fetal

growth such as being small for gestational age (SGA), defined as a birth weight below the 10th percentile for gestational age (World Health Organisation, 1992) and measures of neonatal hypoxia such as Apgar scores at one and five minutes (Apgar, 1952). Assessments of the contribution of OCs to psychotic disorder have assessed complications individually and have used a number of aggregate scales.

However the range of variables analysed in studies of OCs also includes a wide range of demographic variables including maternal age at delivery, marital status, compliance with antenatal care and various measures of socio-economic status (SES), which may be important confounders of any apparent relationship between OCs and psychotic illness, Studies have also included information about previous reproductive health and pregnancies and minor maternal pregnancy symptoms such as fatigue and nausea, which may be confounders of other risks or may be of no relevance. McNeil (1991) suggests that what is considered an OC should be limited to 'somatic complications actually occurring in the current reproduction and having some potential direct relevance for the physical well-being of the offspring'. While some OCs such as pre-eclampsia and non-cephalic presentation fulfil this requirement, some of what has been measured, such as induction of labour or intervention delivery is a medical response to potentially multiple somatic processes. Preterm birth and low birth weight are predictors of infant mortality, morbidity and neurodevelopmental impairment (McCormick, 1985). These, and more modern measures of neonatal well-being, such as low Apgar scores at one and five minutes after birth, may reflect either sub-optimal fetal development or responses to an abnormal uterine environment or delivery process, or both.

Bennedsen (1998) reviewed risk factors for intra-uterine growth retardation (IUGR), premature birth and perinatal death, both in the general population and in women with

schizophrenia. His review indicated that low SES, nulliparity and maternal behavioural characteristics such as smoking and misuse of alcohol, cannabis or cocaine were related to adverse pregnancy outcomes in the general population, and also associated with schizophrenia. Such factors could confound apparent associations between schizophrenia and OCs.

1.3 The early history of obstetric complications research

In the last century, the impact of birth injuries on the later development of mental disorders was first explored in 1934 when Rosanoff (1934b) found poorer obstetric histories in twins affected by a range of developmental, behavioural and psychiatric conditions compared to their unaffected co-twins in a study of 1,014 twin pairs. In the 142 twin pairs discordant for schizophrenia, the affected twin was more often first-born or subject to trauma or infection than the well twin, which led the authors to suggest 'that a large proportion of such psychoses originate in a cerebral trauma at birth or in childhood; that such cases are more prevalent in the male than in the female sex, and in young subjects than in those over 30 years'. Rosanoff suggested that premature and low birth weight infants had an increased risk of small cerebral haemorrhages, leading to a 'decerebration syndrome' with a number of consequences including epilepsy, cerebral palsy and psychosis. Rosanoff's ideas are echoed in modern hypotheses of how obstetric adversity may manifest in illness, but his findings attracted little interest for twenty years until Pasamanick *et al* (1956) reported an association between obstetric adversity and behavioural problems in childhood, in a study of 1,151 children in special education services in Baltimore. This research indicated a higher rate of toxaemia, hypertension in pregnancy and prematurity in the births of children who later developed a heterogeneous range of behavioural problems compared to their classmates. The study also found that obstetric complications (OCs) had occurred more frequently in children with epilepsy, learning disability, cerebral palsy and speech disorders, than in controls (Lilienfeld *et al,* 1957). Pasamanick suggested that obstetric insult could result in outcomes ranging from mild abnormalities to fatality, and encapsulated the concept as a 'spectrum of reproductive casualty' (Pasamanick *et al,* 1956; Pasamanick & Knobloch, 1960). This initial interest in OCs and childhood developmental and behavioural problems extended into

consideration of whether OCs may be related to mental illness in adults in the 1960s when Lane & Albee (1966) reported that subjects with schizophrenia were on average 6oz lighter than their well siblings at birth and Stabenau & Pollin (1967) confirmed that in 100 pairs of twins discordant for schizophrenia, the affected twin was more likely to have been the lighter of the pair, to have had a history of any birth complications and to have had birth asphyxia. Low birth weight and other obstetric adversity were examined in a series of further studies, but these failed to find significant differences in birth weight between patients with schizophrenia and their well siblings using maternal recall of birth weight (Pollack *et al,* 1966; Woerner *et al,* 1971) or that recorded in birth records (Woerner *et al,* 1973) and again interest temporarily waned.

Further research since the 1970s falls into four epochs, as described by Cannon *et al* (2002a), beginning with studies of high risk subjects, followed by studies investigating the neuropathology of schizophrenia and other psychoses. Case-control studies comparing schizophrenic subjects to a variety of other non-schizophrenic controls then began to be published, during which time several scales for the evaluation of OCs were developed. Finally, population based studies compared index cases of psychosis and other illness to large numbers of controls without illness. However, the range of specific hypotheses examined in relation to OCs and psychosis has been wide and both those at high risk of illness, and those who were overtly ill, have been studied. Subjects have been compared with a variety of comparator groups, or divided into two or more subgroups on the basis of clinical and other features and compared to each other. Correlations between OCs and other markers of prenatal maldevelopment such as minor physical anomalies (MPAs), neuropathological findings, gender, age of onset, presence or absence of a family history and clinical symptoms, have been sought. Over the same time, findings from such studies contributed significantly

to the development of theories of the aetiology of psychotic illness including the idea of a stress-diathesis model which proposes that schizophrenia results from the action of hazardous environmental factors on an already genetically predisposed individual (Rosenthal, 1970; Shields, 1978) and the concept of schizophrenia as a neurodevelopmental disorder (Murray *et al,* 1988).

1.4 Studies of high risk subjects

Studies of subjects at higher than usual risk of schizophrenia provide opportunities to explore the familial and aetiological aspects of any relationship between OCs and schizophrenia or other psychosis and may shed light on the relationship between the genetic liability and environmental influences in the aetiology of these conditions. There are at least three potential ways in which such genetic and environmental factors may interact. Firstly, obstetric complications may represent truly independent risk factors for schizophrenia, contributing just as much to the likelihood of developing illness in those with and those without an increased genetic loading. Secondly, obstetric complications may interact with genetic liability, such that schizophrenia is more common in those with both a genetic liability to illness and obstetric complications than in those with either risk alone. Thirdly, OCs may themselves be an expression of increased genetic liability to schizophrenia, epiphenomena which play no independent aetiological role in the development of the disorder (Goodman, 1988; Sacker *et al,* 1995). These suggestions were initially tested by examination of the pregnancies and deliveries of schizophrenic women, and follow-up of the infants born to allow later comparisons of those who developed schizophrenia with those who did not. McNeil & Kaij (1973) have argued that if OCs occur no more frequently in the pregnancies of women with schizophrenia, and are shown to be associated with an increased risk of illness in their offspring, the hypothesis that OCs modulate a genetic susceptibility to schizophrenia is strengthened. However, if OCs do occur more commonly in women with schizophrenia than in the general population and increased rates of OCs are found in their offspring who become ill, the possibility that OCs modulate a genetic susceptibility to schizophrenia is weakened, as some of the increase in schizophrenia in the offspring of schizophrenic mothers may be due to excess OCs, rather than the increased genetic risk. So, before studies

examining the question of whether OCs are associated with later schizophrenia in that individual are considered, it is necessary to answer the more basic question of whether women with schizophrenia have a higher rate of OCs than do the general population. There were good reasons for thinking that this might be the case, including the expectation that schizophrenic mothers would be of lower social class, would be more likely to smoke and to misuse drugs and less likely to care well for themselves during pregnancy and attend for antenatal care. The investigation of whether the incidence of OCs in mothers with schizophrenia differs from that of non-schizophrenic women was addressed initially in a number of case-control studies, which are now examined.

1.4.1 Obstetric complications in psychotic mothers

In a study of whether schizophrenic women showed altered endocrine response to the stress of late pregnancy, Wiedorn (1954) assessed rates of toxaemia in 72 schizophrenic women and 54 control women over a series of their pregnancies. Toxaemia of pregnancy, defined as hypertension, albuminuria or oedema during pregnancy, was found to be twice as common in the schizophrenic mothers than in controls. The author's conclusion, that toxaemia of pregnancy may be termed a psychosomatic disease, was much in keeping with psychoanalytical theories of the time, and this finding was largely overlooked by those interested in births to women with psychosis. Although high risk cohort studies in schizophrenia were initiated in the 1950s with the New York Infant Study (Fish *et al,* 1965), use of these types of studies in the assessment of any contribution of OCs to schizophrenia did not develop until the 1970s, when researchers began to examine the births of individuals at higher risk of illness compared to the general population, largely the offspring, and later the siblings, of psychotic patients. The New York infant study assessed physical growth,

motor and cognitive development and proposed that infants born to schizophrenic mothers had higher rates of 'pandevelopmental retardation', related to their genetic history of schizophrenia but not to OCs (Fish, 1977). Several other high risk cohort studies are ongoing, and have reported on the relationship between maternal psychosis and OCs, as well as comparing the rates of OCs in those who later became ill, with the rates in those who did not.

The Copenhagen High-Risk study, begun by Mednick and Sculsinger, is a longitudinal study of 207 offspring of severely schizophrenic women (the high-risk group) and 104 offspring of control women. Anoxia, prematurity, prolonged labour, placental difficulties, umbilical cord complications, illness in mothers during the pregnancy, multiple births and breech presentations were examined. The initial analysis of the birth records found a trend towards the high risk group generally having births that were 'attended with more difficulties', were longer and had more placental abnormalities (Mednick & Schulsinger, 1968). A subsequent analysis found 70% of those who developed schizophrenia in early adult life to have had at least one OC, compared with only 15% of those who had not become unwell and 33% of a control population with no parental history of schizophrenia (Mednick, 1970). No individual OC was specifically implicated, but these findings led Mednick to propose that OCs result in anoxia which selectively damages the hippocampus. At ten year follow-up, 173 of the high risk and 91 of the control subjects were re-assessed by diagnostic interview, by which time 15 of the high risk subjects had developed a psychotic illness. Those who developed schizophrenia had significantly higher rates of OCs than those who did not (Mednick *et al,* 1987).

In a later study, which examined 116 of the high risk subjects and 90 controls, the investigators found that the increased rate of complications in high risk subjects was limited to first-born males. Complications in the schizophrenic mothers tended to be more severe than in controls, although this was not statistically significant. Schizophrenic mothers did not show the increase in complications with age that was seen in control mothers, and there were no differences in the schizophrenic mothers who gave birth before their first illness episode compared to those who gave birth after becoming ill. Within the high risk subjects, complications were highest in the first-born child, although the reverse was true for controls (Mirdal *et al,* 1974). The mental health of these children born to the schizophrenic mothers was later assessed at interview and comparison made across diagnostic groups. High risk subjects who had been diagnosed with schizophrenia were compared to those who had not become ill, and to a group diagnosed with DSM-III schizotypal personality disorder. Schizophrenic subjects had the highest rates of obstetric complications, but those with schizotypal personality disorder had the lowest rates, with normal controls having a rate midway between the two. Only the difference between schizophrenia and schizotypal personality disorder was statistically significant on weighted scores of complications. Abnormal fetal position was the only individual complication that occurred more frequently in the schizophrenic group, but numbers with this complication were small (Parnas *et al,* 1982).

The Swedish high risk study of 171 births to 99 women who had been admitted to a psychiatric facility in Sweden, indicated similar rates of OCs between 42 women with schizophrenia and other psychosis and demographically matched controls, lending support to the developing ideas of gene-environment interaction. However, the small sample size of 20 mothers with schizophrenia and 22 with other psychosis may have masked potentially

interesting findings; fetal distress was twice as common in the infants born to psychotic mothers compared to controls and these high risk infants tended to be lighter at birth compared to those of control mothers, although this difference lacked statistical significance (McNeil & Kaij, 1973). Complications were found to be more common in schizophrenic mothers than in normal controls or mothers with personality disorder, but were also more common in mothers with depression and related more to duration of illness than to diagnosis (Sameroff & Zax, 1973).

The Finnish high risk study is often cited as indicating an increase in OCs in schizophrenic mothers compared to controls, but requires further examination. Wrede *et al* (1980) compared 171 births to schizophrenic women in Helsinki with births to unmatched controls and found increased delivery complications, including prematurity and evidence of fetal distress in the schizophrenic mothers, who were less likely to have attended antenatal care and more likely to have had third trimester heartburn, hypertension and proteinuria. At delivery the schizophrenic mothers were more likely to have been agitated and physically unwell, lighter than controls and to have had a smaller weight increase during pregnancy compared to control mothers. Infants born to the women with schizophrenia were more often rated by nurses as 'unhealthy', both at birth and during the first week of life. The findings are unlikely to be biased by the nurses' knowledge of the mothers' schizophrenia, as the majority of the schizophrenic mothers became ill some time after the births examined. However, the schizophrenic and control mothers were not demographically matched and the mothers with chronic schizophrenia differed both from those with milder schizophrenia, characterised by fewer admissions, and from normal controls. The variables assessed as OCs in this study included maternal factors such as height and age at menarche, minor pregnancy symptoms such as heartburn and backache, mother's pulse at delivery, and failure to attend a Well-Baby

clinic; these fall outside McNeil's definition of somatic complications likely to cause harm. In a further analysis of this cohort, Niemi *et al* (2005) found that female infants born to schizophrenic mothers were shorter at birth than controls, but there was no difference in male infants and no differences between groups for birth weight or ponderal indices.

Goodman & Emory (1992) assessed whether illness severity and measures of social and personal disadvantage influenced OCs in a high risk study in Atlanta, Georgia. Schizophrenic mothers of low socio-economic status (SES) were compared with depressed and well mothers from the same localities on assessments of social competence, IQ and illness severity measured by the global assessment scale (GAS). Obstetric variables were identified from birth records using Littman and Parmelee's procedure which produces a standardised pregnancy and birth complications (PBC) score from 41 individual variables. The three groups were similar in marital, racial and socio-economic status, although they differed on age at delivery and education. Lower birth weight was found in the infants of depressed women, but when the mother's age, education, IQ and GAS were taken into account as covariates, the effect disappeared. The children born to schizophrenic mothers had the lowest Apgar scores at 1 minute, a finding which persisted when the demographic, IQ and educational variables were controlled for. Neither schizophrenia nor depression in the mother was associated with total PBC score, but illness severity was, with more severely disturbed women having more PBCs. Statistical analysis of outliers showed that infants with the poorest PBC scores were more likely to have schizophrenic than depressed or well mothers, and were born to younger mothers, who had lower IQ, lower GAS ratings, lower SES and were more likely to be unmarried. A multiple regression analysis showed correlations between low SES and prematurity, premorbid social competence and low birth weight and also between GAS rating and total PBC score. Diagnosis was correlated with

measures of prenatal care, as was IQ; both the schizophrenic mothers and those of lower IQ began to attend for antenatal care later in their pregnancies and attended less often than controls. This raised the question of whether any increased rate of OCs in psychotic women compared to controls might be due to differences in maternal behaviour, particularly compliance with antenatal care.

In a later attempt to resolve this question, Cannon *et al* (1993) compared 207 children of hospitalised schizophrenic women to 104 control children matched on sex, age, years of education, rural or urban residence and institutional or family upbringing. No specific data on individual obstetric complications are presented, but there was a general trend for the high risk subjects to have had births which took longer and were associated with more difficulties, especially more placental abnormalities.

Emerging evidence of increased rates of OCs in those who later developed illness were often interpreted as evidence that such complications have adverse consequences for brain development which increase the risk of psychosis. However, an alternative hypothesis proposes that OCs are a consequence of already acquired brain abnormalities that impair the ability of the fetus to 'prepare itself for a favourable delivery' (Goodman, 1988; O'Callaghan *et al,* 1992; Günter-Genta *et al,* 1994). If this were the case, any increase in OCs would be related to underlying maldevelopment rather than independent of it. To test this idea, data from the Swedish high risk cohort were re-examined to assess whether infants with abnormalities on neurological examination on the third or fourth day of life, which served as proxy measures of maldevelopment, had more complications of fetal presentation and of the umbilical cord than those without such abnormalities. The study found more neurological abnormalities in the infants of psychotic mothers compared to control mothers but no

relationship between neurological abnormalities and these obstetric complications. The authors believe this supports their view that OCs are aetiologically important in psychosis and not merely an epiphenomenon (McNeil *et al,* 1996a).

With conflicting views of the evidence from case-control studies, researchers began to use other methods to answer the question of whether schizophrenic mothers have more OCs. This was examined in a large Danish case register study of 2,212 births to women with schizophrenia and 122,931 births to control women. The investigators found that mothers with schizophrenia were more likely to have had preterm deliveries and babies who were lighter, shorter and more likely to be small for gestational age than controls (Bennedsen *et al,* 1999). The study included women who gave birth before, and after, being diagnosed with schizophrenia. However, although the study controlled for parity, maternal smoking and certainty of last menstrual period (LMP) and therefore gestational age, it did not control for socio-economic class and the schizophrenic mothers tended to have given birth earlier in the study period than controls, which may represent an ascertainment bias. Infants born in the early years of the study had their gestational age ascertained by date of LMP and the schizophrenic women were more likely to be uncertain about this than controls. In contrast, the gestational age of infants born later in the study was ascertained by ultrasound scanning, which may lead to different results and introduce further bias, especially since the other primary OCs examined, birth weight and birth length, and measures derived from them, small for gestational age (SGA) and ponderal indices, may be expected to correlate highly with gestational age. This difficulty could have been overcome by selecting controls matched on, or close to, the subjects' dates of birth, but was addressed to some degree in the analysis, which examined historical epochs separately. A further study of the same sample found that schizophrenic women have fewer antenatal visits than controls but a lower rate of pre-

eclampsia, which the authors suggest may be due to higher rates of smoking. The schizophrenic mothers had more induction of labour, more drugs given to stimulate labour, more assisted vaginal deliveries and more caesarean sections that control women. Babies of schizophrenic women tended to have lower Apgar scores, but only an Apgar score at 1 minute of <10 was significantly more common in the infants of schizophrenic women. McNeil-Sjöström scores (see 1.5.1) were significantly higher, indicating more complications, for women with schizophrenia, but this difference disappeared when gestational age and birth weight were controlled for. One individual complication, placenta praevia, was found to have occurred less frequently in primiparous schizophrenic mothers compared to controls (Bennedsen *et al,* 2001).

An Australian case register study of women with schizophrenia, unipolar and bipolar affective disorders compared the births of their 3,174 children to those of unmatched control mothers with no psychiatric case register diagnosis of psychosis. Crude ORs for illness on the basis of OCs were calculated and those that were significant were adjusted for maternal age, marital status, infant sex, plural births, parity and race. The adjusted ORs indicated an increased risk of placental abruption, administration of an opiate antagonist after delivery and delivery of an infant with lower than expected weight, in the mothers with schizophrenia. Mothers with bipolar disorder had more placenta praevia and antepartum haemorrhage (APH) and those with unipolar depression had increased rates of administration of an opiate antagonist in their newborn infants. Babies born to schizophrenic mothers had more cardiovascular congenital abnormalities and tended to be small for gestational age. There were significant differences in the age, parity and racial distribution of the mothers with schizophrenia, unipolar and bipolar disorder, who were more often unmarried. Comparison of births occurring before and after psychiatric diagnosis showed conflicting results. Overall,

complications were more common after diagnosis, particularly for the schizophrenic mothers, but the complications most associated with schizophrenia, placental abruption, congenital cardiovascular abnormalities and low birth weight for gestational age, were equally common before and after the mother developed schizophrenia (Jablensky *et al,* 2005).

McNeil & Kaij (1978) reviewed 20 studies of reproduction by schizophrenic parents which had not relied on maternal recall, but obtained information from birth certificates or other records. The majority of studies found no differences in OCs or birth weights between the offspring of schizophrenic and control mothers, but suggested a possibly increased rate of fetal and neonatal deaths or malformations in the offspring of both schizophrenic and non-schizophrenic psychiatric patients. There was inconsistent evidence on whether any increase in OCs was related to the onset or severity of schizophrenia in the mothers. In a later review of approximately thirty studies, the same author again concludes that the majority of studies found no differences in birth weight or other obstetric complications between the offspring of schizophrenic mothers and the offspring of control mothers and suggests that findings in this area, such as that of Wrede *et al* (1980) represent greater levels of mental, behavioural and social problems in schizophrenic mothers, but similar levels of what he terms somatic complications (McNeil, 1991). He further concludes that OCs do not occur more commonly in mothers with more severe, rather than milder illness. However, the opposite conclusion is drawn by Sacker *et al* (1996) in a meta-analysis of 14 case-control studies of schizophrenic parents (mainly mothers) compared to normal controls, in studies that controlled for at least some potential confounders such as maternal age, parity, sex of child and SES. Low birth weight and OCs, whether considered together or split into PBCs and NCs, were correlated with schizophrenia in the parent, but the effect sizes were small. The effect was strongest for mothers with schizophrenia, who have been more extensively studied. The few studies that

have examined OCs in children of schizophrenic fathers have shown no increase in OCs, suggesting this argues against a genetic liability to OCs which is associated with the genetic liability to schizophrenia. Further analysis of births to schizophrenic mothers, prior to and following diagnosis, supports the original finding of Mirdal *et al* (1974) that any increase in OCs in women with schizophrenia is present prior to their diagnosis.

Bennedsen (1998) reviewed factors associated with intrauterine growth retardation, preterm birth and perinatal death in a review of studies of pregnancy outcomes of women with schizophrenia. He concluded that findings of increased rates of low birth weight and IUGR in some studies were likely to be influenced by small sample size and by an inability to adequately control for factors known to be associated with IUGR such as lower socio-economic class, smoking, misuse of alcohol and other substances and psychological factors. Once again, studies seemed to point to an excess of perinatal death in the children of schizophrenic mothers compared to controls, but, as perinatal death is related to IUGR, prematurity and low birth weight and is a comparatively rare event, further research was needed to control for such interactions.

In the most recent review, it is suggested that the finding that schizophrenic women are less likely to attend for antenatal care may be related to social class differences between schizophrenic and control mothers. Psychotic mothers were found to have a higher rate of gestational diabetes, especially if they were taking antipsychotic medication, and more likely to have been malnourished and to have misused alcohol. Thus samples of psychotic mothers are likely to differ from control mothers in terms of social, psychological and medical risks. Women with schizophrenia do appear to have lower birth weight babies, but the evidence of increased OCs remains unconvincing. There is little agreement on whether any effect may be

due to poorer antenatal care in these women, maldevelopment leading to a 'clumsy fetus' which is more liable to have delivery complications, or a genetic susceptibility to OCs (Howard, 2005).

Studies of mothers with non-schizophrenic psychoses are much less common, but Wals *et al* (2003) found that lower birth weight was strongly associated with the development of both affective and non-affective illness in children born to bipolar parents and that this effect was independent of the degree of genetic loading, as assessed by family history.

1.4.2 Twins

At the same time as the question of OCs in mothers with psychosis was being investigated, interest was growing in the possible predictive value of OCs in the development of psychosis in the individual. In a number of studies, the obstetric histories of subjects with schizophrenia were compared to subjects without schizophrenia including their co-twins, their siblings, non-schizophrenic psychiatric patients and unrelated well controls. While all of these types of studies can investigate whether OCs are more common in the birth histories of adults with schizophrenia compared to those without, the studies using co-twins and siblings, born to the same mother as the index subject, also allow exploration of familial risk of OCs and may be likely to suffer less from potential confounding due to maternal social class and behaviour, assuming these factors to be relatively stable. In addition, twins share the intra-uterine environment and have most pregnancy and labour variables in common, but differ in their delivery and neonatal complications. Comparison between monozygotic (MZ) and dizygotic (DZ) twins offers the opportunity to examine if individual obstetric adversity correlates with the development of psychiatric disorder in discordant twin pairs, but before

this can be addressed, the question of whether twins are at greater risk of schizophrenia, affective or other psychosis than non-twins requires to be answered. This problem has been easier to address than the question of whether schizophrenic mothers have more OCs. No increase in rates of schizophrenia, bipolar disorder, unipolar affective illness, other non-affective psychosis or neurotic depression were found in either MZ or DZ twins using Swedish twin and psychiatric registers compared to singleton births (Kendler *et al,* 1996).

Studies of twins discordant for schizophrenia emerge early in the psychiatric literature and are of interest for several reasons. Monozygotic (MZ) twins were found in a number of studies to have higher rates of concordance, that is both twins having schizophrenia, than dizygotic (DZ) twins (Rosanoff, 1934b; Pollin & Stabenau, 1968). Shields (1978) reviewed the data from 11 comparisons of MZ and DZ twins discordant for schizophrenia involving some 1,300 pairs. He noted that in all but one study the MZ concordance rate for schizophrenia was about three times that of the DZ concordance rate, but cautions that flawed assessment of twin zygosity, sampling biased in favour of finding concordant pairs and possibly more shared environmental factors in MZ compared to DZ twins could have influenced these findings. The very wide range of MZ concordance rates, ranging from 0 to 86% may reflect such difficulties and other methodological problems, particularly small sample size and age at ascertainment of concordance. Despite these limitations, Shields concluded that MZ concordance rates were higher (~50%) than DZ concordance rates (~17%) and that shared family environment was not a plausible explanation for this finding and that the difference was genetic. However, such a genetic predisposition clearly was not the only risk for schizophrenia, some non-genetic factor, or combination of factors was implicated (Gottsman & Shields, 1976a). As the psychoanalytical view of schizophrenia as entirely due to the influence of upbringing weakened in the face of growing evidence that

schizophrenia was in considerable part a genetic disorder (Gottsman & Shields, 1976b), the 'stress-diathesis' model evolved.

Following the early suggestions by Rosanoff (1934b) of greater obstetric adversity in the ill twin, a number of studies set out to investigate the relationship between OCs and psychosis, mainly schizophrenia, in twins. Stabenau & Pollin (1967) investigated 100 MZ twin pairs discordant for schizophrenia to assess which characteristics best discriminated the ill from the well twin on the basis of interviews with the twins themselves and with their parents. Twenty-six, mainly psychological, characteristics were inquired about, but the authors also assessed which twin was lighter at birth, and whether either twin had asphyxia or any other birth complication, according to the parents' reports. Any birth complication, birth asphyxia and being the lighter at birth all appeared to increase the risk of schizophrenia, however the study was based on samples of twins published in the literature and may not have been representative of discordant twins in general. Pollin & Stabenau (1968) then assessed 15 pairs of twins discordant for schizophrenia again using information gathered from interviews with the parents. The affected twin was the lighter in 12 of the 15 pairs and had more neonatal complications, such as cyanosis at birth and infection, and more neurological soft signs than the unaffected twins. Asphyxia at birth and any complication were more common in the schizophrenic twin within discordant pairs. The authors believe that their findings 'derive from a common subtle but significant difference in intrauterine experience, where, as a result of differences in fetal circulation, differences in fetal positioning and consequent crowding, and other similar mechanical factors, one twin is born at a different and higher state of physiological and biological maturation and competence than is the other.' However, the study has been criticised by McNeil & Kaij (1978) because the inherent difficulties of using maternal recall to assess birth complications some twenty or more years later may be

magnified considering mothers were being asked to remember differences in the deliveries of same-sex, frequently 'identical' twins and were not blind to each twin's status as well or ill.

The issue of whether, in discordant twin pairs, the twin who developed schizophrenia was more likely to be the lighter of the pair attracted significant interest. Gottsman & Shields (1976a) concluded that neither birth weight nor other perinatal difficulties were likely to have a specific role in the aetiology of schizophrenia. However, a different view of the literature was taken by Torrey (1977), who found that when only the more methodologically robust studies were considered, the pre-schizophrenic twin was significantly more likely to have been ~8 oz lighter at birth.

Onstad *et al* (1992) assessed inter-pair birth weight difference in 16 discordant and 8 concordant MZ twin pairs and found no difference and no association between OCs and illness. A similar study of 40 MZ twin pairs by McNeil *et al* (1994b) found OCs to be most frequent in discordant pairs and least frequent in normal pairs, but also found no differences in OCs between ill and well twins. Further analyses of complications confined to pregnancy, which were the same for each twin, found no increased rates of PCs in twin pairs discordant or concordant for schizophrenia compared to control pairs in which neither twin had schizophrenia. MRI scanning of 22 of the 23 discordant MZ pairs showed an association between labour-delivery and neonatal complications and later ventricular and hippocampal size in the ill twins (McNeil *et al,* 2000b). Data from this same sample later indicated that ill twins had more minor physical anomalies (MPAs) (Cantor-Graae *et al,* 1994c) and more neurological abnormalities than their well co-twins, although this latter finding did not reach statistical significance (Cantor-Graae *et al,* 1994a). The authors hypothesised two pathways, one associated with PCs and the development of MPAs, and another associated with labour,

delivery and neonatal complications and associated with the CT scan findings of increased ventricular size and smaller hippocampal volume, both of which may be associated with the development of schizophrenia. The Swedish Twin Register provided the basis for a further study of same-sex twin pairs born between 1926 and 1958; the study compared 88 pairs of twins discordant for schizophrenia with 11,272 pairs with no known history of schizophrenia. Complications in pregnancy did not differ between those who developed schizophrenia and those who did not, but prematurity, a birth weight of <2,300g and a small head circumference were all associated with an increased risk of schizophrenia (Nilsson *et al,* 2005). These findings in twin studies led to OCs being increasingly considered to be 'independent stressful factors that seem to interact with the genetic influences and are a risk-increasing factor to be taken seriously' (Shields & Gottsman, 1977).

Twin studies have likewise indicated a similarly higher MZ than DZ concordance rate for bipolar disorder (Bertelsen *et al,* 1977; McGuffin *et al,* 2003; Kieseppa *et al,* 2004), mania (Kendler *et al,* 1993), schizoaffective disorder (Cardno *et al,* 1999) and unipolar depression (Allen, 1976; Torgersen, 1986). However, no studies have, to my knowledge assessed the relationship between OCs and affective illness or other non-schizophrenic psychosis in twins.

1.4.3 Well siblings

Comparisons between psychotic subjects and their siblings share a number of the advantages of twin studies as both allow modelling of genetic and environmental liability to disease. The incidence of schizophrenia and bipolar disorder in the siblings of individuals with these conditions is approximately ten-fold that of the general population. Siblings of patients share approximately 50% of their genes and represent a high risk group in which development of

schizophrenia is more likely than in the general population (Tsuang *et al,* 2001). Studies of such high risk cohorts are likely to yield more schizophrenic subjects which enhances the statistical power of these studies in comparison to population based cohorts in which development of schizophrenia is a rarer event. Siblings, like twins, usually share at least some aspects of upbringing, but may vary significantly in obstetric histories. If obstetric complications were found to be more common in schizophrenics than their well siblings, and more common in schizophrenics than in control subjects, the case for OCs having an aetiological role in the development of the condition would be strengthened. Eagles *et al* (1990) have recommended the use of unaffected siblings as the most appropriate controls for studies of the relationships between OCs and schizophrenia. The use of siblings helps to control for the possibility that mothers of children who later develop psychosis are more liable to OCs than mothers whose children remain well, and sibling-controls are typically well matched with index subjects on measures of socio-economic class and aspects of upbringing. While the question of whether schizophrenic mothers have more OCs than the general population has been addressed, the question of whether the siblings of schizophrenics are at higher risk of OCs has been less well considered. Even fewer studies compare subjects with other psychotic illnesses to their well siblings, and these are considered later (1.6.1 & 1.6.2)

In a now classic study Lane & Albee (1966) compared 52 schizophrenic patients with their 115 well siblings and found the schizophrenic subjects to be lighter at birth than their siblings in 70% of cases, with the mean difference being 6 oz. Prematurity was twice as common in the schizophrenic group but this difference failed to reach statistical significance. The authors proposed that illegitimacy, maternal mental disorder, physical disorder or seriously disrupted family life during pregnancy adversely affect the developing fetus, resulting in the

birth of a physically disadvantaged infant, born to a mother who is less well able to cope. They suggested that this combination of physical disadvantage and inferior maternal care increases the risk of the development of schizophrenia. Using similar methods, Woerner *et al* (1971) compared the birth weights of 34 schizophrenics with their 42 siblings and found the schizophrenics to be 5.8 oz lighter, but this difference failed to reach statistical significance and no differences in prematurity were found. Neither of these studies was able to fully adjust for parity or birth order. These early studies relied on data obtained from the birth certificate, but Woerner *et al* (1973) gathered hospital birth record data to augment both the birth certificate information and that gained from maternal interview and found an overall complication rate of 37% of schizophrenic subjects compared to 17% of their well siblings. However, 'abnormal' siblings, defined in the study as those in need of psychiatric out-patient treatment, had a complication rate very similar to that of the schizophrenic subjects (38%) and overall the comparison between schizophrenic subjects and their siblings was non-significant.

DeLisi *et al* (1987) found schizophrenic subjects to have almost twice the rate of OCs (23.6%) compared to their well siblings (12.8%) and, although no statistical analysis of individual OCs is presented, found that prematurity, postmaturity, long labour, maternal illness and bleeding during pregnancy occurred more commonly in the ill siblings. A history of complications of pregnancy and of delivery was more common in schizophrenic patients when compared to their well siblings but not when compared to siblings who had a history of any psychiatric disturbance, supporting the idea that such findings may not be specific to schizophrenia. However, some of the OCs rated in this study as 'mild' included premature rupture of membranes, manual or forceps rotation, prolonged labour and umbilical cord wound around the neck, all of which would be considered to be potentially more harmful

using modern classifications. When a different weighting was used for these variables, the differences between schizophrenic patients and their well siblings failed to reach significance. DeLisi *et al* (1988a) found approximately twice the rate of OCs in 123 schizophrenic subjects compared to their 148 well siblings on the basis of maternal interview, with OCs rated using their own scale (see 1.7.1).

These initial findings in American studies were replicated in Europe. Eagles *et al* (1990) found significantly higher rates of OCs on three separate summary measures of OC frequency, highest severity level and total severity score in 27 schizophrenics compared to their well siblings, using hospital birth records, but this sample too was small and the study open to criticism of selection bias in favour of more severely ill patients (Owen & McGuffin, 1990). In a study of 42 schizophrenic subjects, 40 siblings and 174 normal controls, Günter-Genta *et al* (1994) found that umbilical cord complications, atypical presentation and poorer scores on the Lewis & Murray scale (see 1.7.1) were associated with a higher risk of schizophrenia compared to either siblings or controls. Asphyxia was associated with a higher risk when subjects were compared with their siblings, but not with normal controls. More OCs were found in 29 patients with DSM-III schizophrenia or schizoaffective disorder compared to their 39 well siblings by Kinney *et al* (1994a). Cantor-Graae *et al* (2000) compared 55 schizophrenic patients with 19 non-psychotic siblings and found an increased rate of OCs in patients compared to their well siblings, but this was not associated with increased neurological abnormality in adult life. In the sibling group, OCs were associated with adult neurological abnormalities, leading to speculation that the increased rates of neurological abnormalities in schizophrenics and their siblings, compared to the general population, may have separate aetiologies. Neurological abnormalities in adult schizophrenic patients may be related to factors other than OCs, including the manifestation of the illness

process, although the finding is perhaps limited by poor ascertainment of siblings. Willinger *et al* (2001) found more OCs, as measured on the Lewis & Murray scale, and lower birth weight in 36 schizophrenic and schizoaffective patients compared to their siblings. More definite OCs were also found in a study of 199 schizophrenic patients compared to their 213 siblings (Amore *et al,* 2002). Ohara *et al* (2005) compared 18 unaffected siblings to 15 controls using data from the Japanese Maternal & Child Health Handbook and also found increased rates of OCs compared to the general population.

Walshe *et al* (2005) found higher rates of OCs in familial, but not non-familial, schizophrenics compared to their siblings, and no difference in rates of OCs between siblings and normal controls using the Lewis & Murray scale. Kunugi *et al* (1996) found more severe OCs, assessed using the Parnas scale (Parnas *et al,* 1982), in female schizophrenics compared to their siblings and to controls, but not in male subjects. The suggestion of increased OCs in patients with a younger age of onset was examined by Nicolson *et al* (1999) who found no differences in OCs between DSM-III-R schizophrenics with onset by age 12 and their unaffected siblings. However, more OCs were found in schizophrenic and schizoaffective patients than in their well siblings by Heun & Maier (1993). Analysis by gender indicated significantly more OCs in male schizophrenics compared to their well brothers, and significantly more OCs in females with schizoaffective disorder than their well sisters. Within the patient group, those with OCs had siblings with a higher rate of OCs and more first degree relatives with major psychiatric disorder, compared to those without OCs. This could indicate some co-variance for the risk of OCs and that of schizophrenia. A higher total score of OCs on the Parnas scale was also found in 64 male schizophrenic subjects compared to 81 of their well brothers (Bersani *et al,* 2003).

In contrast, a comparison of the obstetric histories assessed by maternal interview found no difference in the frequency of OCs between 54 schizophrenic patients and their 114 well siblings (McCreadie *et al,* 1992). Ichiki *et al* (2000), who compared 187 schizophrenic subjects with paired siblings, found no differences in birth weight or head circumference and concluded there was 'no marked difference in intrauterine physical growth between schizophrenics and their healthy siblings'. Rosso *et al* (2000) compared 61 pairs of schizophrenics and their non psychotic siblings using a conditional logistical regression analysis and found that hypoxia associated OCs did not increase the risk of schizophrenia. Ordonez *et al* (2005) found no differences in OCs between 60 cases with childhood onset schizophrenia and their 48 well siblings, Walshe *et al* (2005) also failed to find a difference between schizophrenic subjects and their well siblings, using the Lewis & Murray scale, and Yun *et al* (2005) found no relationship between OCs and transition to psychosis in a sample of 74 adolescents at high risk.

These diverse findings are difficult to reconcile and it is likely that different findings in such studies are related to the differences in sampling, the use of different methods for gathering obstetric information and assessment of quite different ranges of complications in the various studies. In addition, although in comparisons with unrelated controls, subjects are usually sex-matched (see 1.5.2) studies of siblings have often compared index subjects to non-sex-matched siblings. As there are well established relationships between gender and OCs, this may have confounded findings further.

1.4.4 Conclusions

It seems likely that pregnant women who have schizophrenia are not at significantly greater risk of obstetric complications than other women, although their infants may be more at risk of perinatal death. Research so far does not exclude the possibility that women with schizophrenia have a slightly greater risk of some OCs, but if they do, there is some support for this being related to differences in maternal lifestyle and behaviour. The examination of the rate of OCs in psychotic mothers cannot directly inform the debate on whether OCs contribute to schizophrenia in the offspring (McNeil & Kaij, 1978). Twin studies have tended to indicate more obstetric adversity in the twin who develops schizophrenia than in the well co-twin. Studies comparing schizophrenic subjects with their well siblings have not found any conclusive difference in the rate of OCs, which somewhat supports the suggestion of OCs as epiphenomena, but this cannot be confidently concluded due to the relative paucity of methodologically robust studies, with sufficiently informative numbers, comparing subjects to their same-sex well siblings.

Of the three possible mechanisms by which genetic predisposition and environmental factors may interact, the evidence from studies of high risk groups can only address the possibility that OCs may themselves be an epiphenomenon of increased genetic liability to schizophrenia (Goodman, 1988; Sacker *et al,* 1995). If this were the case, rates of OCs would be found to be similar in schizophrenic subjects and their well siblings, but both groups would show increased rates compared to normal controls. The hypothesis that OCs represent an independent risk factor for schizophrenia predicts that schizophrenic subjects would have more OCs than their siblings, who would show similar rates to normal controls. Finally, the hypothesis that OCs interact with genetic liability predicts a increasing trend in the rate of OCs, lowest in normal controls, intermediate in well siblings and highest in

schizophrenic subjects as the combination of higher genetic risk plus OCs would result in a higher rate of development of schizophrenia than either risk alone. From the evidence so far, studies have found support for all three of these possibilities and no firm conclusions can be drawn.

1.5 Comparisons between patients with schizophrenia and normal controls

The vast majority of studies of OCs and adult mental disorder have examined schizophrenia and have attempted to answer the question of whether OCs are more common in those with schizophrenia compared to normal control subjects using two main strategies, case-control studies and cohort analyses. In case-control studies, the selection of schizophrenic subjects is, of necessity, restricted to those for whom obstetric information is available, which may introduce selection biases, and has often relied on potentially flawed maternal recall (see 1.7.2), but the diagnosis of schizophrenia in the subjects is usually made according to standardised diagnostic criteria based on examination of the case notes or interview with the subjects themselves. In contrast, cohort studies rely on contemporaneous obstetric information free from recall bias and are capable of examining very large numbers of births, but risk introducing bias if not all births are traced, or information on psychiatric outcome is incomplete. In addition, the majority of cohort studies have relied on case register diagnoses which may not be reliable as these diagnoses are usually cross-sectional (Byrne *et al,* 2005). Such studies therefore risk including a higher proportion of patients who would not be considered to have schizophrenia on the basis of case record or face to face interview diagnosis.

Numerous case-control studies have compared subjects with schizophrenia to normal controls, using either a composite measure of OCs or by examining the risks of individual OCs and some studies have exploited both techniques. Before examining such studies, it is necessary to consider these composite measures further.

1.5.1 Composite measures of obstetric complications

The initial studies of OC began by examining birth weight and continued to assess obstetric complications individually. These early studies often found one or two factors to be associated with an increased risk of schizophrenia, most of which were not confirmed in other studies, leading to a lack of specificity about which OCs may be important and no clarity about the timing, intensity or duration of exposure required to increase the risk of schizophrenia. As more studies suggested that examination of individual OCs was unlikely to produce consistent results and unable to assess the effects of the severity of the complications, a number of scales emerged in an attempt to aggregate complications into a measure of the total burden of OCs to the affected infant. Those which have been most widely used are the Parnas scale (Parnas *et al,* 1982), the De-Lisi scale (DeLisi *et al,* 1988b), the Lewis & Murray scale (Lewis *et al,* 1989) and the McNeil-Sjöström scale (McNeil & Sjöström, 1994). These scales are now described; the relative strengths and weaknesses of each scale are discussed later (1.7.1).

The Parnas scale represents the earliest systematic attempt to combine obstetric complications into aggregate measures. It assesses 17 complications, mainly of the current pregnancy, assigning a weight of 1 to 4 to each (see below). Scoring both the presence and severity of each complication allows three scores to be generated; a frequency score, which is the number of complications irrespective of severity, a severity score, which is the severity of the most severe complication present, and a total score, which is the sum of the severity scores for each complication present (Parnas *et al,* 1982). For example, a singleton birth delivered using forceps because of malposition after a labour of >36 hours would have three complications; forceps delivery (weighted 1), bad fetal position (weighted 2) and labour

duration >36 hours (also weighted 2). The frequency score would be 3, the severity score 2 and the total score 5.

The Parnas scale

Weight	
0	No complications
1	Forceps used Caesarean section Placental defects Previous foetal loss Bleeding after delivery Adipositas Narrow pelvis Maternal illness during pregnancy Twins Labour duration > 24 hours
2	Serious maternal illness Placental infarcts Bad fetal position Premature rupture of the membranes Contractions of the pelvis during delivery* Primary uterine inertia Signs of prematurity with birth weight > 2500g Labour duration >36 hours
3	Secondary uterine inertia Bleeding during delivery Labour duration >48 hours
4	Asphyxiation Umbilical cord complications Eclampsia Signs of prematurity with birth weight < 2500g

* This has no clear obstetric definition

The DeLisi scale (DeLisi *et al,* 1988b) divides OCs into those occurring during pregnancy, delivery and in the neonatal period. Eight complications of pregnancy; vaginal bleeding, seizures or convulsions due to toxaemia, Rhesus incompatibility, Rubella or other infection, serious injury, treatment for depression or schizophrenia and the use of other medications, are rated. Delivery complications of prolonged labour (>24hours), premature delivery, late delivery and breech presentation are assessed. Neonatal complications included in the rating are umbilical cord around the neck, baby 'blue' at birth, slow heart beat, convulsions, jaundice, infant requiring oxygen, blood transfusion or the use of an incubator. In addition the scale also includes a high fever or serious infection in the first year of life. Some aspects of this scale are imprecisely defined, e.g. no criteria are listed for slow heart beat or what constitutes a serious injury in pregnancy or a serious infection in the first year of life. The scale does not include delivery by forceps or Venteuse extraction, nor does it include caesarean section.

The Lewis & Murray scale assesses 15 complications, six of which are scored as definite, one as equivocal and the remaining eight as either equivocal or definite; each OC is classed as present or absent. In population samples the frequency of Lewis & Murray scale complications is approximately 25%-30% (Cannon *et al,* 2002a). The inclusion in this scale of a labour of less than 3 hours, found no support among senior obstetricians practising in Dublin, who would not consider a labour of this duration to be even an equivocal complication (O'Callaghan *et al,* 1990b).

The Lewis & Murray scale

	Definite	Equivocal
Antepartum	Rubella or syphilis	
	Rhesus incompatibility	
	Pre-eclampsia: severe and /or leading to early induction or hospitalization	Pre-eclampsia NOS
	Antepartum haemorrhage or threatened abortion	
Intrapartum	Premature rupture of membranes >24 hours	
	Labour >36 hours or <3 hours	Labour >24 hours or "long"/ "difficult"/ "precipitate" NOS
	Twin birth, complicated	Twin birth NOS
	Cord prolapse	Cord knotted around neck
	Gestational age < 37 or >42 weeks	"Premature"/ "Post mature" NOS
	Caesarean section complicated or emergency	Caesarean section NOS
	Breech or abnormal presentation	
	High or "difficult" forceps	Forceps or other instrumental delivery NOS
	Birth weight < 2,000g	Birth weight <2,500g or "small" NOS
	Incubator >4 weeks	Incubator / resuscitation / "blue" NOS
	Gross physical anomaly	

The McNeil-Sjöström scale (McNeil *et al,* 1994a), the most modern and comprehensive of the scales, developed as a result of the limitations of previous scales. A large number of pregnancy, labour-delivery and neonatal potential complications are included and each is graded on a six point scale reflecting the potential severity of harm to the fetus. Complications graded at severity level 4 indicate clearly potentially harmful or relevant complications such as mild pre-eclampsia or breech delivery. Level 5 complications are potentially of great harm or relevance including serious pre-eclampsia or some asphyxia. Those at level 6 are of great harm e.g. extreme fetal distress or asphyxia. Most studies using this scale have analysed a summary score equal to the number of complications at and above severity level 4 and the scale has been described as having a 'gating, rather than weighting, function' (Cantor-Graae *et al,* 1994c). Scores can be divided into those for pregnancy complications (PC), labour-delivery complications (LDC) and neonatal complications (NC) as well as total OCs.

The McNeil-Sjöström scale

Level:	Descriptor:	Examples:
1	Not harmful or relevant	Fatigue First trimester nausea
2	Not likely to be harmful or relevant	Nosebleed Headache
3	Possibly, but not clearly harmful or relevant	Non-pre-eclamptic hypertension Hyperemesis
4	Clearly potentially harmful or relevant	Mild pre-eclampsia Pneumonia Pyelonephritis Oligohydramnios Breech delivery
5	Clearly potentially greatly harmful or relevant	Serious pre-eclampsia Ablatio placentae* Asphyxia
6	Great harm to or deviation in the offspring	Severe fetal distress or asphyxia Postnatal seizures and tremor Life-threatening viral infection

* Placental abruption

1.5.2 Case-control studies

A number of studies have used composite measures of OCs, without analysis of individual obstetric variables. Using the Parnas scale, the frequency, severity and total scores of 23 schizophrenic subjects were found to be greater than those of 23 control subjects, although this effect was confined to female subjects (Verdoux & Bourgeois, 1993a). Kunugi *et al* (1996) compared 59 DSM-III-R schizophrenic subjects with 108 unmatched controls and found greater mean severity scores in schizophrenic subjects compared to controls; analysis by gender showed that female schizophrenics had greater mean frequency, severity and total scores on the Parnas scale, but male schizophrenics showed no differences on any of the three scales compared with controls. In a comparison of 70 RDC schizophrenic subjects with 70 controls higher mean scores on the McNeil-Sjöström scale were found in the subjects, particularly those who were male, first-born, born in winter and without a family history of psychosis (Cantor-Graae *et al,* 1994b; Cantor-Graae *et al,* 1997). Kinney *et al* (1998a) found higher mean OC scores for 18 DSM-III or DSM-III-R schizophrenic subjects compared to a control group which included both normal controls and patients with other psychiatric conditions but failed to provide evidence that this difference was statistically significant in itself; the combination of an OC score of 3 or more and abnormalities of eye tracking occurred more commonly in schizophrenia, but the authors also fail to specify which of the three Parnas scale scores (frequency, severity and total score) was used. In a similar study, the same group found that the combination of at least one LDC and poor performance on the Trail Making test accurately distinguished schizophrenic subjects from their well siblings and from controls. No effect was found for the combination of PCs and poor performance on the Trail Making test, and although there were more OCs in the schizophrenics than in either their siblings or controls, this difference did not reach statistical significance, probably due to

the small size of but the study group which contained only 9 schizophrenic subjects (Kinney *et al,* 1994b). An increased risk of at least one definite OC on the Lewis & Murray scale increased the risk for schizophrenia in a Japanese sample of 52 DSM-IV schizophrenic subjects compared to normal controls (Kawai *et al,* 2004). Significantly more prenatal complications were found using the Lewis & Murray scale in 36 schizophrenic patients compared to 60 controls (Walshe *et al,* 2005), the presence of at least one definite OC was also increased, but this fell just short of conventional statistical significance.

Following their review of early American studies of OCs comparing patients with schizophrenia to their well siblings, McNeil & Kaij (1978) examined 54 pairs of schizophrenic patients and controls matched on sex, place of birth, maternal age, parity, social class and marital status. Those with schizophrenia had higher rates of neonatal complications and total OCs than controls. Pre-eclampsia, inertia of labour and a physician assessment of 'prematurity, immaturity or dysmaturity' were significantly more common in those with schizophrenia compared to controls.

Case registers have been extensively used to assess potential differences between schizophrenics and controls. Kendell *et al* (1996) compared 115 early onset Scottish schizophrenics with matched controls and found increased complications particularly pre-eclampsia and the use of forceps, manipulation of the fetus or caesarean section in the schizophrenic population. However, the findings disappeared four years later when the same cohort, now containing 296 schizophrenic subjects and controls were re-examined. This is likely to have been due to a selection bias towards less complicated control births in the original study (Kendell *et al,* 2000). However, in a second cohort, free of the same methodological bias, emergency caesarean section, prolonged labour and fetal

malpresentation were associated with an increased risk of schizophrenia. Using the Dublin psychiatric case register to identify potential cases, Byrne *et al* (2000) compared 431 patients with schizophrenia to matched controls and found no differences in the rate of OCs using either the Lewis & Murray or Parnas scales. A similarly large Swedish register study of 524 schizophrenic subjects did find differences, lower birth weight and more evidence of asphyxia at birth in the subjects compared to 1,043 controls (Dalman *et al,* 2001), but the study was criticised for using an estimation of Apgar scores in the majority of cases (79%) and for collapsing Apgar scores at three time periods into a single variable. Despite the significant sample size, the study may have been underpowered to find an effect (Crow *et al,* 2001; McIntosh & Lawrie, 2001). Lower birth weight and smaller head circumference were found in a study of 70 schizophrenics matched with controls from the same birth series (McNeil *et al,* 1993) and were exclusive to female cases. Increased rates of OCs were also found to be associated with schizophrenia in a comparison of 23 patients with 23 controls, and again the effect was exclusive to females (Verdoux & Bourgeois, 1993a). In a further study of 167 schizophrenic subjects and normal controls, maternal multiparity, bleeding in pregnancy and birth in late winter were associated with schizophrenia (Hultman *et al,* 1999).

Other studies have sought to assess which individual OCs are associated with schizophrenia and these are summarised in table 1.5.2.

Table 1.5.2 OCs found more commonly in schizophrenic than normal control subjects.

Study	Diagnostic criteria	Number of schizophrenic subjects : Number of controls	Method of ascertainment of OCs	Composite OC measure	Risk of schizophrenia by composite OC measure: OR (95% C.I.)	Specific OCs / maternal factors implicated	Gender effects
(McNeil & Kaij, 1978)	Hospital register diagnosis	54 : 34	Hospital birth records	Authors own rating	Increased rates of total OCs and NCs	Pre-eclampsia Inertia of labour Prematurity / dysmaturity	Not examined
(Jacobsen & Kinney, 1980)	Not specified	63 : 63	Midwife birth records	Parnas scale	Increased rates of OCs	Prolonged labour	Not examined
(O'Callaghan *et al,* 1992)	ICD-9	65 : 65	Hospital birth records	Parnas scale Lewis & Murray scale	At least one OC: 2.44 (1.08-6.03)	Fetal distress	Male patients more vulnerable
(McNeil *et al,* 1993)	Case note analysis RDC	70 : 70	Hospital birth records	N/A	Not examined	Reduced head circumference	Specific to females
(Cantor-Graae *et al,* 1994b)	Not specified	63 : 63	Hospital birth records	Parnas scale	Increased total rates of OCs	Prolonged labour	Not examined
(Günter-Genta *et al,* 1994)	Bleulerian criteria	42 : 174	Hospital birth records	Lewis & Murray scale	No difference	Atypical presentation: 3.78 Cord knotting: 2.20 (no 95% C.I. given)	No difference

Study	Diagnostic criteria	Number of schizophrenic subjects : Number of controls	Method of ascertainment of OCs	Composite OC measure	Risk of schizophrenia by composite OC measure: OR (95% C.I.)	Specific OCs / maternal factors implicated	Gender effects
(Kendell *et al,* 1996)	Scottish National psychiatric register	115 : 115	Obstetric register	Register record of any PC, LDC or NC	Any PC: 6.20 (2.39-20.4). Any delivery complication: 18.00 (2.84-750)	Pre-eclampsia, non spontaneous delivery, forceps delivery, longer infant stay in hospital (Findings later retracted due to problems with design)	Longer stay in hospital for females. No other differences
(Dalman *et al,* 1999)	Swedish National psychiatric register ICD-9	238 : 507,278	Obstetric register	Authors' own rating	Not examined	Pre-eclampsia	Pre-eclampsia risk confined to males
(Hultman *et al,* 1997)	DSM-III	82 : 164	Hospital birth records	Authors' own rating of optimality	SZ (11%) > controls (4%)	Increased birth weight to birth length ratio.	No difference
(Hultman *et al,* 1999)	Swedish National psychiatric register ICD-9	167 : 835	Obstetric register	N/A	Not examined	Maternal multiparity, bleeding in pregnancy, late winter birth	SGA, later in birth order, bleeding in late pregnancy for males alone
(Byrne *et al,* 2000)	Dublin psychiatric case register ICD-9	431 : 431	Hospital birth records	Parnas scale Lewis & Murray scale	No differences	Caesarean section: OR 4.00 (95% C.I. 1.08-22.1).	Caesarean section in males only, low birth weight in females only
(Eaton *et al,* 2000)	Danish psychiatric case register	132 : 33,320	Obstetric register	N/A	Not examined	Maternal multiparity	Not examined

Study	Diagnostic criteria	Number of schizophrenic subjects : Number of controls	Method of ascertainment of OCs	Composite OC measure	Risk of schizophrenia by composite OC measure: OR (95% C.I.)	Specific OCs / maternal factors implicated	Gender effects
(Ichiki *et al,* 2000)	Interview DSM-IV	312 : 517	Birth records	Authors' own rating	Not examined	Gestational age <36 weeks	No difference
(Kendell *et al,* 2000)	Scottish National psychiatric register ICD-9 / ICD-10	296 : 293	Obstetric register	Register record of any PC, LDC or NC	No differences in PCs, LDCs or NCs	Fetal malpresentation more common in controls	Fetal malpresentation more common in controls in females only
		156 : 156	Obstetric register		No differences in PCs, LDCs or NCs	Duration of labour >12 hours Emergency c/s	No difference
(Preti *et al,* 2000)	Case note analysis ICD-9	44 : 44	Hospital birth records	McNeil-Sjöström scale	At least one definite OC: 2.07 (0.83-5.15)	Apgar score at 5 minutes < 7	More OCs in males than females
(Dalman *et al,* 2001)	Stockholm case register ICD-8 / ICD-9	524 : 1043	Hospital birth records	Authors' own rating	Signs of asphyxia at birth: 2.7 (1.5-4.8)	Birth weight < 2,500g Gestational age < 33 weeks	Not examined
(Kotlicka-Antczak *et al,* 2001)	DSM-IV	50 : 30	Birth record	Lewis scale	At least one definite OC: 4.64 (1.29-17.51)	Gestational age < 37 weeks	Non significant excess of OCs in males
(Sørensen *et al,* 2003)	ICD-8	84 : 7,782	Obstetric data base	N/A	Not examined	Maternal schizophrenia: 11.12 (4.60-29.91) Hypertension: 1.69 (1.02-2.80) Diuretic treatment in 3rd trimester: 2.55 (1.21-5.37)	Not examined
(Gunnell *et al,* 2005)	Swedish case register	736 : 718,740	Obstetric register	N/A	Not examined	Birth weight inversely related to schizophrenia	Not examined

However, a number of other case-control studies have failed to find differences in rates of OCs between schizophrenic and control subjects (Gunduz *et al,* 1997; Gunduz *et al,* 1999; Nicolson *et al,* 1999; Thomas *et al,* 2001; McIntosh *et al,* 2001). Case-control studies have attracted criticism for a number of reasons, including non-standardised measures of OCs (Morrison & Hackett, 1993), failure to control for genetic loading and maternal antenatal care and behaviour (Eagles, 1993) and the use of maternal recall and sampling biases (Lewis *et al,* 1993).

1.5.3 Cohort studies

Cohort studies employ a different strategy and await the development of psychosis in a fixed group for whom risk factors have already been determined. Data from the British Perinatal Mortality Survey (BPMS) of births between the 3rd and 9th of March 1958 has been used in two important studies of OCs and schizophrenia generating controversial findings. The study was based on the Mental Health Enquiry which recorded all psychiatric admissions between 1974 and 1986. All those born between the 3rd and 9th of March 1958, who were aged 16 to 28 at the time of the Mental Health Enquiry, were identified and data from their psychiatric case notes was extracted and used to generate diagnoses using Catego criteria. In the first study a logistic regression model was constructed based on all 16, 977 births in the cohort and an equation developed which incorporated and weighted all variables which had predictive value in determining the risk of stillbirth or perinatal death. The 57 subjects who met Catego diagnostic criteria for broad schizophrenia by the age of 28 were compared to the remaining 16,812 by applying this equation to the data collected for each birth to produce a composite risk of neonatal death, which was found not to differ between schizophrenics and controls. No individual delivery complications were associated with an increased risk of

schizophrenia, although low maternal weight and the administration of non-routine drugs to the infant were, although this latter finding was based on two cases only. The authors decisively concluded that 'if there is an effect of perinatal trauma on the later development of psychotic illness it is weak, difficult to define, and apparently absent in typical schizophrenia of early onset' (Done *et al,* 1991). These findings significantly contradicted those of many case-control studies of an increased risk of schizophrenia following OCs and in an attempt to explain this discrepancy, the data was re-analysed by comparing index cases to controls on all variables, rather than the composite risk of fetal or infant death. This analysis revealed differences in maternal physique and lifestyle, previous obstetric history and bleeding during pregnancy between schizophrenic subjects and controls, and also found delivery by untrained persons and low birth weight to be more common in those who became ill. The differences were most striking in the area of maternal physique and lifestyle and included low pre-pregnancy maternal weight, psychological problems, Rhesus negative status, smoking during pregnancy and having fewer than ten antenatal clinic visits. Poor maternal antenatal clinic attendance, a history of previous low birth weight babies, bleeding during pregnancy and delivery by an untrained person remained as independent contributors to the risk of schizophrenia when interactions between these variables were explored in a logistic regression model (Sacker *et al,* 1995).

A Scandinavian cohort study of 76 schizophrenics and 1,074 controls also found low birth weight and the combination of low birth weight and short gestation to be more common in schizophrenic subjects, but no differences between maternal demographics or previous obstetric history (Jones *et al,* 1998). Zornberg *et al* (2000b) found schizophrenia to be much more common in those with a history of hypoxic-ischemic complications than those without,

and found this difference persisted when patients with psychotic mood disorders, as well as those with schizophrenia were included.

In a large follow-up study of the National Collaborative Perinatal Project, 693 individuals from a cohort of 1,068 births were traced, interviewed and diagnosed using DSM-III criteria. Rates of psychoses, which included schizophrenia and schizophreniform disorder, were similar in those who had experienced prematurity or other OCs compared to those whose births were uncomplicated. However, those with a history of chronic fetal hypoxia (defined as severe pre-eclampsia, maternal hypertension, hypotension, anaemia or diabetes), showed twice the rate of psychoses as uncomplicated births, although this failed to reach statistical significance (Buka *et al,* 1993). A recent follow-up of a Swedish birth cohort indicated no relationship between birth weight and the later development of schizophrenia, but there was a relationship with birth length; shorter babies had a higher risk of developing schizophrenia (Gunnell *et al,* 2005). The development of schizophrenia was found to be significantly higher in 535 male infants with Rhesus incompatibility than in 1,332 controls in a Danish birth cohort (Hollister *et al,* 1996) and suggests this may partly explain previous findings of schizophrenia being increased in those later in the birth order, in whom Rhesus incompatibility is likely to be more problematic.

1.5.4. Systematic reviews and meta-analyses

Despite the variety of methodologies used in early studies, McNeil & Kaij (1978) concluded that 'the extensive number of significant, positive relationships between OCs and schizophrenia allows us to reject [the hypothesis] that OCs have no relationship to schizophrenia' and that there was at least some face value evidence for the 'continuum of

casualty' hypothesis that 'a broad range of OCs increase the risk for all types of schizophrenia'. In a largely narrative review Goodman (1988) proposed that the evidence available was consistent with the notion that a genetic liability to schizophrenia could result in OCs rather than OCs having any independent aetiological role. This 'epiphenomenon hypothesis' may be seen to be in keeping with models of schizophrenia as a neurodevelopmental disorder with very early onset which is variously manifest at different stages of life. The normal foetus is an active participant in the birth process, but a neurodevelopmentally impaired fetus may be less than optimally able to prepare itself for birth, and liable to experience more OCs for that reason.

The first meta-analysis of studies comparing the obstetric histories of schizophrenic patients with controls examined the odds ratios for schizophrenia following OCs in 16 studies which compared schizophrenic subjects to non-schizophrenics and were published between 1966 and 1994. In 9 of the 14 case-control studies, OCs were found to increase the risk of schizophrenia with ORs that ranged from 2.1 (95% C.I. 1.1 – 4.2) (DeLisi *et al,* 1987) to 4.4 (95% C.I. 1.3 – 15.6) (Verdoux & Bourgeois, 1993a), but in the remaining five case-control studies and the two historical cohorts studies (Done *et al,* 1991; Buka *et al,* 1993) no increase in risk following OCs was found. The authors caution against accepting their pooled OR of 2.0 (95% C.I. 1.6 – 2.4) across studies as evidence that OCs double the risk of schizophrenia, as they detected a publication bias against small studies finding no association and were concerned at the apparent difference in findings between the case-control and cohort studies. The majority of the case-control studies had selected schizophrenic subjects resident in hospitals, which may not be representative of the schizophrenic population in general. A variety of comparator groups had been used, including siblings, other psychiatric patients, and unrelated well controls (Geddes & Lawrie, 1995).

Geddes *et al* (1999) re-examined individual patient data from 12 case-control studies of OCs in schizophrenia that used the Lewis & Murray scale to assess possible relationships with gender, birth order, family history and age of onset and found an association between schizophrenia and increased number of OCs. Seven of the studies used maternal recall and one of the five that used obstetric records was Kendell *et al* (1996) which was later reported as inaccurate due to sampling biases (Kendell *et al,* 2000). The OR for schizophrenia following any definite OC in the pooled sample of 700 schizophrenic subjects and 835 controls was 1.38 (95% C.I. 1.05-1.84). However, the relative absence of published small negative studies, suggesting a publication bias, could have resulted in this modest increase in risk being an overestimate. When individual OCs were examined, premature rupture of the membranes, gestation <37 weeks and the use of resuscitation or incubator were all associated with an increased risk. Forceps delivery and birth weight < 2,500g also increased the risk, although just below conventional statistical significance. The studies using contemporaneous birth records, but not those using maternal recall, showed pre-eclampsia to be associated with a higher risk, but the studies using maternal recall found an increased risk with forceps delivery, which was not found by the studies using birth records. Umbilical cord complications were a risk factor in studies using well siblings as controls, but not in those using unrelated controls. The authors argued that fetal hypoxia is a likely mechanism, and that premature membrane rupture and short gestation contribute to the hypoxia, which itself is associated with lower birth weight and therefore a higher likelihood of requiring the use of resuscitation or an incubator. A further analysis of these data indicated a higher risk for those with a younger age of onset and implicated abnormal fetal presentation and complicated c/s (Verdoux *et al,* 1997). However, the authors included assessment of OCs by maternal recall, which was criticised by Schaub *et al* (1998).

A further estimate of a pooled OR for schizophrenia following individual OCs was calculated in a meta-analysis of seven population based case-control studies. Diabetes in pregnancy, birth weight <2,000g, and <2,500g, emergency c/s, congenital malformations, uterine atony, Rhesus incompatibility or potential incompatibility, asphyxia, bleeding in pregnancy and pre-eclampsia were all associated with an increased risk of schizophrenia, with the strongest effects being seen for asphyxia and birth weight <2,500g (Cannon *et al,* 2002a). Low birth weight was considered to be a significant risk for schizophrenia, with a pooled ORs of 2.6 (95% C.I. 2.0 – 3.3) in a further analysis (Kunugi *et al,* 2001). Effect sizes for individual complications are relatively small. Cannon *et al* (2003) calculated pooled odds ratios of between 1.0 and 1.5 for winter birth and prenatal poliovirus infection, between 1.5 and 2.5 for prenatal influenza or other respiratory infection, prenatal famine, pre-eclampsia and low birth weight and higher odds ratios for maternal rubella infection, maternal bereavement, Rhesus incompatibility, hypoxia related OCs and perinatal brain damage. Overall, OCs were again associated with an approximate doubling of the risk of schizophrenia (Cannon *et al,* 2003).

1.5.5 Studies of correlates of OCs in schizophrenia

A number of studies have investigated whether any relationship between OCs and schizophrenia could be a manifestation of another underlying risk for both OCs and schizophrenia. If this were the case, any findings of increased OCs in schizophrenia would be likely to be valid, but aetiologically unimportant. Following the findings of the British Perinatal Mortality Survey study, Sacker *et al* (1995) suggested maternal characteristics as one such factor. Their findings of differences in maternal physique and lifestyle between mothers of schizophrenics and mothers of control subjects are said to represent a 'pattern of

anomalies' among the mothers of schizophrenic patients, which increase the risk of OCs. They believe that this deviant maternal behaviour, along with more conscientious obstetric recording of information in such higher risk deliveries, explains previous findings of increased OCs being found to be associated with later schizophrenia. This assertion was refuted however, on the basis that studies finding increased rates of OCs in schizophrenic patients compared to their well siblings are not likely to be explained by differences in maternal behaviour (Rifkin & Takei, 1995) and that the authors had no direct evidence of the suggested recording bias (Mortensen *et al,* 1995). This criticism provoked a re-examination of the Swedish cohort data to assess if their previous finding of increased OCs in schizophrenia compared to controls could be explained by maternal characteristics. When the sample was stratified by maternal age, parity and SES, there were more OCs in first-born schizophrenics than first-born controls and a non-statistically significant trend for the mothers of schizophrenics to be older than mothers of controls, but socio-economic status was unrelated to the rate of OCs. LDCs were increased in first-born schizophrenics compared to controls and included prolonged labour, fetal distress, hypertension, pre-eclampsia, administration of analgesic, asphyxia and being small for gestational age (Cantor-Graae *et al,* 1997). Maternal behaviour, however, could not be examined. Maternal body mass index (BMI) in early and late pregnancy and maternal attendance at antenatal care were assessed in 52 schizophrenic subjects and 284 controls. There were non-significant trends for the mothers of schizophrenic patients to have had fewer antenatal visits and a greater BMI at both stages of pregnancy, but the incorporation of both of these variables into a logistic regression model reduced the OR found for schizophrenia following OCs from 3.13 (95% C.I. 1.26 - 7.77) to 2.82 (95% C.I. 0.70 – 10.41), indicating no statistically significant increase in risk (Kawai *et al,* 2004).

1.6 Affective disorder and other psychosis

From the beginning of the modern era of research into OCs and mental illness, psychosis has emerged as the condition of interest and within this schizophrenia has been the primary focus. The overwhelming majority of comparisons between psychotic patients and normal controls have been for schizophrenia and, unless other conditions are examined, this could be potentially misleading. The research described above applies largely to schizophrenia, but has included a wide variety of diagnostic criteria and sampling of different groups of patients, ranging from long term hospital patients to community based samples. Many studies have relied either on a case note or case register diagnosis of a recording of schizophrenia on one occasion only. Many other studies have applied standardised diagnostic criteria, but these are likely to have been influenced by changes in classification of diagnostic systems and the tools used. The possibility that what had been found for schizophrenia may apply to other psychiatric conditions, in particular to other psychoses, required to be explored, and it is worth remembering that early studies assessed OCs in a variety of psychiatric conditions (Rosanoff & Rosanoff, 1931; Rogers *et al,* 1955; Pasamanick *et al,* 1956). Schizophrenia shows considerable clinical overlap with schizoaffective disorder, bipolar affective disorder and other functional psychosis; it lacks definitive symptoms, signs or investigative tests, and research using discriminate function analysis has been repeatedly unable to confidently distinguish between schizophrenia and bipolar disorder (Kendell & Gourlay, 1970; Everitt *et al,* 1971; Fleck *et al,* 2001). Evidence from genetic studies suggests considerable overlap in familial liability to schizophrenia and bipolar disorder, as evidenced by relatives of schizophrenic subjects having an increased risk of bipolar disorder, as well as of schizophrenia (Bramon & Sham, 2001). In studying affective psychosis, greater diagnostic difficulties arise than when studying schizophrenia. Although there are many different views

on the diagnosis of schizophrenia, clinical and research criteria have existed sufficiently long for there to be reasonable agreement on what constitutes schizophrenia, at least for the typical syndrome.

In contrast, there is no consensus on what constitutes affective psychosis, or on whether this is an appropriate comparator group to schizophrenia. Although there is some tendency for psychotic symptoms to correlate with more severe affective illness, many, perhaps the majority, of depressive or manic episodes do not result in psychotic symptoms. Patients may have psychotic symptoms in some episodes and not in others. The distinction between unipolar and bipolar depression is similarly unclear, and the age at which subjects are ascertained plays an important role. While conventionally, a single manic episode results in a diagnosis of bipolar disorder, considerable numbers of patients have unipolar depressive episodes before the emergence of a significant manic episode. Restricting the concept of affective psychosis to only those with bipolar disorder will fail to include patients with recurrent depressive psychosis, and may include patients with no psychotic symptoms. Mood symptoms are frequent in schizophrenia and psychotic symptoms, including those of first rank type, occur by definition in both manic and depressive psychoses. Although diagnostic classifications attempt to distinguish schizophrenia from affective psychoses, the clinical distinction is often unclear, as the emergence of the concept of schizoaffective disorder testifies (Kempf *et al,* 2005).

1.6.1 Affective disorder

The initial finding of a relationship between OCs and schizophrenia has raised the question of whether this putative relationship is specific to schizophrenia, or may extend to other psychoses. From the large series of twins studied in the 1930s, MZ and DZ concordance rates for manic-depressive illness were found to be 70% and 16% respectively in the 90 pairs where at least one twin had a diagnosis of manic-depressive illness. This was seen by the author to support the idea that manic-depressive disorders are 'the most hereditary of the commoner psychoses' (Rosanoff, 1935). However, in contrast to the findings in schizophrenic twins, the histories of these twins were not suggestive of high rates of cerebral trauma, but in the few cases with such a history, the onset of illness tended to be at a relatively early age. The authors suggested that manic-depressive syndromes are highly heritable, but may also be caused by organic cerebral lesions and by psychogenic factors. The possible relationship between OCs and affective psychoses has been less extensively studied than that between OCs and schizophrenia and early investigations were often small case-control studies. In a large study of first admissions with psychosis, patients with bipolar disorder and unipolar depression showed higher rates of OCs than patients with other non-schizophrenic psychoses, neuroses, personality disorder and substance misuse (Lewis & Murray, 1987). Cohort studies have compared the birth records for those who go on to develop affective disorder with the remainder of the cohort who do not. The original analysis of the 1958 British Perinatal Mortality Survey sample (Done *et al,* 1991) found no increase in risk of perinatal death in 32 patients who developed affective psychosis compared to controls, but the subjects had shorter gestation and higher rates of administration of vitamin K than controls. Use of this later factor as an obstetric complication was criticised by Lewis & Stewart (1991), as administration of this drug is more likely to be an indicator of, rather than

a risk for, poor neonatal condition. The re-analysis of all available variables in the same cohort found more prematurity, unruptured membranes, non-spontaneous delivery, influenza and pyrexia in pregnancy in the individuals who later developed affective psychosis compared to controls. However, the mothers of those who developed affective psychosis were older, more parous, more likely to be Rhesus negative and to have previously had heavier babies (> 4000g) than controls (Sacker *et al,* 1995).

Guth *et al* (1993) found more OCs in 47 patients with early onset major depression or bipolar I disorder compared to a sample of later onset cases, matched for diagnosis, race, sex and socio-economic class. In studies comparing bipolar patients to their well siblings, a higher rate of OCs on the Parnas scale was found in those affected using both record derived and maternally recalled OCs (Kinney *et al,* 1993; Kinney *et al,* 1998b). In a further study, low birth weight was found to be associated with a higher risk of depression in the elderly (Thompson *et al,* 2001).

In contrast, no difference was found in the rates of OCs between patients with major affective disorder and control subjects using mainly maternally recalled OCs rated using the McNeil-Sjöström scale (Gunduz *et al,* 1997; Gunduz *et al,* 1999). Similarly, Stöber *et al* (1997) found no association between maternally recalled OCs and manic-depressive psychosis in a comparison of 40 cases with controls. In a follow-up of the National Collaborative Perinatal Project in the USA, rates of affective disorder at age 18 – 27 were similar in the 373 complicated and 320 uncomplicated births (Buka *et al,* 1993). Verdoux & Bourgeois (1993a) compared 23 bipolar patients and 23 controls, using maternal recall and found no differences in the rates of specific OCs and no increase in total OC scores between the two groups.

As studies using register linkage have achieved greater statistical power, associations have tended to diminish or disappear. In a comparison of 198 patients with affective psychosis and 990 controls, Hultman *et al* (1999) found only uterine atony and late winter birth to be associated with affective psychosis. The OCs recorded in a national register of two cohorts of Scottish patients with a diagnosis of affective psychosis were compared to matched controls by Bain *et al* (2000), who found that the overall rates of any complication of pregnancy, delivery or the puerperium did not differ between those with affective psychosis and controls. When individual OCs were examined, abnormal fetal presentation, in the larger cohort, and artificial rupture of the membranes, in the smaller cohort, were associated with an increased risk of illness, but the authors conclude this was likely to have arisen by chance. No association between OCs and later mania was found in a similar Irish case register study of 76 patients compared to matched controls (Browne *et al,* 2000). Further support for a lack of association between OCs and affective disorder was provided from studies using Danish case registers, which found similar rates of bipolar disorder in twins compared to singletons and argued that as OCs are known to occur more frequently in twin than in singleton births (Flemming *et al,* 1990), OCs were not associated with an increased risk of bipolar disorder (Kläning *et al,* 2004). In another study employing these registers, Øgendahl *et al* (2006) found no association between gestation or birth weight and the risk of bipolar disorder overall or in male subjects, but found that a gestational age of <37 weeks was associated with an increased risk of bipolar disorder in females. However, the subjects of the study were no older than 26 at the time of ascertainment and represent a younger onset group. No differences in rates of OCs were found between patients with major affective disorder and normal controls using maternal recall (Gunduz *et al,* 1997; Gunduz *et al,* 1999) or obstetric databases (Zornberg *et al,* 2000b; Sørensen *et al,* 2003).

A recent systematic review of this literature found 22 studies that measured OCs using a stated method and compared patients with bipolar disorder to a well defined control group. In eight studies comparing bipolar patients to well controls, two found OCs to increase the risk of bipolar disorder and both of these used a sibling control group. Numbers of bipolar patients in these studies are generally small, ranging from 13 to 76, with similar numbers of controls and are likely to be underpowered to find small increases in risk (Scott *et al,* 2006). Large scale studies of bipolar disorder compared to controls have not been carried out, but the existing evidence has been interpreted as suggesting that OCs do not increase the risk of bipolar disorder (Tsuchiya *et al,* 2003; Murray *et al,* 2004).

1.6.2 Other functional psychosis

Schizoaffective disorder has generally been included with schizophrenia rather than examined separately (Willinger *et al,* 2001). Relatively few studies have examined other psychoses that are neither schizophrenic nor affective. McNeil *et al* (1996b) compared 30 patients with RDC schizoaffective or other functional psychosis to non-psychotic controls and found no difference in rates of OCs, but smaller head circumference among the patients than the controls. The authors suggest that the finding of smaller head circumference, also found in schizophrenia, may be a risk factor for psychosis, rather than diagnosis specific. Hultman *et al* (1999) found multiparity, but not OCs, to be associated with reactive psychosis. Preti *et al* (2000) examined cases of paranoid states and atypical psychoses and found an overall increase in definite OCs compared to controls when both groups were considered together, but not for either diagnosis separately. However, severe complications were more common in subjects compared to controls. Symptoms of non-affective psychosis have occurred more commonly in those exposed to first trimester rubella infection than in

those not so exposed (Brown *et al,* 2000). There are a small number of studies of other psychoses, which have been largely negative. Buka *et al* (1993) followed up a cohort of 1,068 births and found no increase in the rates of psychiatric disorder including psychosis and affective disorder by age 27, in those who had any pregnancy or birth complications compared to those who had not.

1.6.3 Comparisons between psychoses and other conditions

In an early attempt to examine the specificity of OCs for schizophrenia compared to other functional psychosis, Pollack & Greenberg (1966) studied 71 first admissions to the Hillside hospital, of whom 51 had schizophrenia, 11 had personality disorder and 7 had affective disorder. Obstetric complications, assessed by maternal recall, were categorised as absent, moderate or severe. Severe OCs occurred most commonly in the personality disordered patients. For all 71 patients and for the schizophrenic patients alone, mean age of onset was lowest in those with severe complications and highest in those with no complications. Lewis & Murray (1987) assessed the obstetric histories recorded in the psychiatric case notes of a series of first admissions to the Maudsley hospital over a three year period using the Lewis & Murray scale. They found a history of OCs in 17% of schizophrenic patients, 11% of those with bipolar affective disorder, 10% of those with unipolar depression and 7% of those with other psychosis. The 207 schizophrenic patients had significantly more OCs than the remaining 748 with other diagnoses, suggesting some specificity for schizophrenia. Schwarzkopf *et al* (1989) compared 21 schizophrenic and 10 bipolar subjects and found more OCs in those with schizophrenia, in particular prolonged labour and delivery using forceps. Foerster *et al* (1991) found more OCs and lower birth weight in 45 patients with schizophrenia than in 28 with affective psychosis, with a tendency for more male than female

schizophrenics to have had OCs. However, the birth weight finding disappeared when controlled for race and parental social class.

Verdoux & Bourgeois (1993b) compared 23 DSM-III-R schizophrenics with 23 bipolar patients using obstetric information obtained from maternal interview and scored using the Parnas scale. Pregnancy complications and birth weight did not differ between the two groups, but schizophrenic subjects had significantly higher frequency, severity and total scores than bipolar subjects for complications of labour, delivery and the neonatal period. The effect was more marked for females, but there were no differences between those with a younger rather than older age of onset, or those with, rather than without, a family history of psychosis.

Maternal recall was used to assess birth weight in 100 patients with schizophrenia and 67 with affective psychosis. The mean birth weight of the schizophrenic patients was 224g (9 oz) lighter than those with affective psychosis, and the finding of a lower birth weight in schizophrenic subjects persisted when the effects of gender, ethnicity and parental social class were controlled for. There was a non-significant trend for the schizophrenics to have had at least one definite OC on the Lewis & Murray scale more often than controls, when the definition was broadened to include equivocal OCs, these occurred significantly more frequently among the schizophrenic than the affective patients (Rifkin *et al,* 1994). Increased rates of OCs in schizophrenic subjects have been found in studies comparing schizophrenia to mania (Gureje *et al,* 1994) and to bipolar disorder (Verdoux & Bourgeois, 1993a). Reddy *et al* (1989) found a trend towards a lower rate of OCs in bipolar patients compared to those with schizophrenia. In a study of original birth records and using controls from the BPMS, pregnancy complications and gestational age <38 or >41 weeks were found

to correlate both with schizophrenia and with affective disorder, with higher ORs for affective disorder than for schizophrenia, although the difference between the two groups was not significant (Nadeem, 2001).

In a systematic review of OCs and bipolar disorder, Scott *et al* (2006) identified six studies comparing bipolar to schizophrenic patients, and five comparing patients with bipolar disorder to those with unipolar depression. Two studies found that OCs decreased the risk of bipolar disorder when schizophrenic subjects were used as the comparison group, which presumably reflects an increased risk of schizophrenia, rather than a decreased risk of bipolar disorder in these studies. This provides some evidence that OCs are specific either to schizophrenia, or to non-affective psychoses. No evidence was found that OCs increase the risk of bipolar, rather than unipolar depression.

Obstetric complications have been found to increase the risks of other conditions, particularly developmental disorders. Prematurity and low birth weight have been found to increase the risk of mental retardation (Rosanoff, 1934a), while prematurity, breech presentation and low Apgar score at 5 minutes have been associated with an increased risk of autism (Larsson *et al,* 2005). Increased rates of OCs compared to normal controls have been found for childhood behavioural problems (Pasamanick *et al,* 1956) and cerebral palsy (Lilienfeld *et al,* 1957; Nelson & Ellenberg, 1986). Within the spectrum of adult psychiatric conditions, increased rates of OCs have been found in anorexia nervosa (Lewis & Murray, 1987) and in neurosis (Done *et al,* 1991) as well as in psychotic disorders, which suggests that findings may not be specific to any one diagnostic group (Verdoux & Sutter, 2002).

1.7 Strengths and limitations of previous methods of investigation

1.7.1 Scales used to measure OCs

The most commonly used scales in research into the relationship between OCs and psychiatric disorder have been those of Parnas, Lewis & Murray and McNeil-Sjöström. These three use very different approaches to the classification of OCs and differ markedly in the number of potential complications assessed and the weighting given to each, leading to inconsistent representation of what constitutes OCs across studies (McNeil, 1995). The use of different scales may enhance differences, or may obscure them if subjects tend to have a different pattern of complications than controls (Bennedsen *et al,* 2001). OCs have been recorded and classified in various ways and the choice of scale for scoring OCs can produce different results from the same data set (McNeil *et al,* 1994a). The Parnas scale assesses only a narrow range of OCs and the descriptions of the complications are open to some degree of interpretation, which may have hindered its use (McNeil *et al,* 1994a). The Lewis & Murray scale is limited by the use of only five complications of pregnancy and by the fact that the maximum score is achieved with only one definite complication, which permits no further assessment of the cumulative amount of obstetric adversity. Its use in samples in which large numbers of potential obstetric complications are recorded is therefore limited.

A number of studies have used multiple scales and compared the results obtained by each. The three major scales were compared in the 70 schizophrenic subjects and 70 matched controls from the Swedish birth cohort. Rating on all three of the Parnas, Lewis & Murray and McNeil-Sjöström scales showed an increase in OCs in the schizophrenic subjects

compared to controls, although for the Parnas scale, this failed to reach statistical significance, indicating relative concordance between the scales. Within the McNeil-Sjöström scale, LDCs, NCs and total OCs were increased in schizophrenia, but PCs were not (McNeil *et al,* 1994a). The subjects were grouped into winter (January – April) and non-winter births, and also into those with, and without, a family history. In the season of birth analysis, an increased risk of schizophrenia was found for those born in winter on the McNeil-Sjöström scale only, for those born in summer an increased risk of schizophrenia was found only for those with at least one definite OC on the Lewis & Murray scale. In subjects without a family history, the risk of schizophrenia was increased when OCs were assessed using the McNeil-Sjöström and Lewis & Murray scales, but not the Parnas scale, and in 'familial' cases, only the presence of one or more OCs on the Lewis & Murray scale was associated with an increased risk (McNeil *et al,* 1997). Stöber *et al* (1993) found more OCs in schizophrenic subjects compared to controls using the Parnas, but not the Lewis & Murray scales.

1.7.2 The use of maternal recall

Studies relying on maternal recall (e.g. Marcelis *et al,* 1998; Bennedsen *et al,* 2001) are open to criticism for introducing bias. A number of studies have compared maternal recall to routinely collected obstetric information as a reference standard. Two types of error may occur; errors of omission, in which the mother denies at interview a complication which is documented in the case record, and errors of commission, in which the mother declares a complication at interview which is absent from the case record.

Maternal recall of OCs, but not of infections during pregnancy, was found to correlate well with obstetric records analysed using the Lewis & Murray scale in 24 mothers of patients with schizophrenia or bipolar disorder (Franzek & Stöber, 1995). Complete concordance on the presence or absence of any definite OC has also been reported (O'Callaghan *et al,* 1990a). O'Callaghan *et al* (1990b) also found maternal recall correlated well with birth records when both were scored using the Lewis & Murray scale in 21 mothers of (mostly schizophrenic) subjects attending a depot clinic. They reported that 91.5% of the sample was correctly classified as having no complications or at least one definite OC by both methods. Two mothers recalled a definite OC and two an equivocal OC that was not recorded in the case notes. However, Cantor-Graae *et al* (1998) found that mothers of schizophrenics tended to make more omission errors, that is to recall fewer labour and delivery complications than were recorded in their obstetric records. Overall the reliability of maternal recall in the study was poor with only four of the 62 mothers who had had OCs, having the same information obtained by maternal interview as from the obstetric record analysis. Interestingly, stratification of the sample by family history showed that mothers of patients with no family history tended to recall events not recorded in their notes, while the mothers of patients with a family history, and control mothers tended to be more likely to omit information that was recorded. The authors suggested this may represent an attempt to explain the development of illness in their children. Buka *et al* (2000) proposed that if this were true, a systematic over-reporting of OCs should be found in the mothers of psychotic patients, while an under-reporting of OCs would be more expected in the mothers of control subjects, and tested this idea in a study of 39 mothers of psychotic patients and 39 control mothers. Although good agreement was found between maternal recall and obstetric case records for previous obstetric history, agreement was poor for bleeding or hypertension in pregnancy or cord complications. Pregnancy complications were particularly poorly recalled by the mothers of

psychotic patients, who were twice as likely to make an omission, rather than commission error, leading the authors to suggest that previous findings of an approximately two-fold increase in risk conferred by OCs in studies using maternal recall might be an underestimate.

In their meta-analysis Geddes & Lawrie (1995) found no differences in the ORs for schizophrenia obtained from studies of maternal recall rather than those based on hospital records and other contemporaneous data, and suggested that difficulties in obtaining birth records might further increase sample selection bias, although this would not avoid biases involved in finding and obtaining consent from mothers. In contrast McIntosh *et al* (2001) demonstrated that although maternal recall identified more OCs in schizophrenic and high risk patients compared to normal controls, examination of the obstetric records using the McNeil-Sjöström scale showed no such increase, indicating a tendency for mothers of both schizophrenic and high risk subjects to make more commission errors.

Studies of the validity of maternal recall have therefore not agreed whether maternal recall may result in under- or over-reporting of OCs. It has been noted that 'paradoxically, the main similarity between studies is their collective weakness: the use of retrospective assessment of obstetric variables, even if assessed blindly' (Lewis, 1989).

1.7.3 Sample size and confounding factors

A significant limitation of much of the research, particularly in the non-schizophrenic psychoses, is small sample size which results in a lack of statistical power and an increased risk of a type II error. Many studies are of small sample size (Eagles *et al,* 1990; Nicolson *et al,* 1999; Preti *et al,* 2000; Kotlicka-Antczak *et al,* 2001; Willinger *et al,* 2001), and unable to control for confounding factors which may have over represented the contribution of OCs to schizophrenia. Conversely, insufficient power may have contributed to a failure to find an association between OCs and schizophrenia (Buka *et al,* 1993; Cannon *et al,* 2002a). Overall, case-control studies show inadequate adjustment for confounding, different diagnostic criteria for schizophrenia, imprecise and varying measures of OCs studied and insufficient power (Bennedsen, 1998).

The array of demographic, genetic and previous obstetric factors which may influence OCs is extensive and a significant criticism of much of the literature is the reporting of crude odds ratios for illness by OCs, with no controlling for confounding factors. In those studies that take account of confounding factors, controlling for such variables has not confirmed previously reported associations (Dalman *et al,* 1999). An initial finding of birth weight differences between schizophrenic subjects and controls disappeared when the data were controlled for race and social class (Foerster *et al,* 1991).

In case-control studies, it is important to exclude the condition of interest in the control subjects, which has not always occurred. There is considerable evidence that genetic liability to illness is a significant factor and many studies have been unable to control for this. Maternal socio-economic status, health and behaviour, particularly attendance for antenatal

care, are likely to confound relationships between OCs and diagnoses of interest. Few studies have been able to adequately control for all these factors.

Some authors have suggested that the use of biased maternal recall, small sample sizes and evidence of 'missing' small negative studies from the published literature are sufficient to explain the apparent excess of OCs in schizophrenia, and that the large negative cohort studies (Done *et al,* 1991; Buka *et al,* 1993) which find no effect of OCs on the risk of schizophrenia further add to this argument (Crow, 2003). In contrast, the findings of excess OCs in schizophrenia may be real, but artefactual due to confounding by socio-economic class, parity and other maternal characteristics.

1.8 Conclusions

A number of issues have made the study of the relationship between OCs and psychosis difficult to investigate. Any classification or even definition of OCs is to some extent arbitrary and the mechanisms of subtle fetal insult conferred by each of the wide range of OCs studied are imprecisely understood. Although some attempts have been made to divide OCs into those which may adversely affect fetal development, and those that might give rise to injury at the time of birth, the methods of investigation have depended either on maternal recall or on data recorded many decades previously. Maternal recall may well be biased and mothers are not blind to their children's status as ill or well. Birth record and other historical data is constrained by the quantity and quality of what was considered important to record at the time and is not designed to answer modern aetiological theories of the pathogenesis of psychosis. Additionally, few studies have been able to adequately address potentially significant confounding factors such as socio-economic status (SES), maternal age and parity, and confounding by genetic risk.

Despite these limitations, a large body of evidence from case-control and cohort studies testifies to some relationship between OCs and psychosis, particularly schizophrenia. Research into the relationship between OCs and the later development of psychotic illness has been extensive and relatively systematic. Early studies of women with schizophrenia indicate an increased risk of OCs compared to matched controls without major psychiatric illness is unlikely. Any increased rate of OCs in the births of subjects who later develop schizophrenia is therefore not likely to be due to psychiatric illness in the mother, although differences in maternal behaviour may be relevant. The assessment of the possible aetiological role of OCs in the development of schizophrenia and other psychoses has

examined subjects in comparison to their twins, siblings and matched controls, using a variety of techniques to select subjects and to assess OCs. Studies to date suggest that OCs are more common in affected compared to unaffected twins, but have not clearly indicated and increased rate of OCs in schizophrenic subjects compared to their well siblings.

Numerous case-control studies comparing subjects with normal controls indicate an increased risk for schizophrenia, and possibly for other psychoses following OCs. With the exception of large population cohorts, these wide ranging studies have tended to agree that there is a potential aetiological role for OCs in the later development of psychosis, but the effect size of the relationship between OCs and schizophrenia is small, with odds ratios of <2. It is likely that non-genetic factors, such as OCs are indeed implicated in the aetiology of schizophrenia, but the small effect size causes the effect to be difficult to detect, which may offer some explanation for the inconsistency of the evidence, considerable proportion of 'negative' studies and the wide variety of findings (Leask, 2004). The interpretation that there is no role for OCs or other significant environmental factors and that schizophrenia is purely a genetic disorder with evolutionary implications (Crow & Waddington, 2000; Crow *et al,* 2001) does not appear to be supported when the literature is examined as a whole, but it does remain possible that such small effects may be proxy markers of some other exposure, lifestyle or genetic risk.

The following chapter explores the nature of this relationship between OCs and psychosis within patient populations and the identification of relationships between OCs and demographic features such as gender and season of birth, clinical features such as age of onset and treatment response, genetic risk as indicated by family history and neuropathological findings.

Chapter 2:

How are obstetric complications associated with psychosis?

Initial, usually small, case-control studies generally reported positive associations between OCs and schizophrenia, but larger case-control and cohort studies have tended to report either a weaker association or none at all, prompting consideration that OCs may be related either to certain features of schizophrenia, such as age of onset or season of birth, or to other characteristics such as gender and family history and may increase the risk only in certain of these groups. A number of studies have reported such associations, but, once again, findings have tended to raise as many questions as answers, and results have been conflicting.

2.1 Gender differences

Many larger studies have explored associations between OCs and gender. Conflicting results have been obtained when male and female schizophrenics are compared to same-sex controls. OCs have been found to be associated with an increased risk of schizophrenia in males alone (O'Callaghan *et al,* 1992; Dalman *et al,* 1999; Hultman *et al,* 1999) and in females alone (McNeil *et al,* 1993; Verdoux & Bourgeois, 1993a; Verdoux & Bourgeois, 1993b; Takei *et al,* 1994; Kunugi *et al,* 1996; McNeil *et al,* 1996b). Many studies have found no difference in OCs between males and female schizophrenics (e.g. Cantor-Graae *et al,* 1994b; Könnecke *et al,* 2000; Thomas *et al,* 2001), as have two meta-analytic studies (Verdoux *et al,* 1997; Geddes *et al,* 1999). Byrne *et al* (2000) found different obstetric risk factors by gender, with caesarean section being associated with an increased risk for males and low birth weight with an increased risk for females. Racial differences may also be important but have been little explored. Higher rates of at least one definite OC on a slightly modified version of the Lewis & Murray scale were found for British Caucasian and Trinidadian schizophrenic subjects compared to those of African-Caribbean origin, although the difference was not statistically significant (Bhugra *et al,* 2003).

2.2 Season of birth

The observation that more schizophrenics are born in winter and spring than during other seasons was first reported by Tramer (1929). After a number of other studies also found that schizophrenic subjects were more often born in winter months, the available evidence was reviewed Bradbury & Miller (1985). Studies were divided geographically; 23 of 37 studies in the Northern hemisphere, but only 1 of 6 studies in the Southern hemisphere, showed an increase in schizophrenic births during winter. However, early studies tended to be of small sample size, included subjects with diagnoses other than schizophrenia and made comparison with several different control groups including patients with other psychiatric disorders. Only 17 of the studies used control samples born in the same years as the schizophrenic subjects, the other studies may therefore have introduced bias related to environmental factors operating in different years. However, no studies reported an excess of summer births and limiting the evidence to the methodologically more robust studies did not alter the main finding, leading the authors to assert that 'the seasonality effect can be regarded as firmly established'. The phenomenon of excess winter-born schizophrenics was likely to occur more often in patients without a family history of psychosis. No clear gender differences emerged, although there was a tendency for women to be more liable to the effect than men, and possible associations with length of hospitalisation, type of schizophrenia and marital status were inconclusive. Numerous hypotheses emerged in an attempt to explain this finding, including lower temperature, nutritional deficiencies, maternal infection in pregnancy, geomagnetic storms and seasonal variations in the prevalence of obstetric complications (Bradbury & Miller, 1985; Kay, 2004). Boyd *et al* (1986) further reviewed the evidence for a season of birth effect in 39 studies of schizophrenia. Despite the methodological problems of controlling for annual variations in the seasonality of births and

of infant mortality in the general population, the vast majority of studies confirmed a increase in schizophrenic births in winter and spring months, although various definitions of this period were used in different Northern hemisphere studies and included births from November to June, although most found the birth excess in December to March. Nine of these studies further stratified the samples by sex and, of the five which confirmed a sex difference, four found the seasonal effects to be more marked in females. Of the six studies of bipolar disorder, four found a significant excess of births between January and March or January and April.

Information on the place and date of birth of 9,348 schizophrenic subjects, identified from a state wide case register in Queensland, Australia, indicated a winter / spring (January to June) excess of schizophrenic births for those born in the Northern Hemisphere and an autumn / winter excess (April to September) for those born in the Southern Hemisphere (McGrath *et al,* 1995a). 1,299 DSM-III-R schizophrenic subjects were examined on the basis of family history, and an early spring excess of births was found to occur in those without a family history of illness compared to those with a family history (Franzek & Beckmann, 1992). A number of other studies at around the same time have confirmed the winter birth excess to be confined to those without a family history (McNeil, 1987; O'Callaghan *et al,* 1991a; Sacchetti *et al,* 1992; Dassa *et al,* 1996; Torrey *et al,* 1997).

The question of whether OCs might be related to winter birth has been subsequently explored. Machón *et al* (1987) stratified a sample of 166 subjects at high risk of schizophrenia by season and place of birth, as well as by the presence or absence of OCs. The rate of development of schizophrenia was significantly higher in those born in an urban area in winter compared to all other groups. Numbers of actual schizophrenic subjects were

small (16), but the authors suggest that maternal viral infections could occur more commonly in the pregnancies of those who are born in winter and may interact with OCs to increase the risk of schizophrenia. Dassa *et al* (1996) found OCs to occur more frequently in winter or spring-born male, but not female, schizophrenic subjects and more frequently in winter or spring-born subjects without a family history compared to those with a family history of schizophrenia, but found that season of birth was unrelated to clinical features of schizophrenia. However, no relationship was found between OCs and winter birth in a sample of 65 schizophrenic subjects compared to matched controls, but numbers were again small (O'Callaghan *et al,* 1992).

In a further analysis of a large case-control study of OCs in schizophrenia, a lower birth weight in the pre-schizophrenic subjects compared to controls was found only for those born between April and June and the effect was significant only for males and confined to births in the month of May. No differences in birth weight between subjects with affective disorder and controls were found during any month or season (Kendell *et al,* 2002). Cantor-Graae *et al* (1994b) found that winter-born schizophrenics had higher rates of OCs compared to demographically matched controls, but found no difference between schizophrenics born at other times of the year and their controls.

In contrast, fewer OCs were found in schizophrenic subjects who were born in winter compared to those born during other months (Kinney *et al,* 1994a). In schizophrenic mothers, neonatal complications occurred more often in winter and low birth weight peaked in spring, but no seasonal pattern was found for placental abnormalities, birth defects, preterm births or fetal distress (Jablensky *et al,* 2005).

By 1997 over 250 studies of the seasonality of birth effect in schizophrenia, affective disorder and other psychoses had been published and were comprehensively reviewed. The majority of studies were underpowered to find small seasonal excesses, and the use of chi-square tests in many studies was considered inappropriate for cyclical data. The Northern hemisphere studies of schizophrenia, which included over 400,000 subjects, indicated increased rates of schizophrenic births in all months between November and June, with the predominant excess occurring from December to May, with a peak in January and February. Findings in affective illness are less consistent, but indicate a likely winter / spring excess with peak birth rate in December to March for bipolar disorder, and March to May for major depression in the Northern hemisphere. Season of birth effects have also been found for autism, neurosis, personality disorder, alcoholism and eating disorders. Such seasonal effects are not consistent over time, there is evidence of changes in the peak months for conditions over several decades (Torrey *et al,* 1997). Of the studies assessing the relationship between winter birth and OCs, two found more OCs in schizophrenic subjects born in winter / spring (Machón *et al,* 1987; Cantor-Graae *et al,* 1994b) while the remaining two found the opposite, that OCs were more common in subjects not born in winter / spring (Jones *et al,* 1991; Kinney *et al,* 1994a).

A subsequent study based on large Swedish national birth cohort born between 1973 and 1980 found a higher rate of schizophrenia in those born in winter, but this failed to reach statistical significance and no relationship between winter birth and obstetric complications was found (Fouskakis *et al,* 2004). The excess of schizophrenic births in December and January was confirmed in a large study of Polish schizophrenic patients (Bembenek & Kociuba, 2005). In contrast, no increase in winter births was found in Japanese schizophrenic patients (Tochigi *et al,* 2005). Birth in winter or spring was associated with

greater length at birth, greater weight, height and head circumference at age 7 and higher scores on tests of motor development and IQ in childhood than birth in summer or autumn (McGrath *et al,* 2006). Takagai *et al* (2006) examined the risk of OCs for male and female schizophrenic subjects by season of birth, defining winter as January to March. There was no association between OCs measured on the Lewis & Murray scale and subsequent schizophrenia in those born between April and December or in females born in winter. For male schizophrenics born in winter the presence of any definite OC was associated with a significant increase in risk, OR 8.3 (95% C.I. 10.8-81.0), compared to unrelated controls. Smaller head circumference was found in winter-born male subjects, but not in winter-born females or those born at other times of the year. The authors suggest small head circumference is a proxy marker of poor CNS development, but offer no suggestions as to why this occurs more frequently in those born in winter.

Two theories are suggested to explain the excess of winter-born schizophrenics; that there is some seasonally varying factor occurring during intra-uterine or early infant life which affects the developing nervous system, or that the parents of offspring who later develop schizophrenia are more likely to conceive in spring or early summer. If the later hypothesis is correct, an excess of winter or spring births should also be found in the siblings of those with schizophrenia, but of three studies assessing seasonality of birth in siblings of schizophrenic patients, none found a significant effect, although sample sizes were probably too small (Boyd *et al,* 1986). In conclusion, a 5-8% excess of winter births has been confirmed on the basis of several hundred studies and winter birth has been more often found to be more common in subjects without a family history in the majority of studies that have assessed this issue. No consistent findings with regard to the relationship between winter birth and OCs or gender have emerged (Torrey *et al,* 1997).

2.3 Age of onset

The age of onset of schizophrenia is known to be earlier in men than in women. Several studies have investigated the possibility that increased rates of OCs are correlated with younger age of onset in schizophrenia. Increased OCs have been associated with earlier onset of illness (Smith *et al,* 1998; Könnecke *et al,* 2000), especially in males (O'Callaghan *et al,* 1992; Kirov *et al,* 1996). Rosso *et al* (2000) found hypoxia associated OCs increased the risk of early, but not late onset schizophrenia. Although Byrne *et al* (2000) found that rates of OCs did not differ overall between schizophrenic patients and controls, male subjects with onset before the age of 30 did have increased OCs in comparison to controls, although this upper age limit would be considered to be too high compared with most studies of early onset illness. Earlier age of onset in schizophrenic patients with, rather than without OCs, has been found in several studies (O'Callaghan *et al,* 1990a; Schaub *et al,* 1998; Hultman *et al,* 1999; Kotlicka-Antczak *et al,* 2001).

A Dublin case register sample of 409 patients with ICD-9 schizophrenia found a dose-response relationship between OCs and age of onset; as the number of OCs increased the mean age of onset decreased, from 33 years in those with no OCs to 22 years for those with four OCs. The effect was seen in both male and female subjects. Weaker relationships were found between age of onset, the number of affected relatives and social class (Kelly *et al,* 2004). In a study of children with schizophrenia, the subjects had higher scores than children with anxiety disorder on all three of the Parnas scales, and the finding persisted for males, but not females alone (Matsumoto *et al,* 1999). The same finding occurred in a separate group with adolescent onset (Matsumoto *et al,* 2001).

In contrast, a number of other studies have not found a relationship between OCs and age of onset of schizophrenia (Smith *et al,* 1995; Nicolson *et al,* 1999; Thomas *et al,* 2001; Ordonez *et al,* 2005). Verdoux *et al* (1997) used a meta-analytical technique to examine data from 507 schizophrenic patients and found a strong linear relationship between OCs and age of onset, which was not affected by the definition of age of onset, method of collecting obstetric data or diagnostic criteria used. Delivery complications including caesarean section and non-OA presentation were specifically associated with younger age of onset. However, the authors argue this may represent an artefact related to the age of subjects when recruited to studies, as younger onset cases are likely to have been younger at ascertainment than older onset cases. Improvements in obstetric care may have resulted in a trend towards improved survival following OCs which would differentially affect these younger subjects. Few studies have assessed this issue in non-schizophrenic psychoses, but Kirov *et al* (1996) found no relationship between a history of OCs and age of onset in 60 patients with affective psychosis.

Although not entirely clarified, studies as a whole suggest subjects with a history of more OCs, particularly males, have a younger age of onset of schizophrenia. This could be interpreted as supporting the suggestion that OCs modulate an underlying susceptibility to illness, resulting in manifestation of symptoms at an earlier age.

2.4 Clinical features

An increased rate of OCs has been found in schizophrenic patients with poorer treatment response (Alvir *et al,* 1999), those with more negative symptoms (Kotlicka-Antczak *et al,* 2001) and those with more drug induced extra-pyramidal side effects (McCreadie *et al,* 1992). OCs have been found to correlate with paranoid symptoms in a study of 189 subjects with schizophrenic, affective and other psychoses (Guerra *et al,* 2002). Low birth weight has been found to correlate with poor premorbid social adjustment (Foerster *et al,* 1991) and early brain trauma with poor school performance (Gureje *et al,* 1994). Lower birth weight was found to correlate with both poorer premorbid social functioning and cognition in male schizophrenics (Rifkin *et al,* 1994). OCs, including low Apgar scores, have been associated with negative symptoms in schizophrenia (Kotlicka-Antczak *et al,* 2001). Low birth weight has also been found to be associated with an increased risk of suicide or attempted suicide in adolescents (Mittendorfer-Rutz *et al,* 2004).

However, a history of OCs in schizophrenic subjects was found to be unrelated either to poorer premorbid functioning or to greater illness severity (McCreadie *et al,* 1994) and a decreased rate of OCs has been found to be associated with tardive dyskinesia (O'Callaghan *et al,* 1990a).

2.5 Family history

Schizophrenic patients with, and without, a family history of the condition are assumed to differ in their genetic loading for illness. It has been suggested that subjects with a lower genetic predisposition, and thus a 'negative' family history, may be more likely to have experienced environmental insult such as OCs. Studies which fail to either stratify samples by family history or control for this in their analyses may risk masking important findings occurring in certain subgroups, as argued by Murray *et al* (1985). However, identifying those with and those without a family history depends on the methods used for identifying relatives and ascertaining their psychiatric status. Some studies have ascertained only relatives with a diagnosis of schizophrenia, others have included relatives with a diagnosis of any psychosis, and some have included relatives with any psychiatric disorder. Most studies have attempted to ascertain the status of all first degree relatives, some have extended their remit to include second and third degree relatives, making comparison between studies more difficult.

A number of studies have compared the rates of OCs between 'familial' patients, who have a family history of a relevant illness, and 'non-familial' patients, who do not, to investigate whether OCs occur more often in non-familial illness. Several studies have indeed found OCs to be more common in schizophrenic patients without a family history of psychiatric disorder (Lewis & Murray, 1987; Schwarzkopf *et al,* 1989; O'Callaghan *et al,* 1990a; Cantor-Graae *et al,* 1994b) but one study has found OCs to be more common in familial schizophrenics (Walshe *et al,* 2005) while several other studies have found no difference (Nimgaonkar *et al,* 1988; McCreadie *et al,* 1992; O'Callaghan *et al,* 1992; Stöber *et al,* 1993). Among the studies showing increased rates in non-familial schizophrenia, Cantor-Graae *et al* (1994b) found an increased risk of schizophrenia in male, but not female, subjects without a

family history and a tendency for these non-familial subjects to have been born in winter, rather than during the rest of the year.

In a study of 151 patients with a range of psychotic and affective disorders and 100 normal controls, a family history of affective illness, particularly in the mother, was associated with a higher rate of OCs, in both the patients and in the control group (Marcelis *et al,* 1998). This is interpreted as suggesting the possibility that women with a predisposition to depressive disorder are more likely to experience OCs, but that this may be due to maternal behaviour such as substance misuse or poor attendance for antenatal care. Such factors may themselves increase the risk of affective disorder, which might explain why the majority of the mothers only developed affective disorder after the index birth. A family history of schizophrenia, or other psychosis showed no relationship to OCs. Thomas *et al* (2001) found a maternal history of psychosis to be highly correlated to the risk of schizophrenia in a large sample, but found no more OCs in patients with a psychotic mother compared to those whose mother remained well.

A meta-analysis of data from 674 patients also showed no relationship between OCs and family history in schizophrenic subjects, using a variety of definitions (Verdoux *et al,* 1997). This lack of relationship between the rate of OCs and a family history of psychosis suggests that OCs are not manifestations of an increased genetic liability to schizophrenia or other psychosis.

2.6 Maternal infection, malnutrition and stress

The findings of an excess of late winter and spring births in subjects with schizophrenia led to the speculation that a seasonally variable environmental factor could render developing fetuses more susceptible to this condition. Influenza was proposed as such a factor and several studies inquired whether the 1957 influenza pandemic was followed by an increase in births of individuals who later developed schizophrenia. The findings conflict, with two such studies reporting an excess of schizophrenic births following the pandemic (Mednick *et al,* 1988; O'Callaghan *et al,* 1991c) and three others finding no such excess (Kendell & Kemp, 1989; Bowler & Torrey, 1990; Crow *et al,* 1991; Susser *et al,* 1994). A further analysis of schizophrenic births following the 1957 epidemic across Scotland, England and Denmark found an increased number of births of females who later developed schizophrenia within all three databases, for those exposed in mid-pregnancy (Adams *et al,* 1993). Attention then focused on other influenza epidemics. Sham *et al,* (1992) correlated the rates of schizophrenic births in England and Wales with the national death rate from influenza for all years between 1939 and 1960. The study found increased rates of schizophrenic births in those exposed to influenza between the third and seventh month of gestation and proposed that this could explain some of the winter birth excess. In a subsequent study using similar methodology, an increase in births of schizophrenic subjects following periods of increased mortality from influenza was confined to females (Takei *et al,* 1994), and a later paper reported that the female: male sex ratio varied linearly with the prevalence of influenza, further suggesting the effect was most hazardous for female fetuses (Takei *et al,* 1995).

In a Southern hemisphere study, a similar excess of births of female schizophrenics was found four months after the onset of the 1956 influenza epidemic, but an excess of male

births was found following the 1954 epidemic and no excess occurred following the 1957 outbreak (McGrath *et al,* 1994). The study used one-tailed tests of statistical significance, rather than the more usual two-tailed (Cardno & McGuffin, 1996). A recent review of this area postulates that the maternal immune response to viral infection adversely affects oligodendrocyte function, and therefore axonal myelination, leading to white matter abnormalities in exposed fetuses (Harry *et al,* 2006).

The possibility of an interaction between maternal influenza and family history has not yet been adequately explored, but increased rates of maternal infection were found in familial schizophrenic subjects diagnosed using Leonhard's criteria, but not using DSM-III-R criteria (Stöber *et al,* 1992). Similarly, few studies have assessed relationships between maternal infection and other OCs, but infants of mothers exposed to influenza in the second trimester were found to be lighter than those not exposed, and five times more likely to have experienced other OCs in one study (Wright *et al,* 1995).

Exposure to other viral agents has also been examined. Following the 1964 rubella epidemic a cohort of individuals, born after clinically and serologically confirmed rubella infection, was compared to a non-exposed cohort on the basis of psychotic symptoms assessed when subjects were in their early twenties. Those exposed to rubella in the first trimester had a five-fold increased rate of non-affective psychotic symptoms compared to those not exposed (Brown *et al,* 2000). Exposure to poliomyelitis in the second trimester of pregnancy has been associated with an increased risk of schizophrenia in a Finnish study (Suvisaari *et al,* 1999), but was not found to increase the risk of schizophrenia or of affective disorder in an Australian study (Cahill *et al,* 2002). Interest in other respiratory tract infections and herpes simplex virus in the 2nd trimester has also been reported (Brown *et al,* 2006).

Other maternal stressors, which could also be mediated by immune mechanisms, have been investigated. Maternal exposure to famine has been found to increase the risk of later development of schizophrenia (Susser & Lin, 1992; Susser *et al,* 1996) and other studies have suggested a role for exposure to war (van Os & Selten, 1998), although these findings remain controversial (Selten *et al,* 2003). Nutritional deficiencies are known to affect the developing fetus, the most established relationship is between folate deficiency and neural tube defects (Brown *et al,* 1996). Both maternal folate and zinc deficiencies have been postulated as an aetiological mechanism in schizophrenia (Richardson Andrews, 1990; Lewis *et al,* 2005). It is proposed that infections and exposure to nutritional or environmental hazards during pregnancy induce a stress response which may adversely affect development of vulnerable regions of the fetal brain especially at the time of maximal development of regions such as the hippocampus, which are implicated in the neuropathology of schizophrenia (Cannon & Clarke, 2005).

The increased rate of OCs in schizophrenia compared to controls might also be explained by differences in the behaviour of mothers. Kawai *et al* (2004) found evidence that maternal BMI in early and in later pregnancy and the number of antenatal visits attended both contributed significantly to the finding of increased OCs in 52 schizophrenic subjects compared to 284 controls. A higher rate of schizophrenia has been found in the offspring of women with post-natal depression than in controls, which may relate to differences in maternal behaviour that might affect the risk of schizophrenia, or a higher genetic liability to schizophrenia in the offspring of these depressed mothers (Maki *et al,* 2004).

Many of the studies of prenatal viral exposure and the risk of schizophrenia have been of ecological design and have assessed crude rates of births of pre-schizophrenic subjects following pandemics, but have not studied exposure to influenza or other viruses at the individual level and few studies have yet investigated conditions other than schizophrenia (Verdoux, 2004). The literature indicates a potential effect of prenatal exposure to influenza on the development of schizophrenia and that this may be confined to females. Although large numbers of patients have been studied, the size of the effect found is small, and it is not known how such infections in pregnancy affect the risk of other OCs.

2.7 Neuropathology

Thirty years ago reports began to emerge of cerebral ventricular enlargement in schizophrenic patients, which was initially thought to represent a neurodegenerative process, 'the dementia of dementia praecox' (Johnstone *et al,* 1976; Weinberger *et al,* 1987). However, as ventricular enlargement and other structural abnormalities began to be found in individuals prior to the definite onset of illness, to be comparatively stable over time and to show no association with duration of illness (Weinberger *et al,* 1979; Andreasen *et al,* 1982; Owens *et al,* 1985), an alternative hypothesis was required to explain these findings. Abnormalities have been most consistently found for the superior temporal cortices, dorsal thalamus and hippocampal formation and range from a slight reduction in brain size to localized alterations in the morphology and molecular composition of specific neuronal, synaptic and glial populations in these areas (Harrison, 2004; Harrison & Weinberger, 2005). Smaller thalamic nuclei volumes have been found at post mortem in schizophrenic subjects compared to age and sex matched controls (Danos *et al,* 2003), although not all studies have confirmed this finding (Cullen *et al,* 2003). A greater hypothalamic volume has been found in schizophrenic subjects and their well siblings compared to controls (Goldstein *et al,* 2006). Ventricular enlargement is not, however, confined to schizophrenia but has also been found in bipolar disorder (Pearlson & Veroff, 1981; Nasrallah *et al,* 1982; Standish-Barry *et al,* 1982) and in unipolar depression (Scott *et al,* 1983).

As it was realised that the ventricular enlargement was non-progressive and present before the onset of illness, the possibility that these changes represent long standing relatively static sequelae of some, possibly much earlier, events which were themselves aetiologically important, arose. Interest in a possible relationship between OCs and the emerging

neuropathological evidence of schizophrenia grew. In one of the earliest studies to assess the relationship between early development and ventricular enlargement, blindly rated ventricular-brain ratios (VBRs) were examined in 19 schizophrenic and 27 bipolar patients for whom data on perinatal history were available. The study found a tendency for higher VBRs in those with perinatal or neonatal complications (Pearlson *et al,* 1985), and this was confirmed by Owen *et al* (1988) in a study of 61 schizophrenic patients. Several further studies reported that OCs or other measures of early physical trauma were associated with an increased VBR (Reveley *et al,* 1984; Turner *et al,* 1986), but no association between OCs and CT or MRI scan abnormalities has also been found, although the numbers of patients in these studies have been small (Nimgaonkar *et al,* 1988; DeLisi *et al,* 1988a; Reddy *et al,* 1990).

The High Risk studies have also contributed to the evidence of relationship between perinatal development and neuropathological findings in adolescent and adult schizophrenic subjects. Schizophrenic and schizotypal subjects from the Copenhagen High Risk study were compared in an attempt to explore the relationship between genetic risks, OCs and abnormal findings on CT. Using a principal components factor analysis of the CT scan findings, two factors emerged which represented multisite neural deficits and enlarged ventricles. In order to test differential genetic contribution, given that all subjects had a schizophrenic mother, their fathers were examined and enhanced genetic risk was identified in those subjects whose father was found to have a schizophrenia spectrum disorder. Ventricular enlargement was associated with increased obstetric complications, while diffuse neural deficits were associated with increased genetic liability, although numbers in each group were small (Cannon *et al,* 1989). The authors suggest that OCs, particularly delivery complications, may 'decompensate genetically vulnerable individuals to schizophrenic breakdown by adding periventricular brain damage to their existing multisite neural developmental deficits'. A

further comparison was made between those at 'super high risk' (both parents affected) and the remainder of the high risk group (one parent affected). OCs were no more common in either of these high risk groups than in controls, but genetic risk and delivery complications were both associated with a generalised increase in ventricular-brain ratios (Cannon *et al,* 1993). The authors suggest this strengthens the evidence that abnormalities in brain structure are mediated both by a genetic loading, which increases with the number of affected relatives, and by delivery complications, which show a particular association with ventricular enlargement and are not due to women with schizophrenia being at higher risk for OCs.

Cannon & Marco (1994) reviewed the evidence for structural brain abnormalities in schizophrenia and found that ventricular enlargement and reduced limbic structure volumes correlated both with family history and with obstetric complications. In this review, studies comparing schizophrenic subjects to unaffected first degree relatives showed a higher sensitivity than those using unrelated controls, suggesting that part of the deviance may reflect both genetic and environmental factors. The finding that such brain abnormalities correlated with OCs lends further support to the neurodevelopmental hypothesis, which proposes that schizophrenia is associated with a subtle lesion that is acquired early in brain development and related to both genetic and environmental risk (Cannon, 1996). The psychological and behavioural manifestations of such lesions differ over time, probably in response to normal maturation processes. In contrast, Jones *et al* (1994b) found no relationship between enlarged ventricles and either family history of schizophrenia or OCs in 121 subjects with schizophrenia or schizoaffective disorder and Smith *et al* (1996) found increased ventricular size only in those without a history of OCs.

In a comparison of adolescent subjects with schizophrenia or other psychosis and normal controls, significantly larger lateral ventricles were found in the schizophrenic subjects who also showed more of an increase in ventricular size with age compared to controls, leading to speculation that brain growth may be delayed in patients with early onset schizophrenia (James *et al,* 1999). MRI brain abnormalities in adolescence are related to prematurity (Stewart *et al,* 1999), which lends further weight to the argument that ventricular and other brain abnormalities in schizophrenia may be related to early development. Neonatal OCs were found to be related to VBR in a study of 40 schizophrenic subjects (Falkai *et al,* 2003), and reduced grey matter volume has been found to be associated with OCs in high risk subjects (Gilbert *et al,* 2003).

A recent review of 27 studies assessing neuroimaging findings, pre- and perinatal factors and markers of neurodevelopment found before the onset of illness concluded that accelerated loss of grey matter and aberrant connectivity in the prefrontal regions indicated an pre- or perinatal neurodevelopmental insult which renders the brain more vulnerable to further, probably post pubertal, maldevelopment which is associated with the onset of illness (Pantelis *et al,* 2005). Structural MRI studies have consistently found reductions in prefrontal and medial temporal cortical regions in schizophrenic subjects, including those with first episode illness. Reduced activation of these areas has been found using functional MRI (Abou-Saleh, 2006). Neuropathological findings in affective disorder are less established, but studies most frequently find hyperintensities of periventricular white matter (Sassi *et al,* 2003; McIntosh *et al,* 2005; Abou-Saleh, 2006).

The extensive research on neuropathological findings in psychoses finds differences in the brains of subjects with schizophrenia and with affective disorder. The studies provide some

support for the argument that OCs are associated with neurodevelopmental deviance and an increased risk of illness.

2.9 Neurodevelopmental markers

Minor physical anomalies (MPAs) of the head, eyes, ears, mouths, hands and feet are more common in patients with schizophrenia than in the general population (Guy *et al,* 1983; Green *et al,* 1989; Lohr & Flynn, 1993; Green *et al,* 1994a; Trixler *et al,* 2001; Sivkov & Akabaliev, 2003; Gourion *et al,* 2004), but also occur more frequently in those with learning disabilities, autism, hyperactivity and attention deficit disorders (Campbell *et al,* 1978; Alexander *et al,* 1994). Their importance to the issue of OCs in schizophrenia is that these anomalies which include high arched palate, epicanthus, adherent ear lobes, curved 5th finger, a large gap between the 1st and 2nd toes and abnormal hair whorls, are of ectodermal origin, as is the central nervous system, and are likely to represent altered morphogenesis and a disturbance in the development of the neuroectoderm in the first and early second trimesters of fetal life (McNeil *et al,* 2000a). An increased rate of such anomalies strongly suggests impaired neurodevelopment. MPAs have been found to occur more commonly in schizophrenic subjects than their well siblings (Green *et al,* 1994a; Griffiths *et al,* 1998), but have also be found to be increased in the well siblings of schizophrenic subjects compared to normal controls (Ismail *et al,* 1998; Ismail *et al,* 2000) and in the parents of schizophrenic subjects (Gourion *et al,* 2004). MPAs were found to correlate with psychosis rather than acting as markers for any specific diagnosis (McGrath *et al,* 1995b) and a review of the subject also found a lack of specificity for MPAs and schizophrenia (Murphy & Owen, 1996). The findings in affective disorders are less conclusive and at least two studies have not found any increase in MPAs in mood disorders (Lohr & Flynn, 1993; Green *et al,* 1994b). Two studies have: Trixler *et al* (2001) found increased rates of furrowed tongue in patients with bipolar disorder compared to controls, and McGrath *et al* (2002) found an excess of MPAs in both affective and non-affective psychosis compared to controls.

MPAs have been found to be more frequent in non-familial rather than familial schizophrenia (Griffiths *et al,* 1998) and in male rather than female subjects (Akabaliev & Sivkov, 2003). Only a few studies have directly examined the relationship between MPAs and OCs, but MPAs occurred more often in schizophrenic subjects with OCs than those without OCs in two studies (O'Callaghan *et al,* 1991b; O'Callaghan *et al,* 1995).

Finger prints (dermatoglyphics) are patterns of epidermal ridges, unique to each individual, which arise in fetal life and may also act as markers of fetal growth (Wheeler *et al,* 1998; Kucken & Newell, 2005). MPAs correlate with abnormal dermatoglyphics in schizophrenia and both may represent 2nd trimester developmental anomaly (Green *et al,* 1994a). Reductions in palmar a-b ridge count, a dermatoglyphic marker of early developmental deviance, correlated with a history of OCs in schizophrenic subjects, their well siblings and normal controls (Bramon *et al,* 2005). MPAs were found to correlate with enlarged lateral ventricles in a study of childhood onset schizophrenia (Hata *et al,* 2003). McNeil *et al* reviewed the literature on MPAs and schizophrenia and concluded that both MPAs and OCs are consistently found more commonly in those who develop schizophrenia (McNeil & Cantor-Graae, 2000; McNeil *et al,* 2000a). A further review of this area concludes that the findings of increased MPAs and abnormal dermatoglyphic patterns in psychosis are robust, although not necessarily specific to schizophrenia (Buckley, 1998).

Other markers of aberrant neurodevelopment in childhood and adolescence have been associated with schizophrenia, and studies of their relationship to OCs tend to support the hypothesis of schizophrenia as a neurodevelopmental disorder. Isohanni *et al* (2004) found a correlation between poor neuromotor development at the age of 1 year, as indicated by

standing, walking, talking and continence, and school success at age 16 among the Northern Finland 1966 birth cohort. Of interest is their finding of greater deviance of these early neuromotor markers in pre-psychotic subjects compared with controls. The authors suggest this is further evidence of a pre-existing neurodevelopmental abnormality in those who later become ill (Isohanni *et al,* 2004). A higher rate of schizophrenia occurred in infants who were breastfed for less than two weeks, compared with those breast fed for longer (Sørensen *et al,* 2005). Lower premorbid IQ has been found to be a risk factor for schizophrenia, but not for bipolar disorder (Gilvarry, 2000; Rapoport *et al,* 2005; Seidman *et al,* 2006), but lower IQ has also been found to be a non-specific risk for psychiatric disorder in general (Walker *et al,* 2002b).

2.10 Aetiological implications

As early findings began to suggest higher rates of OCs in high risk subjects, particularly the children of psychotic mothers, Mednick hypothesised an interaction between perinatal stress and genetic predisposition in the aetiology of schizophrenia (Mednick *et al,* 1987). This 'stress-diathesis' model suggested schizophrenia is more likely when an already genetically vulnerable individual also experiences an environmental risk such as OCs. This theory predicts that OCs would be related to the development of illness in those with higher genetic liability, i.e. those with a positive family history, and implies that those who develop schizophrenia should have higher rates of OCs than their siblings who remain well. However as studies have generally failed to demonstrate this and have found OCs to be more common in those schizophrenic subjects without a family history, a further model of how OCs influence the development of schizophrenia was required. The neurodevelopmental hypothesis proposes that schizophrenia arises in a proportion of individuals whose brains are subtly, but significantly, different from normal from a very early age. Whether an individual with such abnormalities develops schizophrenia, and at what age, depends on his or her exposure to a number of environmental factors, possibly all of small effect size, none of which is of itself sufficient, or necessary to cause illness (Murray *et al,* 1985; Leask, 2004)

As evidence emerged of a relationship between early development, CT scan abnormalities and schizophrenia, hypotheses regarding possible mechanisms by which OCs could affect CNS development evolved. Intra- or periventricular haemorrhage commonly occurs in premature infants, the latter can cause periventricular necrosis with absorption of the damaged tissue into the lateral and third ventricles, leading to their enlargement. In addition, the cerebral cortex, temporal lobe and hippocampal structures may be particularly vulnerable

to fetal hypoxia in infants born at term (Hill, 1991; Cannon *et al,* 2002b) and have been consistently shown to be abnormal in schizophrenia. Such hypoxic-ischaemic injury may occur either at delivery or during pregnancy if placental functioning is compromised, for example by maternal disease, antepartum haemorrhage or poor nutrition in pregnancy. As early as 1970 Mednick proposed that birth hypoxia led 'to defective hippocampal functioning' which could at least predispose an individual to schizophrenia and may have a role in the development of illness in those with greater genetic risk, despite the study having found such asphyxia in only one of 19 subjects (Mednick, 1970, McNeil & Kaij, 1978). An alternative hypothesis is that the hippocampal damage may be mediated via autoimmune mechanisms, as elevated anti-nuclear and cardiolipin antibodies have been found in first episode neuroleptic naive schizophrenic subjects (DeLisi & Wyatt, 1982; Chengappa *et al,* 1991). Autoantibodies to non-CNS tissues have been found more commonly in schizophrenic subjects with OCs than in those without (Chengappa *et al,* 1995). As autopsy studies of the brains of schizophrenic subjects began to reveal cryroarchitectural abnormalities, the idea that schizophrenia may be a disorder of the development of the brain in very early life, and that such maldevelopment may be linked to conditions in-utero or complications of delivery was suggested (Murray *et al,* 1988). The limbic system, mainly the hippocampal formation and cingulate gyrus, was first proposed by Broca as of primary importance in the processing of the emotional components of cognitive behaviour (Broca, 1878). Abnormalities of this area at post mortem examination have been associated with schizophrenia (Benes, 2000). The smaller hippocampal volume and decreased neuronal population found in schizophrenia are compatible with a developmental abnormality, possibly disordered migration of neurones (Murray *et al,* 1992).

Most of the cells that give rise to brain structures are generated within the first trimester of fetal life in areas around what will later become the ventricular system (Lewis, 1989). Early brain development involves the proliferation and migration of neurones from periventricular to cortical areas, axonal and dendritic proliferation, axonal myelination and programmed cell death or apoptosis. These processes all begin in utero, with proliferation and myelination continuing into the first few years of infant life. All of these processes may be adversely affected in schizophrenia; disordered cell migration is reflected in cryroarchitectural abnormalities of the cerebral cortex in schizophrenia and abnormal apoptotic processes could give rise to reduced VBR and enlarged ventricles without causing gliosis (de Haan & Bakker, 2004). Neuronal synapses are present as early as the 60th day of gestation, the process of axonal myelination begins in mid-pregnancy at around 22 to 24 weeks but is still largely absent from the cerebral hemispheres at birth (Boog, 2004). Possible mechanisms by which OCs might have an aetiological effect include fetal hypoxia, which reduces nutrient delivery to the developing fetal CNS, prematurity, which increases the risk of periventricular haemorrhage and hypoxia at delivery which may result in damage to the hippocampus and cortex (Dalman *et al,* 1999).

The issue of the relationship between OCs and pre-existing fetal abnormality is of interest. The argument that OCs may be increased in individuals who later develop schizophrenia because earlier fetal maldevelopment has rendered the fetus 'clumsy' and less able to manoeuvre itself into an optimal position for delivery as suggested by Goodman (1988) has been tested. McNeil & Cantor-Graae (1999) argued that if this 'epiphenomenon hypothesis' was correct, pre-schizophrenic individuals with labour and delivery complications (LDCs) would show evidence of earlier maldevelopment as reflected in higher rates of MPAs, small head size and congenital abnormalities, and a positive correlation between PCs, which may

interfere with normal fetal development, and LDCs would be evident. Re-examining previously gathered data on singleton and twin births of individuals who had schizophrenia or were born to schizophrenic mothers, did not find a correlation between PCs, small head size at birth or congenital malformations and LDCs. The authors suggested 'parallel aetiological paths' of prenatal maldevelopment and perinatal trauma, which either operate independently or interact with each other to increase the risk of schizophrenia.

Rosso *et al* (2000) suggested that pre-schizophrenic individuals with a history of hypoxia may have reduced numbers of neurons and synapses in temporal regions and may be at greater risk that synaptic pruning in adolescence may further reduce temporal lobe neuronal activity to cross a threshold into psychosis. Cerebral palsy, once thought to reflect damage at birth, is now also considered to have such prenatal origins (Nelson & Ellenberg, 1986; Lamb & Lang, 1992). Attempts to distinguish between complications mediated through disturbance of fetal development, such as pre-eclampsia which could manifest through intrauterine hypoxia, and complications associated with acute hypoxia at birth, revealed potential effects for both (Dalman *et al,* 2001). OCs may therefore interact with second trimester maldevelopment of fetal brain structures in individuals who later develop schizophrenia (Lyon *et al,* 1989).

Hypotheses of schizophrenia as a neurodegenerative disease are held to be unsupported by the current evidence of a lack of gliosis associated with reduced cortical brain tissue and a failure to find progressive changes over time (de Haan & Bakker, 2004). Two further possibilities, that schizophrenia is a disorder of maldevelopment confined to the early development of the brain, or that schizophrenia is the result of a progressive developmental disorder now attract attention. There is considerable support for schizophrenia being a

disorder of neurodevelopment including the evidence of disturbed neuronal migration leading to cryroarchitecture abnormalities, increased MPAs in schizophrenia, reflecting abnormalities of second trimester development, a possible relationship between OCs and schizophrenia, impairments of intellect and social functioning prior to the development of psychosis and enlarged ventricles and other neuropathological abnormalities which also occur before the formal onset of illness. Axonal myelination and synaptic pruning occur during childhood and continue into adolescence and early adulthood in some brain areas, particularly the hippocampus and dorso-lateral prefrontal cortex (DLPFC), which has led to speculation that damage to such areas becomes apparent only when adolescent myelination of these areas occurs and this is offered as an explanation of why schizophrenic symptoms do not develop until this period (Weinberger *et al,* 1987).

The neurodevelopmental model of schizophrenia proposes that abnormal neuronal migration manifests in premorbid cognitive impairment, personality traits and CT scan abnormalities in affected individuals. It suggests that in adolescence, abnormal myelination, pruning or other maturational processes cause the underlying abnormal neuronal circuitry to become active, which renders the individual susceptible to incorrect interpretations of sensory stimuli which results in the formation of symptoms such as delusions and hallucinations, thus triggering the first episode of psychosis (Murray *et al,* 1988). However, while the neurodevelopmental model remains an attractive explanation for schizophrenia of early onset, it accounts best for male subjects who demonstrate poor premorbid social adjustment and cognitive performance and have enlarged ventricles and abnormalities of limbic and hippocampal areas (Olin & Mednick, 1996). It may not explain schizophrenia of later onset, transient schizophrenia-like psychoses and those psychoses with better prognosis (Pilowsky *et al,* 1993), which has led to consideration of schizophrenia as a condition of heterogeneous aetiologies with genetic

loading, prenatal viral infection and OCs all potentially contributing to the risk (Tsuang & Faraone, 1995). Some of the same arguments have been applied to affective disorder, especially bipolar illness, but evidence so far is weaker than for schizophrenia (O'Keane & Scott, 2005).

2.11 Conclusions

OCs have been associated with schizophrenia in different populations, including adult schizophrenics, adolescent and childhood onset schizophrenics, the children of schizophrenic mothers, high risk offspring who develop schizophrenia and schizophrenic twins (Brixey *et al,* 1993). Obstetric complications, particularly markers of fetal maldevelopment and those that occur around the time of delivery, appear to be related to schizophrenia and possibly to other psychotic conditions, but the nature of the relationship remains unclear. There is widespread heterogeneity in the nature of the OCs associated with schizophrenia, which include maternal disease during pregnancy, delivery complications and measures of intra-uterine growth retardation and poor fetal condition.

OCs correlate with many social and maternal factors (Baird, 1975; Wildschut, 1999). Relationships exist between OCs; e.g. pre-eclampsia tends to correlate with low birth weight, operative delivery and poor neonatal outcome. OCs also correlate with each other (MacGillivray, 1958; Dalman *et al,* 2001), with second trimester influenza infection (Wright *et al,* 1995) and with winter birth (Cantor-Graae *et al,* 1994b), all putatively associated with schizophrenia. OCs are more common in males rather than females (Eogan *et al,* 2003). In case-control studies, the choice of controls may lead to spurious positive (Kendell *et al,* 1996; Buka *et al,* 2000; Bhugra *et al,* 2003) and negative findings (Cantor-Graae *et al,* 1998). Following early reports of a strong relationship between OCs and schizophrenia, evidence has weakened in recent years, as study design has moved from case-control to population based investigation, and as studies have become better powered and better able to control for confounding (Dalman *et al,* 1999; Cannon *et al,* 2002a).

Despite decades of research, the non genetic predictors of schizophrenia remain elusive. Associations with later development of schizophrenia have been found for OCs, but also for impaired neuromotor development, cognitive impairment, social functioning and cannabis misuse (Isohanni *et al,* 2005). The importance is not so much whether these variables are associated with the development of schizophrenia and of other psychosis, but whether the association is of aetiological significance and whether the effect size and predictive power are relevant in the development of future hypotheses of the aetiology of psychosis. As methods of investigation have improved, interest has shifted from the original concept of injury at birth, to a greater focus on the prenatal period and factors affecting fetal growth and development, including maternal infection and stressors in mid-pregnancy and neonatal factors which themselves may be consequences of abnormal fetal development.

Division of OCs into those affecting fetal growth and development, other complications of pregnancy such as bleeding or pre-eclampsia and complications of labour and delivery (Cannon & Clarke, 2005), or division into complications causing hypoxia-ischaemia and those related to infection / inflammation (Rees & Inder, 2005) may shed further light on the aetiology of psychosis, particularly schizophrenia (Zornberg *et al,* 2000a). Boog (2004) has suggested that exposure to maternal infection, malnutrition or stress increases the risk of abnormal fetal neurodevelopment, that pregnancy complications including Rhesus incompatibility, bleeding, pre-eclampsia, premature rupture of the membranes and preterm birth increase the risk of schizophrenia and that complications of labour and delivery resulting in acute asphyxia may result in earlier onset of the condition.

It seems likely OCs are a significant aetiological factor in schizophrenia which interact with genetic vulnerability factors to produce illness. OCs are clearly not necessary and are probably insufficient in themselves to cause illness, and are likely to act by interaction with genes for the disorder. Because probands' unaffected siblings are more likely than unrelated controls to carry such genes, comparisons which include both unaffected siblings and unrelated controls may provide a sensitive test of the role of OCs in schizophrenia, and perhaps in other psychotic disorders.

Chapter 3:

Method

3.1 Study design

In order to address the role of OCs in schizophrenia and other psychosis, a case-control study examining the occurrence of OCs in subjects with schizophrenia and in those with non-schizophrenic psychosis was undertaken. The study, which is observational and based on registers of established validity and reliability, was designed to examine the following research questions:

1. Are OCs more common in the birth histories of patients with schizophrenia compared to normal controls, and if so, what is the risk associated with OCs for the development of schizophrenia?
2. Are OCs more common in the birth histories of patients with other psychotic conditions compared to normal controls, and if so, what is the risk for the development of these conditions following OCs?
3. Is any increase in the rate of OCs related to socio-economic status (SES), maternal factors such as marital status, age at delivery, parity, or maternal behaviour?
4. Do OCs increase the risk of psychotic disorders when any identified confounding factors have been controlled for?
5. Is any increased risk following OCs specific to schizophrenia?
6. Do OCs increase the risk in subjects compared to their unaffected siblings, and if so, is this effect disease or gender specific?
7. Do OCs increase the risk of schizophrenia preferentially in those born in winter / spring rather than at other times of the year?
8. Do OCs increase the risk of early onset psychosis?
9. Do OCs increase the risk of psychosis preferentially in non-familial subjects?

3.2 Aims

In designing the study, it was considered preferable to ascertain OCs on the basis of contemporaneous birth records rather than maternal recall, to compare subjects to their well siblings and to unrelated controls, and to have sufficient numbers to detect increases in risk of illness in keeping with estimates from the current literature which suggest ORs of approximately two (Geddes & Lawrie, 1995; Kunugi *et al,* 2001; Cannon *et al,* 2003). A case-control design was chosen based on a representative sample of patients with a diagnosis of psychotic disorder confirmed by examination of their psychiatric case records, with obstetric complications and potentially confounding demographic factors identified from a comprehensive local database. The study relied on linking two existing registers in North East Scotland, the Aberdeen Maternity and Neonatal Data Bank (AMNDB) and the Grampian Psychiatric Case Register (GPCR). The work commenced in 1998 and proceeded though seven stages:

1. The identification of a cohort of subjects born over a twenty year period with an established diagnosis of a functional psychosis and with birth records available in the AMNDB.
2. Confirmation of the diagnoses of these index cases by detailed scrutiny of all volumes of their case records, with data extracted for OPCRIT analysis leading to verification of a cohort of subjects with diagnoses of schizophrenia, affective psychosis and other functional psychosis using standardised diagnostic criteria.
3. Identification of the birth records of these index cases within the AMNDB.
4. Identification of the siblings of each index case and ensuring they did not have any diagnosis of psychosis recorded in the GPCR.

5. The selection of five matched controls for each index case and each sibling, who also had no diagnosis of psychosis recorded in the GPCR.
6. The extraction of relevant obstetric data and data on likely confounding factors for all index cases, siblings and control subjects from AMNDB.
7. The analysis of the data and testing of the research questions listed above.

3.3 Overview

Patients with psychotic illness were first identified from the GPCR and then matched to the AMNDB. The psychiatric case records of potential subjects with birth records within the AMNDB were scrutinised and data extracted for diagnostic analysis using OPCRIT version 3 (McGuffin *et al,* 1991). For confirmed cases who were singleton births, all siblings were identified and included if they had no diagnosis of psychotic illness recorded in the GPCR. For each case and each sibling, five control subjects, also without a history of psychosis within the GPCR were identified. The obstetric histories of patients with schizophrenia, affective disorders and other functional psychosis were then compared to controls and to their siblings. The prevalence of each obstetric complication recorded in the AMNDB for index cases, siblings and controls was compared, after collapsing OCs into simple categories. Chi-squared tests were used to compare the rates of OCs between cases, siblings and controls. Analyses were conducted together and separately by sex. Univariate analyses were used to identify any continuous factors which differed between cases and controls. Multivariate procedures were used to test confounding by factors such as gender, maternal age, parity and socio-economic status. For any identified OC, crude odds ratios for each illness by each obstetric complication were calculated. Logistic regression models were then used to adjust the odds ratios for confounding factors. Similar analyses were carried out with subgroups delineated by season of birth, age of onset and family history.

The study was approved by the Grampian Ethics of Research Committee in 1997. Case note data was extracted and diagnoses made between 1998 and 2000. Identification of siblings and controls and extraction of data from the AMNDB was completed by 2002.

3.4 Setting and registers used

The study utilised two databases that store information for residents in the Aberdeen area of North-East Scotland, where the local population is served by a single psychiatric service based at the Royal Cornhill Hospital and a single obstetric service based at the Aberdeen Royal Maternity Hospital. For 35 years, between 1962 and 1997, the Grampian Psychiatric Case Register (GPCR) recorded psychiatric diagnosis on episode opening and closing, including on every admission to, and discharge from, an in-patient psychiatric facility. A full time case register officer was employed to check coding by ICD criteria, to maintain the GPCR and to interrogate it for research purposes.

Despite the widespread use of case registers, there has been relatively little investigation of their diagnostic reliability. In a study completed prior to the instigation of the work presented in this thesis, I investigated the diagnostic reliability of the GPCR by comparing GPCR diagnosis and that derived from case note analysis using OPCRIT in 449 subjects (McConville & Walker, 2000). This indicated only modest agreement between GPCR and case note derived diagnosis (kappa=0.52). The sensitivity and specificity of a single GPCR diagnosis of schizophrenia were 0.52 and 0.97 respectively; those for affective disorder were 0.69 and 0.84. When multiple GPCR diagnoses were taken into account, sensitivity improved to 0.83 for schizophrenia and 0.87 for affective disorders, with only small decreases in specificity to 0.95 for schizophrenia and 0.76 for affective disorder. The study therefore concluded that GPCR diagnoses were insufficiently robust to stand alone and should be used only as a screening method to identify potential subjects whose diagnoses should then be more scrupulously ascertained. The study also indicated that the use of multiple GPCR diagnoses rather than a single diagnosis was more reliable. This previous

work informed the decision in the current study to select subjects with diagnoses of psychosis recorded on more than one occasion in the GPCR and to subject the case notes of all potential subjects to analysis using OPCRIT.

Maternity services in North-East Scotland are similarly provided by a single service which has developed a comprehensive database, the Aberdeen Maternity and Neonatal Databank (AMNDB), which records information on all deliveries, initially in Aberdeen city, then expanded to include surrounding rural areas. The AMNDB has existed since 1950 and records all births to Aberdeen residents, including to those delivering at home as well as those delivering at the Aberdeen Royal Maternity Hospital and its satellite maternity homes. The AMNDB records 67,084 births registered at Aberdeen city addresses for the years 1954-1973. The AMNDB relies on information obtained at the time of pregnancy and delivery, rather than retrospectively collected information. It records demographic variables for all births, including the mother's education and mother's partner's occupation, which indicate personal measures of socio-economic deprivation. The AMNDB relies on data collected by obstetricians, midwives and nurses at routine antenatal clinic visits and at delivery. Data are entered into the AMNDB following delivery by trained data entry and coding staff, using a consistent coding regime and a data entry programme which subjects data to a large number of validation checks on entry. Data is regularly extracted for quality assurance purposes which results in a low number of errors and allows for the few discrepancies found to be corrected (Samphier & Thompson, 1981; Department of Obstetrics & Gynaecology, 2006). Pregnancy variables recorded include maternal age, parity, bleeding, hypertensive disease and diabetes during pregnancy. Infant variables recorded include gestational age, presentation, head circumference, birth weight, birth length, method of delivery and Apgar scores at one and five minutes after birth. Original records have been kept and can be

consulted. Stringent and consistent criteria are employed throughout for the coding of gestational length, birth weight and pregnancy complications. When metrication was introduced for the recording of height and weight, the earlier records were all converted. Within the AMNDB, a linkage system allows the identification of each woman's complete reproductive history, the computerisation of the entire system in the 1980s allows automated identification of all births to individual women. The use of the AMNDB has several advantages as it records all reproductive events to women resident in a defined geographical area with a relatively stable population and records a wide range of obstetric events and social class data.

3.5 Details of the psychiatric sample and matching to the AMNDB

All individuals with a diagnosis of any non-organic psychosis recorded on more than one occasion in the GPCR, who were born in the period January 1st 1954 to December 31st 1973, were initially ascertained. Restriction of this initial cohort to those with a psychosis diagnosed on two, rather than on only one occasion, was undertaken as a high proportion of subjects with a single diagnosis of a psychotic disorder were likely not to meet more stringent criteria for diagnosis. There were resource limitations on the number of case notes that could be examined within the study period, it was therefore necessary to ensure that a reasonable proportion of those examined would meet diagnostic criteria. Potential index subjects with diagnoses of schizophrenia and related conditions (ICD-9 295.0-295.9) and affective disorders (ICD-9 296.0-296.9) who met these initial criteria were initially matched to the AMNDB on the basis of birth surname, sex, date and place of birth. In those who were initially matched, confirmation of each subject's identity was sought using the mother's birth surname or parental first names. Potential subjects born from multiple pregnancies were excluded, as different intrauterine conditions apply and infants are of lower birth weight.

For all singleton subjects identified within the AMNDB, the psychiatric case records were located and all volumes were examined by two trained raters who extracted data for OPCRIT analysis generating lifetime diagnoses by ICD-9, DSM-III-R and RDC criteria (McGuffin *et al,* 1991). Data was collected on standardised data collection sheets and inter-rater reliability between the two raters was assessed in a random sample of 50 subjects. The case note rating and OPCRIT analysis generated three groups of subjects: those with schizophrenia, those with affective disorder and those with any other non-organic psychosis. These are the index

cases. Data was collected from the psychiatric case notes on age of first admission, family history, severity of illness and response to medication.

The siblings of each index case were then identified within the AMNDB and cross-referenced to the GPCR. Siblings were defined as other singleton offspring born to the same mother who had no GPCR record of a diagnosis of any psychotic illness made at any time, although non-psychotic disorder was not an exclusion criterion. Index cases were expected to have a variable number of siblings identified, and the sibling group therefore represents a 'high risk' sample, rather than paired data. For each index case and for each sibling, five controls were randomly selected from all other singleton births of the same sex, born in the same year and calendar month as the index case or sibling. Potential controls were excluded if they had a diagnosis of any psychotic disorder within the GPCR and another control randomly chosen. For all births, social class was derived from the Registrar General classification of husband's or male partner's occupation (OPCS, 1991). The use of ICD-9 diagnostic criteria had been decided a priori for all analyses, but it was intended to reanalyse potential findings of interest using DSM-III-R and RDC criteria.

Maternal variables extracted from the AMNDB for all cases, siblings and controls included marital status, date of marriage, home address and postcode, occupation, husband's occupation, father's occupation, height, race, blood-group, cigarette smoking habits, parity, date of booking and history of induction of ovulation. Pregnancy variables recorded included antepartum haemorrhage, pre-eclampsia, duration of pregnancy (gestation), date of delivery and date of discharge from hospital. Labour variables recorded included whether labour began spontaneously or was induced, fetal presentation, whether delivery was spontaneous vaginal, instrumental or via caesarean section, the duration of each stage of labour, the

method of placental delivery, placental weight, maternal blood loss and type of perineal wound. Fetal and neonatal variables recorded included Apgar scores at one and five minutes after delivery, birth weight, crown-heel length, crown-rump length, occipito-frontal circumference and feeding habits.

3.6 Data analysis

Raw data for each obstetric complication recorded by the AMNDB were collapsed into dichotomised categories. Antepartum haemorrhage was categorised as present if any degree of bleeding during pregnancy occurred. Pre-eclampsia was categorised as present if moderate or severe, but absent if only mild hypertension occurred. Labour onset was classified as abnormal if labour was induced for any reason or if an elective caesarean section (c/s) was performed. Delivery was categorised as abnormal if instrumental (e.g. forceps, Venteuse) or emergency c/s. Abnormal fetal presentation was defined as any presentation other than occiput anterior (OA). Placental delivery was defined as abnormal if not by maternal effort alone, this included defining controlled cord traction (now the standard practice) as abnormal. Apgar scores of < 7 at one minute and < 8 at five minutes were deemed abnormal.

Birth weight in grams is standardised for sex, parity and gestational age when data are entered into AMNDB, to give a standardised birth weight score (SBS) with a mean of 0 and standard deviation of 1 (Campbell *et al,* 1993). Investigation of weight controlled for these factors is more meaningful than raw birth weight data (McNeil, 1995). However, maternal height also influences birth weight, so the SBS was further controlled for maternal height using standardised residuals of maternal height on SBS, creating a new measure, height standardised birth weight score (HSBS) which also had a mean of 0 and a standard deviation of 1. Low birth weight in this study was defined as HSBS of less than -2.

Several meta-analyses estimate the risk of schizophrenia to be doubled following OCs (Geddes & Lawrie, 1995; Kunugi *et al,* 2001; Cannon *et al,* 2003). Power calculations to

ascertain sample size required were carried out using a standard online calculator (Pezullo, 2007). For comparison with control subjects, given the study design of five controls per subject, the numbers required to achieve 80% power to detect a doubling of risk of illness with 95% confidence, based on a population incidence of OCs of 7% were 180 subjects and 902 controls. If the incidence of OCs were 10% in the control population, the numbers required to detect the same level of difference in the subjects became 121 subjects and 604 controls. For comparison between subjects and siblings, assuming equal numbers of siblings to subjects, 328 subjects would have been needed to detect a doubling of OCs in subjects, based on a population incidence of OCs of 7%. If two siblings were ascertained per subject, the numbers required would be 236 in each group. If the population incidence of OCs were 10%, the numbers of subjects required would be 219 if one sibling and 158 if two siblings per subject were ascertained.

All variables of interest were recorded as present or absent and are thus categorical, dichotomous variables. Data were analysed using SPSS version 13.0 for Windows (SPSS inc., 2004) and two-tailed tests of statistical significance were used throughout. The prevalence of each demographic and obstetric variable was compared between index subjects and controls, between index subjects and their well siblings and between siblings and sibling-controls using ANOVA for continuous data and Chi-squared (χ^2) tests for categorical data. Crude odds ratios were calculated for the risk of illness for both sexes together and for males and females separately. After identification of possible confounders, logistic regression analyses were run to determine factors affecting the risk of psychosis (Hosmer & Lemeshow, 1989; Tabachnick & Fidell, 2001). In order to focus on potential gender differences, in particular a greater propensity to obstetric complications and to schizophrenia in males, and because siblings were not matched to subjects on the basis of sex, index cases were compared

only to their same-sex siblings rather than to the total sibling group. Corrected odds ratios for psychosis by each demographic variable and obstetric complication were calculated using standard logistic regression models using all other categorical predictor variables entered simultaneously which allowed the model to be controlled for all other variables. Conditional logistic regression, which fits and analyses binary outcome data with one or more predictors, where observations are not independent, was used to make comparisons between index cases and siblings, again controlling for all other variables.

Data were analysed for all psychoses together and separately for schizophrenia, affective disorder and other functional psychosis. Analyses of OCs by age of onset, family history and season of birth were carried out using similar methods. Torrey *et al* (1997) suggest that seasonality effects should be assessed by month, rather than season, of birth as any fluctuations that happen to occur in the last month of one quarter and first month of the next quarter could be lost by such an approach, these data were therefore initially examined by month of birth.

Chapter 4:

Main results

4.1 Psychiatric characteristics of the sample

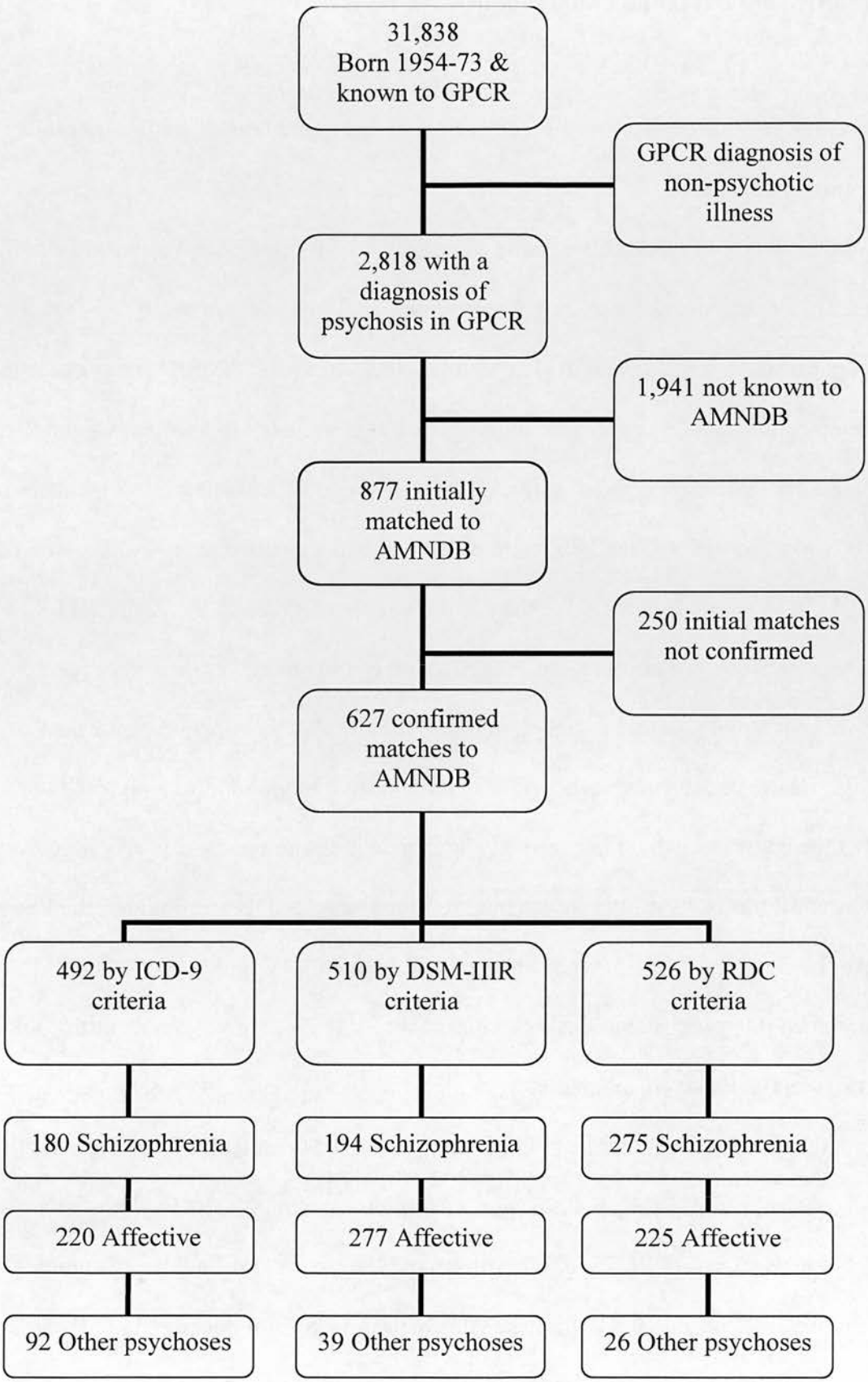
The AMNDB records 67,084 births between 1st January 1954 and 31st December 1973. The GPCR records 31,838 individuals born during the same period, of whom 2,818 had an admission or discharge diagnosis of schizophrenia, affective psychosis or any other functional psychosis. Initial matching to AMNDB on the basis of birth surname, gender, date and place of birth found a potential 877 of these 2,818 listed. In order to be confident that the birth record was that of the potential subject, matching was confirmed only if the psychiatric case notes recorded parental details including mother's birth surname, first name or father's first name and these agreed with the information in AMNDB. This final matching reduced the sample to 627 (296 male & 331 female) index cases. An initial power analysis determined that 435 cases of psychosis would be required to show a doubling of the incidence of OCs, at 80% power at a significance level of $p < 0.05$. Diagnostic analysis using OPCRIT at which time index cases were between 25 and 46 years of age (mean age 37.7 s.d.5.25), indicated 492 cases of psychosis by ICD-9, 510 by DSM-III-R and 526 by RDC criteria. Inter-rater reliability between the two researchers who examined the psychiatric case notes was assessed in a random sample of 50 cases and was found to be reasonable (kappa = 0.71).

By ICD-9 criteria there were 180 cases of schizophrenia (including schizoaffective disorder), 220 cases of affective disorder (bipolar and unipolar) and 92 cases of other functional psychosis. Although potential cases had been selected from the GPCR on the basis of a diagnosis of psychotic illness on more than one occasion, 135 cases failed to meet diagnostic criteria for any ICD-9 diagnosis of interest. The group who met ICD-9 criteria for affective disorder had one of ten diagnoses which included bipolar disorder and several categories of

mania and depression. Thus, this group comprised a mixture of unipolar and bipolar patients, as well as those with psychotic and non-psychotic forms of affective illness. The breakdown by different diagnostic criteria is indicated in figure 1.

The siblings of index cases were selected on the basis of having no diagnosis of psychosis in GPCR and are referred to as 'well' siblings, although it is acknowledged that individuals in this group may have non-psychotic psychiatric disorder.

Figure 4.1 Identification of the psychiatric sample



4.2 Obstetric characteristics of the sample

The 627 potential index cases had 1,047 siblings, with the numbers of siblings per index case ranging from none to nine. 86% of the index cases had at least one sibling. These 1,674 individuals each had five controls making a total of 10,044 births potentially available for analysis. Data on parity, antepartum haemorrhage (APH), pre-eclampsia, type of labour, type of delivery and birth weight were available for all 10,044 cases. Marital status of the mother was available in all but one case. The majority of births occurred to married women (94.5%), the remainder to women who were single (3.9%), divorced or separated (1.0%), cohabiting (0.4%) or widowed (0.1%) and these were combined into a single category of 'not married'. The social class of each mother at the time of delivery is recorded in the AMNDB for each birth. This is derived primarily from the occupation of the mother's husband or partner, for women without a male partner social class is derived from the occupation of the head of household. These data represent the social class of each mother and therefore each individual subject of the study at birth, rather than any aggregate measure per family, and were available for 81.8% of all births. Social class is categorised in the AMNDB according to the Registrar General classification as I, II, III (non-manual), III (manual), IV and V (OPCS, 1991). These were combined into two categories; social class IV or V and other. 28.6% of births, for which social class data were available, were of social class IV or V. Placental delivery data were available for 99.7%, maternal height, which was used to calculate height standardised birth weight scores, for 99.5% of cases, gestational duration for 94.2%, fetal presentation for 90% and Rhesus status for 88.5% of all births. Apgar scores at 1 minute and 5 minutes were available for 55.4% of the 10,044 births, as this measure was introduced only in the late 1960s and came into widespread use in the 1970s. There were no differences in the proportion of each group for which Apgar scores were available. A standardised birth weight

score (SBS), with a mean of 0 and s.d. of 1 is calculated when data are entered into AMNDB. This measure controls for sex, parity and gestation and was present for 88% of births. SBS was further controlled for maternal height using standardised residuals of maternal height on SBS to create a height standardised birth weight score (HSBS) which was also available for 88% of all births. This measure was preferred to raw birth weight data, which is known to correlate with parity, gestation, sex and maternal height, and has been widely used in previous studies based on AMNDB data.

Rhesus negative status occurred in 19.5% of mothers for whom data were available. Antepartum haemorrhage (APH), defined as any bleeding during pregnancy including placenta previa and placental abruption, occurred in 312 (3.1%) of the 10,044 deliveries. Pre-eclampsia is classified in the AMNDB as absent, mild (hypertension only) or moderate to severe; the frequency of any grade of pre-eclampsia was 18.9%. Simple hypertension without other signs of pre-eclampsia is common, therefore only moderate to severe pre-eclampsia or eclampsia was considered to be an OC; this occurred in 2.1%. Gestation was recorded as the number of completed weeks of pregnancy and was classified as abnormal if less than 37 weeks, which occurred in 3.4% of births. Type of labour is recorded as spontaneous, induced or elective c/s and was dichotomised into spontaneous or intervention (induced or elective c/s), which occurred in 26.5% of cases. Fetal presentation was recorded as occiput anterior (OA), posterior (OP), transverse (OT), lateral (OL), breech, face, brow, shoulder, transverse, compound and other. These data were collapsed into OA and non-OA, with non-OA presentation occurring in 4.1% of births. Type of delivery is categorised in the AMNDB as spontaneous vaginal delivery (SVD), vaginal instrumental delivery (forceps or Venteuse) and emergency caesarean section (c/s). These were collapsed into two categories with any intervention delivery occurring in 15.2%.

Placental delivery (stage III labour) is categorised in the AMNDB as maternal effort, controlled cord traction or manual removal under anaesthetic. This was re-categorised into maternal effort and any intervention, the latter occurring in 4.9% of births. Apgar scores at one and five minutes were recorded as interval data and were dichotomised into two categories of normal and abnormal; the score at 1 minute was normal if seven or greater, and that at five minutes was normal if eight or greater. Poor Apgar score at 1 minute occurred in 25.6% and poor Apgar score at 5 minutes in 17.6% of births for which these data were available. The height standardised birth weight score (HSBS) has a mean of 0 and s.d. of 1, and was characterised as abnormal if <-2, this measure being referred to in the subsequent analyses as 'low birth weight'. Low birth weight, by this definition, occurred in 2% of births.

For the years of interest the AMNDB does not reliably record information on maternal diabetes in pregnancy, crown-rump length or head circumference. Data on maternal smoking is present only for 3,202 (31.9%) of births and was not analysed further. A description of each variable included in the subsequent analyses is shown in table 4.2 below. Although a mother delivering for the first time is, strictly speaking, nulliparous until her infant is born, the term primiparous is used to refer to a woman giving birth for the first time and the term multiparous is used to refer to those giving birth for a second or subsequent time in the analyses and discussion.

Table 4.2 Demographic and obstetric variables analysed

	Variable	**Definition**
Demographic	Maternal age at delivery	Age of mother in whole years on date of delivery
	Mother not married	Maternal marital status single, divorced, separated, co-habiting or widowed
	Low social class	Socio-economic class IV or V by Registrar General classification
	Primiparity	Referring to a mother giving birth for the first time
Obstetric	Mother Rhesus negative	Mother's Rhesus status negative (blood group A-, B-, O- or AB-)
	Pre-eclampsia	Any grade of pre-eclampsia except simple hypertension only
	Bleeding in pregnancy	Any degree of antepartum haemorrhage, including placental abruption and placenta previa
	Prematurity	Gestation of less than 37 completed weeks
	Labour induced or c/s	Labour induced for any reason or elective caesarean section
	Non-OA presentation	Any fetal presentation that was not occiput anterior (OA)
	Intervention delivery	Delivery using any instrument or emergency caesarean section
	Low birth weight	Height standardised birth weight score of <2 s.d. below the mean
	Apgar at 1 minute <7	Apgar score at 1 minute after delivery of <7
	Apgar at 5 minutes <8	Apgar score at 5 minutes after delivery of <8
	Any OC	Any one or more of the above ten obstetric complications

4.3 Outline of subsequent analyses

Four main analyses of the data were carried out to assess the effects of obstetric complications on the risk of psychotic illness. Firstly, all the three diagnostic groups were pooled together into an 'all psychoses' group, then each of the three diagnostic groups of schizophrenia, affective disorder and other functional psychosis were examined separately. The term 'all psychoses' is retained as a practical abbreviation for the pooled group meeting diagnostic criteria for schizophrenia, affective disorder or other functional psychosis, although it is acknowledged that this group contains individuals with non-psychotic affective disorder and this issue is addressed further in chapters 6 and 7. Each analysis begins with an assessment of the rate of each demographic variable and OC in each of the four groups, the index cases, the index controls, the well siblings and the controls of the well siblings. Comparisons across these groups indicate which variables are likely to be of interest. Crude odds ratios are then calculated, by comparing index cases with controls, index cases with their well siblings and well siblings with their own controls, referred to as 'sibling-controls'. The intention behind this was to assess if there are differences between siblings of patients and a control population, which could have an impact on apparent differences that arise when index cases are compared with their siblings. In order to present the data in a consistent fashion, the comparison between siblings and sibling-controls is also shown as crude and corrected odds ratios. However, the risk implied by these ORs is the risk of being a sibling of an affected proband and does not relate to the risk of the actual illness. Finally, corrected ORs are calculated using logistic regression models for comparisons between index cases and controls and between siblings and their controls, as these groups are independent, and using conditional logistic regression models for comparisons between index cases and siblings as these groups are not independent.

4.4. Confounding factors

The influence of the demographic variables of maternal marital status, socio-economic status and parity were assessed in the subjects who met diagnostic criteria for schizophrenia, affective disorder or other functional psychosis, their controls, siblings and sibling-controls, a total of 7,734 births. The results are shown in table 4.4. It is clear that these factors confound many of the obstetric variables. Prematurity and induced labour or elective caesarean section were associated with all three of these variables, non-OA presentation and any OC were associated with both maternal marital status and parity, while instrumental delivery or emergency c/s was associated with both social class and parity. Pre-eclampsia was associated with primiparity and low Apgar scores at one and five minutes were associated with maternal marital status.

The relationships between OCs and these demographic variables are likely to confound other apparent relationships between OCs and the psychotic conditions examined in this study. For this reason, all three of these confounding variables were included in the logistic and conditional logistic regression models that follow.

Table 4.4 Confounding factors

	Maternal marital status			Social class			Parity		
	Not married	Married	p	Low (IV or V)	Other (I, II or III)	p	Primi-parous	Mulit-parous	p
Mother Rhesus negative: N (%)	74 (19.1)	1,276 (19.6)	n.s.	320 (18.6)	1,030 (19.9)	n.s.	532 (19.7)	818 (19.4)	n.s.
Pre-eclampsia: N (%)	13 (3.0)	148 (2.0)	n.s.	35 (1.9)	126 (2.1)	n.s.	114 (3.9)	47 (1.0)	<0.01
Bleeding in pregnancy: N (%)	16 (3.7)	221 (3.0)	n.s.	58 (3.2)	179 (3.0)	n.s.	86 (2.9)	151 (3.1)	n.s.
Prematurity: N (%)	2.7 (7.0)	209 (3.0)	<0.01	68 (4.0)	168 (3.0)	<0.05	106 (3.8)	130 (2.9)	<0.05
Labour induced or c/s: N (%)	72 (16.9)	1,974 (27.0)	<0.01	430 (23.5)	1,617 (27.4)	<0.01	833 (28.5)	1,214 (25.2)	<0.05
Non-OA presentation: N (%)	14 (7.4)	274 (4.0)	<0.05	64 (3.9)	225 (4.2)	n.s.	159 (6.2)	130 (2.9)	<0.01
Intervention delivery: N (%)	69 (16.2)	1,117 (15.3)	n.s.	235 (12.8)	952 (16.1)	<0.01	801 (27.4)	386 (8.0)	<0.01
Low birth weight: N (%)	11 (3.2)	132 (2.0)	n.s.	42 (2.7)	101 (1.9)	n.s.	53 (2.0)	90 (2.2)	n.s.
Apgar at 1 minute < 7: N (%)	147 (52.9)	939 (23.1)	<0.01	257 (25.1)	829 (25.0)	n.s.	422 (26.4)	664 (24.2)	n.s.
Apgar at 5 minutes < 8: N (%)	125 (45.0)	634 (15.6)	<0.01	17.6 (17.2)	583 (17.6)	n.s.	257 (16.1)	502 (18.3)	n.s.
Any OC: N (%)	279 (65.3)	4,110 (56.3)	<0.01	1,022 (55.8)	3,368 (57.1)	n.s.	1,861 (63.6)	2,529 (52.6)	<0.01

4.5. All psychoses

4.5.1 Demographic details and obstetric complications for all psychoses

All 492 cases meeting ICD-9 diagnostic criteria for schizophrenia, affective illness or other functional psychosis were initially examined together to test the hypothesis that OCs are related to psychosis, rather than to schizophrenia alone. Initially index cases, controls, siblings and sibling-controls were compared on all demographic and obstetric factors as shown in table 4.5.1. Maternal age at delivery and marital status do not differ between the groups, but social class and parity are strongly related to case-control status, and, as expected, act as significant confounders. Low social class is more common in index cases and their siblings compared to controls. Siblings of index cases have a lower rate of primiparity than sibling-controls, although index cases do not differ from their controls.

Only two obstetric complications vary when comparison is made across all four groups: intervention delivery and abnormal placental delivery. Intervention delivery is less common in siblings of index cases than in the other groups, which may relate directly to this group being less likely to be born to primiparous women. Placental delivery does not differ between index cases and their controls or between siblings and sibling-controls. However siblings have a much greater rate of intervention for placental delivery compared to index cases. Standard obstetric practice in Aberdeen changed in 1975 when controlled cord traction, rather than maternal effort alone, became the norm. Prior to 1975, 1.6% of deliveries are by controlled cord traction; this figure rises to 90.2% after this date ($p<0.01$). A univariate analysis model indicates that this difference between index cases and their siblings disappears when year of delivery, dichotomised into pre & post 1975, is controlled

for. These data are not analysed further, as controlled cord traction became a standard procedure rather than a complication and is unlikely to further influence the already delivered infant.

Measures of total numbers of OCs may be unreliable, as OCs correlate with each other, so data were not summed, but were analysed on the basis of any of the 10 OCs: pre-eclampsia, bleeding in pregnancy, maternal Rhesus negative status, prematurity, induced labour or elective c/s, non-OA presentation, intervention delivery, low birth weight and low Apgar scores at 1 and 5 minutes after delivery. When any of the above obstetric variables are considered, the incidence of any OC rises to 50% but there are no differences between the groups.

Table 4.5.1 All psychoses. Demographics details and obstetric complications

	Index cases	Controls	Siblings	Sibling-controls	p
N (% male)	492 (48.8)	2,460 (48.8)	797 (50.9)	3,985 (50.9)	
Maternal age at delivery: Mean (s.d.)	25.8 (5.5)	26.15 (5.5)	25.95 (5.2)	25.96 (5.3)	n.s
Mother not married: N (%)	16 (3.3)	150 (6.1)	42 (5.3)	220 (5.5)	n.s.
Low social class: N (%)	138 (28.0)	531 (21.6)	253 (31.7)	909 (22.8)	<0.01
Primiparity: N (%)	192 (39.0)	975 (39.6)	202 (25.3)	1,556 (39.0)	<0.01
Mother Rhesus negative: N (%)	91 (19.8)	430 (19.4)	147 (19.3)	682 (19.7)	n.s.
Pre-eclampsia: N (%)	11 (2.2)	44 (1.8)	10 (1.3)	94 (2.4)	n.s.
Bleeding in pregnancy: N (%)	14 (2.8)	69 (2.8)	24 (3.0)	130 (3.3)	n.s.
Prematurity: N (%)	19 (4.1)	68 (2.9)	28 (3.8)	121 (3.2)	n.s.
Labour induced or c/s: N (%)	132 (26.8)	620 (25.2)	207 (26.0)	1,088 (27.3)	n.s.
Non-OA presentation: N (%)	16 (3.5)	98 (4.5)	31 (4.3)	144 (4.0)	n.s.
Intervention delivery: N (%)	75 (15.2)	382 (15.5)	72 (9.0)	658 (16.5)	<0.01
Low birth weight: N (%)	9 (2.1)	42 (1.9)	19 (2.8)	73 (2.1)	n.s.
Placental delivery by intervention: N (%)	8 (1.6)	43 (1.7)	56 (7.0)	279 (7.0)	<0.01
Apgar at 1 minute < 7: N (%)	67 (13.6)	361 (14.7)	107 (13.4)	551 (13.8)	n.s.
Apgar at 5 minutes < 8: N (%)	52 (10.6)	252 (10.2)	80 (10.0)	375 (9.4)	n.s.
Any OC: N (%)	292 (59.3)	1,380 (56.1)	435 (54.6)	2,283 (57.3)	n.s.

4.5.2 Crude odds ratios for all psychoses

Crude odds ratios for all 492 cases are shown in table 4.5.2. When ill subjects are compared to normal controls, lower social class is associated with an increased risk of illness, but being born to an unmarried mother is associated with a decreased risk. No obstetric variable is associated with an increased or decreased risk of illness. This initial examination of all cases together, before separate diagnoses are considered, illustrates potentially significant confounding of findings by maternal parity, marital status and socio-economic class. One obstetric variable, intervention delivery, appears to increase the risk of illness when subjects are compared to their siblings, and the comparison between siblings and sibling-controls indicates that intervention delivery appears to reduce the risk of being a sibling of an index case.

Table 4.5.2 All psychoses. Crude odds ratios and 95% C.I.

	Index cases compared to controls			Index cases compared to siblings			Siblings compared to sibling-controls		
	All	Males	Females	All	Males	Females	All	Males	Females
Mother not married	**0.52** **0.31-0.88**	0.58 0.29-1.18	**0.45** **0.21-0.99**	0.60 0.37-1.09	0.75 0.34-1.68	0.48 0.20-1.14	**1.86** **1.32-2.60**	0.94 0.58-1.54	0.97 0.61-1.55
Low social class	**1.42** **1.14-1.76**	1.22 0.89-1.67	**1.64** **1.21-2.22**	0.84 0.66-1.07	0.74 0.49-1.11	0.92 0.65-1.29	**1.57** **1.33-1.86**	**1.43** **1.02-2.01**	**1.62** **1.27-2.05**
Primiparity	0.97 0.80-1.19	0.87 0.65-1.16	1.09 0.83-1.43	**1.89** **1.48-2.40**	**1.64** **1.09-2.47**	**2.06** **1.47-2.90**	**0.53** **0.45-0.63**	**0.53** **0.38-0.75**	**0.53** **0.41-0.68**
Mother Rhesus negative	1.03 0.80-1.32	1.25 0.87-1.78	0.85 0.60-1.23	1.03 0.77-1.38	1.05 0.65-1.69	1.09 0.71-1.67	0.97 0.80-1.19	1.07 0.72-1.59	0.84 0.63-1.13
Pre-eclampsia	1.26 0.64-2.45	1.00 0.34-2.95	1.47 0.63-3.45	1.50 0.66-3.42	1.08 0.24-4.88	2.21 0.69-7.03	0.63 0.35-1.16	0.75 0.22-2.54	0.60 0.24-1.54
Bleeding in pregnancy	1.01 0.57-1.82	0.52 0.18-1.47	1.64 0.79-3.39	0.94 0.48-1.84	0.64 0.17-2.42	1.75 0.70-4.38	0.92 0.59-1.43	0.83 0.32-2.16	0.69 0.34-1.39
Prematurity	1.41 0.84-2.37	1.40 0.69-2.87	1.42 0.67-3.02	1.07 0.59-1.94	1.52 0.51-4.54	1.56 0.61-3.99	1.21 0.80-1.84	0.76 0.29-1.97	0.92 0.45-1.88
Labour induced or c/s	1.09 0.87-1.36	0.96 0.70-1.32	1.23 0.91-1.66	1.05 0.81-1.35	0.93 0.61-1.44	1.08 0.76-1.53	0.93 0.79-1.11	1.07 0.75-1.52	0.92 0.72-1.18
Non-OA presentation	0.78 0.45-1.33	0.93 0.46-1.86	0.61 0.26-1.45	0.82 0.45-1.53	0.86 0.34-2.17	0.77 0.28-2.08	1.07 0.72-1.59	1.37 0.65-2.92	0.81 0.44-1.52
Intervention delivery	0.98 0.75-1.28	0.87 0.60-1.26	1.15 0.78-1.71	**1.81** **1.28-2.56**	1.44 0.83-2.51	**3.45** **1.91-6.23**	**0.50** **0.39-0.65**	**0.62** **0.39-0.99**	**0.27** **0.17-0.45**
Low birth weight	1.07 0.52-2.21	1.36 0.55-3.40	0.75 0.22-2.54	0.72 0.32-1.62	1.08 0.30-3.91	0.76 0.19-3.06	1.38 0.83-2.30	1.72 0.55-5.34	0.77 0.32-1.83
Apgar at 1 minute < 7	0.90 0.67-1.22	0.84 0.55-1.28	0.98 0.64-1.50	1.05 0.74-1.50	0.82 0.47-1.45	1.21 0.73-1.99	0.96 0.76-1.22	1.02 0.65-1.60	1.01 0.72-1.43
Apgar at 5 minutes < 8	1.04 0.75-1.45	0.83 0.50-1.37	1.26 0.81-1.97	1.10 0.75-1.62	0.78 0.40-1.51	1.46 0.86-2.48	1.08 0.83-1.41	1.04 0.62-1.74	1.17 0.80-1.71
Any OC	1.14 0.94-1.39	1.03 0.78-1.37	1.26 0.95-1.65	1.21 0.97-1.53	1.21 0.83-1.77	1.34 0.97-1.84	0.90 0.77-1.04	0.84 0.62-1.14	0.86 0.69-1.07

4.5.3 Logistic regression modelling for all psychoses

The three demographic variables, social class, marital status and parity and all ten individual obstetric complications were entered into logistic and conditional regression models as previously described. The results of both of these analyses are shown in table 4.5.3.

Low social class is associated with an increased risk of illness when cases are compared to controls in all subjects and in females alone. For females, being born to a mother who was not married is associated with a decreased risk of illness, but a poor Apgar score five minutes after delivery is associated with an increased risk. In comparison with siblings, being born to an unmarried mother is associated with a decreased risk of psychosis in all subjects.

There are multiple findings when siblings are compared to sibling-controls. The findings for social class, primiparity and intervention delivery occur in both males and females separately, as well as for all cases together, but for the sake of clarity, these have not been included in table 4.5.3. For all cases together, but not for either sex alone, non-OA presentation was associated with an increased risk and for males alone, low birth weight and the presence of any OC was associated with an increased risk. The comparison between siblings and sibling-controls produces a corrected odds ratio for being a sibling of an infant who later develops psychosis. This is not to suggest that perinatal factors affecting the sibling have any influence on the already born or not yet conceived individual who later develops psychosis. The results are presented in this manner in order to clarify whether any increased risk in comparison with siblings may be due to those siblings being different from their control group, rather than due to individuals who develop psychosis having a higher rate of a particular complication than unrelated controls.

Table 4.5.3 All psychoses. Logistic regression coefficients and corrected odds ratios

Comparison	Variable	Subgroup	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
OR for all psychoses compared to controls	Low social class	All	0.91	0.31	0.12	1	<0.01	1.36 (1.09-1.71)
	Mother not married	Females	0.81	-0.89	0.41	1	<0.05	0.41 (0.18-0.92)
	Low social class		0.81	0.50	0.16	1	<0.01	1.64 (1.19-2.26)
	Apgar 5 < 8		0.81	0.96	0.46	1	<0.05	2.62 (1.06-6.49)
OR for all psychoses compared to siblings	Mother not married	All		0.92	0.45	1	<0.05	0.40 (0.16-0.96)
OR for siblings of all psychoses cases compared to sibling-controls	Low social class	All *	0.77	0.34	0.09	1	<0.01	1.41 (1.18-1.68)
	Primiparity		0.77	-0.61	0.09	1	<0.01	0.54 (0.45-0.65)
	Intervention delivery		0.77	-0.67	0.16	1	<0.01	0.51 (0.37-0.70)
	Non OA presentation		0.77	0.56	0.24	1	<0.05	1.75 (1.10-2.80)
	Low birth weight	Males	0.61	0.94	0.37	1	<0.05	2.55 (1.23-5.29)
	Any OC		0.61	-0.42	0.20	1	<0.05	0.66 (0.45-0.97)

* similar findings occur for low social class, primiparity and intervention delivery in males and in females separately.

4.5.4 Summary

Individuals with psychoses and their siblings are more often born into lower social class families than control subjects; being of lower social class was the only risk associated with an increased risk of psychotic illnesses compared to controls in all subjects. For females, low social class and a low Apgar score at 5 minutes after delivery were associated with an increased risk of psychosis compared to normal controls once other OCs and confounding factors had been controlled for.

Although being born into a lower social class family was associated with an increased risk of psychosis in all subjects and in females, somewhat paradoxically, being born to an unmarried mother was associated with a decreased risk of psychosis in all subjects compared to their well siblings and in females when compared to controls. The women classed as unmarried were mainly single (71.2%) but this category also included those who were separated (13.3%), divorced (6.1%) cohabiting (7.0%), and widowed (2.3%). It might be expected that mothers who were not married would be of lower socio-economic class. 21.3% of unmarried mothers belong to the lower social class group, as do 23.8% of the married women; this difference was not statistically significant, and this does not provide a ready explanation of the finding. Parity, however, was strongly related to martial status; 58.8% of the women who were not married were giving birth for the first time, compared to 36.6% of the married women (χ^2 $p<0.01$), and it is possible the difference in maternal marital status relates to parity.

4.6 Schizophrenia

4.6.1 Demographic details & obstetric complications for schizophrenia

180 index cases (68.3% male) met ICD-9 criteria for schizophrenia, including schizoaffective disorder. These 180 index cases had 306 siblings (52.6% male). After inclusion of controls, 2,916 births were available for analysis. Data were initially explored by comparing all four groups (index cases, controls, siblings and sibling-controls) on all OCs and possible confounding variables, and the results are shown in table 4.6.1. This comparison reflects what has already been seen when all cases were considered together; maternal age at delivery and marital status did not differ between groups, but social class and parity were strongly related to case-control status. Siblings of schizophrenic probands were more often of social class IV and V compared to controls, and more likely to have been born to multiparous women compared to both to index cases and to sibling-controls. Intervention delivery again appears to occur less frequently in the siblings of schizophrenic subjects than in the subjects or controls, but there are no other differences in the rates of OCs across the four groups.

Table 4.6.1 Schizophrenia. Demographic details & obstetric complications

	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	180 (68.3)	900 (68.3)	306 (52.6)	1530 (52.6)	n.s.
Maternal age at delivery: mean (s.d.)	26.33 (5.6)	26.31 (5.7)	25.53 (4.9)	26.0 (5.3)	n.s.
Mother not married: N (%)	8 (4.4)	59 (6.6)	21 (6.9)	74 (4.8)	n.s.
Low social class: N (%)	47 (26.1)	186 (20.7)	89 (29.1)	348 (22.7)	<0.05
Primiparity: N (%)	64 (35.6)	350 (38.9)	81 (26.5)	594 (38.8)	<0.05
Mother Rhesus negative (N, %)	31 (18.6)	145 (17.7)	52 (17.7)	270 (20.6)	n.s.
Pre-eclampsia: N (%)	5 (2.8)	26 (2.2)	5 (1.6)	31 (2.0)	n.s.
Bleeding in pregnancy: N (%)	0	25 (2.8)	8 (2.6)	41 (2.7)	n.s.
Prematurity: N (%)	6 (3.5)	21 (2.5)	12 (4.3)	56 (3.9)	n.s
Labour induced or c/s: N (%)	56 (31.1)	228 (25.3)	70 (22.9)	406 (26.5)	n.s
Non-OA presentation: N (%)	5 (3.0)	35 (4.4)	9 (3.2)	53 (3.8)	n.s.
Intervention delivery: N (%)	27 (15.0)	144 (16.0)	29 (9.5)	232 (15)	<0.01
Low birth weight: N (%)	5 (3.1)	13 (1.6)	5 (1.9)	29 (2.1)	n.s.
Apgar at 1 minute < 7: N (%)	25 (13.9)	145 (16.1)	39 (12.7)	183 (12.0)	n.s.
Apgar at 5 minutes < 8: N (%)	16 (8.9)	100 (11.1)	31 (10.1)	113 (7.4)	n.s.
Any of the above OCs: N (%)	109 (60.6)	508 (56.4)	156 (51.0)	860 (56.2)	n.s.

4.6.2 Crude odds ratios for schizophrenia

Crude odds ratios for OCs and major demographic factors associated with schizophrenia were calculated for all cases together and separately by sex, and are shown in table 4.6.2. In comparison with normal controls, for all subjects together and for males alone, no OCs or confounding factors were associated with an increased risk of schizophrenia. For females, induced labour or elective c/s and the presence of any OC were associated with an increased risk of schizophrenia.

In comparison with their well siblings, primiparity, induced labour or elective c/s and any OC were associated with an increased risk of schizophrenia in all subjects and in females alone. Intervention delivery was associated with an increased risk of schizophrenia only in females.

It was hypothesised that siblings of schizophrenic probands would show a rate of OCs intermediate between index cases and normal controls. Table 4.6.2 indicates that in all cases and in females alone, the siblings of schizophrenic probands are of lower social class, and less likely to have had an intervention delivery than their controls. Male siblings are less likely to have been of low birth weight than controls. Primiparity was associated with a lower risk of having a schizophrenic sibling when all cases were considered together and for males and females separately.

Table 4.6.2 Schizophrenia. Crude odds ratios (95% C.I.)

	Schizophrenia compared to controls			Schizophrenia compared to siblings			Siblings compared to controls		
	All	Males	Females	All	Males	Females	All	Males	Females
Mother not married	0.66 0.31–1.41	0.58 0.22–1.49	0.88 0.25–3.09	0.63 0.27–1.46	0.64 0.21-1.92	0.68 0.18-2.52	1.45 0.88–2.39	1.23 0.60-2.52	1.78 0.87-3.61
Low social class	1.18 0.81–1.73	1.03 0.65-1.64	1.58 0.82-3.04	0.74 0.48-1.13	0.83 0.49-1.42	0.98 0.50-1.90	**1.41** **1.06-1.87**	1.20 0.82-1.75	**1.66** **1.11-2.46**
Primiparity	0.87 0.62-1.21	0.77 0.51-1.16	1.11 0.62–1.98	**1.53** **1.03-2.88**	1.37 0.82-2.29	**1.90** **1.00-3.63**	**0.57** **0.43-0.75**	**0.55** **0.38-0.80**	**0.59** **0.39-0.88**
Mother Rhesus negative	1.06 0.69-1.63	1.15 0.69-1.92	0.89 0.41-1.95	1.06 0.65-1.73	1.05 0.56-1.95	1.02 0.44-2.37	0.83 0.60-1.54	0.93 0.59-1.46	0.74 0.46-1.19
Pre-eclampsia	1.26 0.47-3.40	1.44 0.30-7.00	1.16 0.32–4.22	1.72 0.49–6.03	0.87 0.14-5.29	3.97 0.65-24.43	0.80 0.31–2.08	0.94 0.27-3.25	0.66 0.15-2.93
Bleeding in pregnancy	*	*	*	*	*	*	0.97 0.45-2.10	1.78 0.74-4.29	0.23 0.03-1.74
Prematurity	1.43 0.57-3.60	0.94 0.27-3.27	3.02 0.74-13.04	0.81 0.30-2.20	0.46 0.12-1.76	1.88 0.41-8.67	1.11 0.59-2.10	1.26 0.57-2.79	0.89 0.30-2.62
Labour induced or c/s	1.33 0.94-1.89	1.12 0.72-1.73	**1.86** **1.03-3.36**	**1.52** **1.01-2.30**	1.42 0.82-2.47	**1.97** **1.03-3.77**	0.82 0.62-1.10	0.86 0.57-1.30	0.79 0.52-1.18
Non-OA presentation	0.67 0.26-1.73	0.61 0.21-1.78	0.97 0.11-8.43	0.93 0.31-2.81	1.01 0.27-3.87	0.64 0.07-5.84	0.84 0.41-1.72	0.88 0.33-2.31	0.79 0.27-2.31
Intervention delivery	0.93 0.59–1.45	0.84 0.49-1.43	1.21 0.53- 2.76	1.69 0.96-2.95	1.22 0.62-2.38	**2.80** **1.00-7.85**	**0.59** **0.39-0.88**	0.94 0.57-1.55	**0.29** **0.14-0.61**
Low birth weight	1.80 0.86-3.66	1.97 0.92-4.21	1.00 0.11-8.71	2.04 0.83-5.04	1.58 0.41-6.02	0.24 0.03-1.98	0.72 0.35-1.46	1.86 0.58-5.92	0.29 0.04-2.19
Apgar at 1 minute < 7	0.82 0.50–1.34	0.76 0.42–1.37	0.97 0.40–2.36	0.96 0.54-1.72	0.78 0.37-1.64	1.29 0.49-3.40	1.09 0.73-1.62	0.97 0.56-1.69	1.24 0.69-2.22
Apgar at 5 minutes < 8	0.76 0.43–1.36	0.80 0.28-2.27	0.75 0.37–1.49	0.74 0.38-1.44	0.65 0.28-1.53	0.89 0.29-2.71	1.47 0.94-2.28	1.37 0.74-2.54	1.58 0.84-2.98
Any OC	1.18 0.85-1.64	0.95 0.64-1.40	**1.95** **1.07-3.57**	**1.48** **1.02-2.15**	1.37 0.86-2.20	**1.91** **1.00-3.65**	0.81 0.63-1.04	0.82 0.58-1.14	0.80 0.56-1.15

* An odds ratio cannot be calculated as no index cases had bleeding in pregnancy

4.6.3 Logistic regression modelling for schizophrenia

Logistic and conditional logistic regression models were developed to test whether the apparent risk factors in the crude OR analysis remained as risk factors once maternal marital status, social class and parity were controlled for, and the results are shown in table 4.6.3. The increased risk of schizophrenia in females in comparison with normal controls following induced labour or elective c/s and after any OC does not persist once the potential confounding factors of parity and social class are entered into the model. In comparison with siblings, only primiparity is associated with an increased risk of schizophrenia, and only in females. However, primiparity is associated with an increased risk, at least in males, when the siblings are compared with sibling-controls, lending support to the idea that this represents a parity difference between siblings and their controls. As with the analysis for all psychoses (see 4.5.3), multiple other differences between siblings and their controls are evident. With the exception of lower social class and mother being unmarried, which are associated with an increased risk only in females, all other significant variables result in lower corrected odds ratios, indicating again that siblings of schizophrenic patients, perhaps due to their lower rates of being first-born, have decreased rates of several OCs.

Table 4.6.3 Schizophrenia. Logistic regression coefficients and corrected odds ratios

Comparison	Variable	Subgroup	Hosmer-Lemeshow	β	SE	d.f.	P	OR (95% C.I.)
OR for schizophrenia compared to controls	No OC or demographic factor associated with risk of schizophrenia							
OR for schizophrenia compared to siblings	Primiparity	Females		-1.2	0.61	1	<0.05	3.57 (1.15-11.11)
OR for siblings compared to sibling-controls	Primiparity	All	0.46	-0.59	0.15	1	<0.01	0.56 (0.42-0.74)
	Intervention delivery		0.46	-0.59	0.25	1	<0.05	0.60 (0.67-0.98)
	Primiparity	Males	0.77	-0.69	0.21	1	<0.01	0.50 (0.33-0.76)
	Any OC		0.77	-0.86	0.33	1	<0.01	0.42 (0.22-0.81)
	Mother not married	Females	0.41	0.85	0.40	1	<0.05	2.33 (1.07-5.08)
	Low social class		0.41	0.44	0.21	1	<0.05	1.55 (1.02-2.34)
	Pre-eclampsia		0.41	-0.46	0.22	1	<0.05	0.63 (0.41-0.96)
	Intervention delivery		0.41	-1.20	0.45	1	<0.01	0.30 (0.13-0.72)

4.7 Affective disorder

4.7.1. Demographic details and obstetric complications for affective disorder

220 (31.8% male) of the 627 potential index cases met ICD-9 criteria for affective disorder. These 220 index cases had 356 siblings (52.2% male). Each of these 576 individuals was matched with five controls, making the total number of births available for analysis 3,456. Index cases, controls, siblings and sibling-controls were compared on all variables and the results are shown in table 4.7.1. As is the case for all psychoses and for schizophrenia, maternal age at delivery and maternal marital status do not differ between the groups, but social class and parity are strongly related to case-control status and likely to act as confounders. Index cases do not differ from controls in terms of parity, but siblings of index cases are more likely to be born to multiparous women compared to index cases and to sibling-controls. Low social class is also more common in index subjects with affective disorder and their siblings than in controls.

The lower rate of intervention delivery in siblings may reflect these differences in social class and parity. Siblings of patients with affective disorder have fewer intervention deliveries than their controls. Of the complications of pregnancy, only maternal Rhesus negative status differs between the groups, and appears to be more common in index cases and siblings than in either of their control groups, a finding which was not seen for schizophrenia or for all psychoses considered together. No neonatal complications (low birth weight or low Apgar scores) differ between the groups.

Table 4.7.1. Affective Disorder. Demographic details & obstetric complications

	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	220 (31.8)	1,100 (31.8)	356(52.2)	1,780 (52.2)	n.s.
Maternal age at delivery: mean (s.d.)	25.29 (5.40)	26.11 (5.45)	25.82 (5.26)	25.91 (5.39)	n.s
Mother not married: N (%)	6 (2.7)	74 (6.7)	19 (5.3)	100 (5.6)	n.s.
Low social class: N (%)	66 (30.0)	223 (20.3)	120 (33.7)	406 (22.8)	<0.01
Primiparity: N (%)	89 (40.5)	442 (40.2)	91 (25.6)	707 (39.7)	<0.01
Mother Rhesus negative N (%)	48 (23.1)	205 (20.4)	85 (24.9)	290 (18.5)	<0.05
Pre-eclampsia: N (%)	4 (1.8)	15 (1.4)	4 (1.1)	46 (2.6)	n.s.
Bleeding in pregnancy: N (%)	11 (5.0)	28 (2.5)	9 (2.5)	68 (3.8)	n.s.
Prematurity: N (%)	8 (3.9)	30 (2.9)	10 (3.1)	47 (2.8)	n.s.
Labour induced or c/s: N (%)	60 (27.3)	277 (25.2)	90 (25.3)	509 (28.6)	n.s.
Non-OA presentation: N (%)	7 (3.4)	42 (4.4)	16 (4.9)	72 (4.5)	n.s.
Intervention delivery: N (%)	27 (12.3)	166 (15.1)	28 (7.9)	325 (18.3)	<0.01
Low birth weight: N (%)	3 (1.5)	20 (2.1)	10 (3.4)	33 (2.1)	n.s.
Apgar at 1 minute < 7: N (%)	29 (13.2)	172 (15.6)	49 (13.8)	277 (15.6)	n.s.
Apgar at 5 minutes < 8: N (%)	24 (10.9)	127 (11.5)	34 (9.6)	198 (11.1)	n.s.
Any OC: N (%)	133 (60.5)	623 (56.6)	212 (59.6)	1,050 (59.0)	n.s.

4.7.2. Crude odds ratios for affective disorder

Table 4.7.1 indicates that for affective disorder, intervention delivery and maternal Rhesus negative status are the only obstetric variables which differ between groups, but that social class and parity act as confounders. Crude odds ratios for OCs and these major confounding factors were calculated for all cases of affective disorder together and separately by sex, and the results are shown in table 4.7.2.

When index cases are compared to normal controls, low social class is associated with an increased risk of affective disorder, but being born to an unmarried mother is associated with a decreased risk when both sexes are considered together, but not for males or females separately. Bleeding in pregnancy is associated with an increased risk of affective disorder in females only. No other obstetric complication is associated with the risk of affective disorder in comparison to normal controls. When index cases of affective disorder are compared to their well siblings, primiparity is associated with an increased risk of affective disorder in all subjects and in both genders separately. For females alone, intervention delivery is associated with an increased risk of affective disorder.

When siblings of those with affective disorder are compared to sibling-controls low social class and maternal Rhesus negative status are associated with an increased risk, but primiparity and intervention delivery are associated with a decreased risk in analyses together and separately by gender.

Table 4.7.2. Affective Disorder. Crude odds ratios and 95% C.I.

	Affective disorder compared to controls			Affective disorder compared to siblings			Siblings compared to sibling-controls		
	All	Males	Females	All	Males	Females	All	Males	Females
Mother not married	**0.39** **0.17-0.90**	0.39 0.09-1.68	0.42 0.15-1.18	0.50 0.20-1.27	0.52 0.11-2.42	0.49 0.15-1.63	0.95 0.57-1.57	1.04 0.52-2.10	0.56 0.41-1.78
Low social class	**1.49** **1.07- 2.08**	1.54 0.86-2.73	1.41 0.94-2.11	0.69 0.48-1.01	0.91 0.51-1.63	0.84 0.52-1.36	**1.79** **1.38-2.32**	**1.72** **1.23-2.41**	**1.72** **1.20-2.46**
Primiparity	1.01 0.75-1.36	0.82 0.49-1.38	1.12 0.78-1.60	**1.98** **1.38-2.83**	**1.97** **1.10-3.53**	**1.96** **1.22-3.15**	**0.52** **0.40-0.67**	**0.49** **0.34-0.69**	**0.56** **0.39-0.52**
Mother Rhesus negative	1.17 0.82-1.67	1.34 0.72-2.51	1.10 0.71-1.70	0.91 0.61-1.36	0.87 0.45-1.67	1.04 0.60-1.78	**1.46** **1.11-1.93**	**1.56** **1.08-2.25**	1.35 0.88-2.05
Pre-eclampsia	1.34 0.44-4.08	1.26 0.26-6.05	1.43 0.30-6.97	1.63 0.40-6.58	1.34 0.24-7.47	1.14 0.16-8.16	0.43 0.15-1.20	0.66 0.23-1.89	0.62 0.14-2.72
Bleeding in pregnancy	2.02 0.99-4.11	1.08 0.13-8.76	**2.61** **1.20-5.69**	2.03 0.83-4.98	0.52 0.06-4.57	2.96 0.91-9.66	0.65 0.32-1.32	0.75 0.29-1.95	0.56 0.20-1.60
Prematurity	1.34 0.61-2.97	1.64 0.43-6.23	1.21 0.45-3.26	1.26 0.49-3.24	1.24 0.30-5.10	1.42 0.37-5.39	1.12 0.56-2.23	1.14 0.47-2.80	1.09 0.36-3.24
Labour induced or c/s	1.11 0.80-1.54	0.92 0.51-1.64	1.22 0.83-1.81	1.11 0.76-1.62	0.94 0.50-1.76	1.26 0.76-2.09	0.84 0.65-1.10	0.89 0.62-1.27	0.80 0.54-1.17
Non-OA presentation	0.78 0.35-1.76	1.97 0.60-6.50	0.43 0.13-1.42	0.69 0.28-1.71	0.95 0.29-3.08	0.68 0.16-2.88	1.10 0.63-1.92	1.57 0.78-3.16	0.66 0.26-1.71
Intervention delivery	0.79 0.51-1.2	0.61 0.29-1.29	0.91 0.53-1.55	1.64 0.94-2.86	1.05 0.46-2.39	**4.50** **1.63-12.44**	**0.38** **0.26-0.58**	**0.52** **0.33-0.83**	**0.17** **0.07-0.43**
Low birth weight	0.72 0.34-1.55	0.60 0.13-2.68	0.78 0.32-1.88	0.66 0.28-1.55	0.46 0.09-2.36	0.77 0.28-2.10	1.21 0.71-2.04	1.99 0.77-5.12	1.28 0.42-3.88
Apgar at 1 minute < 7	0.80 0.42-1.27	0.95 0.43-2.07	0.73 0.42-1.27	1.01 0.60-1.71	1.13 0.49-2.61	0.97 0.49-1.93	0.85 0.60-1.20	0.80 0.50-1.28	0.92 0.55-1.52
Apgar at 5 minutes < 8	0.93 0.57-1.51	1.03 0.59-1.80	0.70 0.26-1.91	1.25 0.71-2.23	0.88 0.30-2.57	1.32 0.64-2.71	0.83 0.56-1.24	0.68 0.38-1.19	1.04 0.60-1.82
Any OC	1.17 0.87-1.57	1.22 0.72-2.07	1.15 0.80-1.64	1.04 0.74-1.46	0.90 0.51-1.58	1.24 0.80-1.94	1.02 0.81-1.29	1.14 0.82-1.58	0.92 0.66-1.28

4.7.3. Logistic regression modelling for affective disorder

Logistic and conditional logistic regression analyses, shown in table 4.7.3, indicate that for all cases together and for females alone, low social class is associated with an increased risk, and being born to an unmarried mother is associated with a decreased risk of affective disorder when index cases are compared to controls. When index cases are compared to their siblings no risk factors for affective disorder remains significant when confounding variables of parity, social class, maternal marital status and other OCs are included in the conditional logistic regression model.

When siblings of affective disorder are compared to their controls, lower social class is associated with an increased risk for all cases and intervention delivery is associated with a decreased risk in all cases. A similar effect for intervention delivery is also seen in males and in females separately, but is not shown in table 4.7.3. For all cases and for males, but not for females, primiparity is associated with an increased risk and maternal Rhesus negative status is associated with a decreased risk.

Table 4.7.3 Affective disorder. Logistic regression coefficients and corrected odds ratios

Comparison	Variable	Subgroup	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
OR for affective disorder compared to controls	Mother not married	All	0.70	-0.88	0.44	1	<0.05	0.41 (0.17-0.98)
	Low social class		0.70	0.47	0.17	1	<0.01	1.60 (1.14-2.24)
	Low social class	Females	0.74	0.48	0.21	1	<0.05	1.61 (1.06-2.44)
	Bleeding in pregnancy		0.74	1.32	0.45	1	<0.01	3.73 (1.56-8.94)
	Apgar at 5 minutes <8		0.74	1.33	0.67	1	<0.05	3.77 (1.02-13.88)
OR for affective disorder compared to siblings	No OC or demographic variable associated with risk of affective disorder							
OR for siblings compared to sibling-controls	Low social class	All*	0.57	0.47	0.13	1	<0.01	1.60 (1.23-2.07)
	Intervention delivery		0.57	-0.92	0.25	1	<0.01	0.40 (0.26-0.65)
	Primiparity		0.57	-0.57	0.14	1	<0.01	0.57 (0.43-0.75)
	Mother Rhesus negative		0.57	0.37	0.14	1	<0.05	1.45 (1.09-1.92)

* A similar finding for intervention delivery occurs in both males and females separately. Similar findings for primiparity and maternal Rhesus negative status occur in males.

4.8 Other functional psychosis

4.8.1 Demographic details and obstetric complications for other functional psychosis.

92 (51.1% male) of the 627 potential index cases met ICD-9 criteria for other functional psychosis (delusional disorder and other non-organic psychoses). These 92 index cases had 135 siblings (43.7% male). After matching, there were 1,362 births available for analysis.

Table 4.8.1 indicates the demographic and obstetric variables in each group. There are greater differences between cases, controls, siblings and sibling-controls for this diagnostic group than for schizophrenia, affective disorder or all psychoses considered together. Maternal marital status, social class and parity differ between the groups; being born to a mother who was not married is more common in sibling-controls than in other groups, while low social class is more common and primiparity less common, in siblings than in other groups.

Both index cases and siblings have lower rates of maternal Rhesus negative status than their control groups but higher rates of abnormal Apgar scores at one and five minutes. Induced labour or elective c/s is less common in index cases, but more common in siblings than in control groups.

Table 4.8.1 Other functional psychosis. Demographic details & obstetric complications

	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	92 (51.1)	460 (51.1)	135 (43.7)	675 (43.7)	
Maternal age at delivery: mean (s.d.)	26.00 (5.49)	25.93 (5.41)	27.22 (5.48)	26.03 (5.41)	n.s.
Mother not married: N (%)	2 (2.2)	17 (3.7)	2 (1.5)	46 (6.8)	<0.01
Low social class: N (%)	25 (27.2)	122 (26.5)	44 (32.6)	155 (23.0)	<0.05
Primiparity: N (%)	39 (42.4)	183 (39.8)	30 (22.2)	255 (37.8)	<0.01
Mother Rhesus negative: N (%)	12 (14.1)	80 (20.1)	10 (7.8)	122 (21.1)	<0.01
Pre-eclampsia: N (%)	2 (2.2)	9 (2.0)	1 (0.7)	17 (2.5)	n.s.
Bleeding in pregnancy: N (%)	3 (3.3)	16 (3.5)	7 (5.2)	21 (3.1)	n.s.
Prematurity: N (%)	5 (5.9)	17 (3.9)	6 (4.8)	18 (2.8)	n.s.
Labour induced or c/s: N (%)	16 (17.4)	115 (25.0)	47 (34.8)	173 (25.6)	<0.05
Non-OA presentation: N (%)	4 (4.9)	21 (5.0)	6 (4.9)	19 (3.1)	n.s.
Intervention delivery: N (%)	21 (22.8)	72 (15.7)	15 (11.1)	101 (15.0)	n.s.
Low birth weight: N (%)	1 (1.3)	9 (2.2)	4 (3.5)	11 (1.8)	n.s.
Apgar at 1 minute < 7: N (%)	13 (14.1)	44 (9.6)	19 (14.1)	91 (13.5)	<0.01
Apgar at 5 minutes < 8: N (%)	12 (13.0)	25 (5.4)	15 (11.1)	64 (9.5)	<0.01
Any OC: N (%)	50 (54.3)	249 (54.1)	67 (49.6)	373 (55.3)	n.s.

4.8.2 Crude odds ratios for other functional psychosis

Table 4.8.2 shows the crude ORs for other functional psychosis. Due to the smaller numbers in this diagnostic group, considerably more ORs cannot be calculated because no cases of a particular complication occurred in some of the groups. No male index case had pre-eclampsia and both of the male infants born to unmarried mothers developed illness. No male siblings had an unmarried mother. No female cases had unmarried mother, bleeding in pregnancy or low birth weight. For index cases of other functional psychosis compared with normal controls, none of the demographic variables is associated with risk, but a low Apgar score at one minute is associated with an increased risk in females and a low Apgar score at five minutes is associated with an increased risk in males and in all subjects considered together.

When index cases are compared with siblings, primiparity is associated with an increased risk of other functional psychosis in all cases and in both genders. Induced labour or elective c/s is associated with a decreased risk in all cases and in females. Intervention delivery is associated with an increased risk in all cases and in females, with a non-significant trend toward the same finding in males. A low Apgar score at five minutes is associated with an increased risk for females only. There are considerable differences when siblings of those with other functional psychosis are compared to controls. Low social class is associated with a decreased risk in all subjects and in males, primiparity and unmarried maternal marital status are associated with a decreased risk in all subjects and in females. Induced labour or elective c/s is associated with an increased risk of illness when all subjects are considered together. Maternal Rhesus negative status is associated with a decreased risk in females only.

Table 4.8.2 Other functional psychosis. Crude Odds Ratios and 95% C.I.

	Index cases compared to controls			Index cases compared to siblings			Siblings compared to sibling-controls		
	All	Males	Females	All	Males	Females	All	Males	Females
Mother not married	0.58 0.13-2.55	2.04 0.38-10.87	*	1.48 0.20-10.68	*	*	**0.21** **0.05-0.86**	*	0.33 0.08-1.40
Low social class	0.93 0.55-1.55	0.67 0.32-1.40	1.31 0.63-2.72	0.65 0.38-1.18	0.55 0.23-1.31	1.04 0.47-2.31	**1.63** **1.29-2.12**	**2.08** **1.14-3.79**	1.34 0.78-2.30
Primiparity	1.11 0.71-1.75	1.28 0.68-2.40	0.96 0.50-1.85	**2.58** **1.44-4.60**	**2.37** **1.04-5.38**	**2.71** **1.19-6.16**	**0.47** **0.30-0.73**	0.63 0.33-1.18	**0.37** **0.20-0.68**
Mother Rhesus negative	0.66 0.34-1.27	1.37 0.62-3.00	0.17 0.04-0.75	1.94 0.80-4.72	2.81 0.89-8.91	0.37 0.07-2.02	0.32 0.16-0.63	0.38 0.14-1.00	**0.27** **0.11-0.70**
Pre-eclampsia	1.11 0.24-5.24	*	2.57 0.46-14.47	2.98 0.27-33.33	*	3.49 0.31-39.61	0.29 0.04-2.19	*	0.49 0.06-3.91
Bleeding in pregnancy	0.94 0.27-3.28	1.53 0.41-5.80	*	0.62 0.16-2.45	1.27 0.24-6.62	*	1.70 0.71-4.09	1.26 0.35-4.62	2.29 0.69-7.64
Prematurity	1.54 0.55-4.28	1.99 0.60-6.56	0.83 0.10-7.11	1.24 0.37-4.20	0.96 0.24-3.84	1.76 0.11-28.83	1.76 0.69-4.54	2.95 0.96-9.01	0.61 0.08-4.98
Labour induced or c/s	0.63 0.35-1.13	0.66 0.30-1.45	0.60 0.25-1.42	**0.39** **0.21-0.75**	0.54 0.22-1.35	**0.30** **0.12-0.76**	**1.55** **1.05-2.30**	1.47 0.79-2.72	1.62 0.97-2.70
Non-OA presentation	0.96 0.32-2.89	0.89 0.19-4.12	1.07 0.22-5.15	1.00 0.27-3.66	0.89 0.14-5.62	1.10 0.18-6.87	1.60 0.63-4.09	1.89 0.48-7.37	1.39 0.38-5.11
Intervention delivery	1.59 0.92-2.76	1.29 0.61-2.73	2.10 0.93-4.71	**2.37** **1.15-4.88**	1.50 0.57-3.90	**4.06** **1.29-12.78**	0.71 0.40-1.26	0.87 0.42-1.83	0.52 0.20-1.37
Low birth weight	0.60 0.14-2.15	1.16 0.24-5.59	*	0.40 0.08-1.99	0.72 0.13-4.11	*	1.93 0.80-4.68	**4.77** **1.24-18.31**	1.01 0.28-3.61
Apgar at 1 minute < 7	1.68 0.81-3.47	0.92 0.34-2.48	**4.26** **1.36-13.35**	1.39 0.61-3.18	0.80 0.25-2.55	2.72 0.81-9.15	1.05 0.60-1.85	1.22 0.55-2.71	0.92 0.41-2.04
Apgar at 5 minutes < 8	**2.93** **1.34-6.40**	**9.22** **2.58-32.93**	1.39 0.47-4.11	1.68 0.70-3.99	0.73 0.21-2.49	**4.43** **1.22-16.17**	1.21 0.65-3.24	1.59 0.69-3.69	0.89 0.35-2.27
Any OC	1.01 0.64-1.58	1.02 0.54-1.92	1.00 0.53-1.90	1.21 0.71-2.06	1.40 0.65-3.02	1.05 0.50-2.19	0.80 0.55-1.16	0.73 0.42-1.28	0.85 0.52-1.40

*Odds ratio could not be calculated

4.8.3 Logistic regression modelling for other functional psychosis

Logistic regression analysis indicates that for all cases together, but not for either sex alone, a low Apgar score at 5 minutes is associated with an increased risk of other functional psychosis in comparison with controls. Induced labour or elective c/s is associated with an increased risk compared to siblings, but this may be due to lower rates of this complication in the siblings, rather than an increased rate in the subjects (table 4.8.3).

Table 4.8.3 Other functional psychosis. Logistic regression coefficients and corrected ORs

Comparison	Variable	Subgroup	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
OR for other functional psychosis compared to controls	Apgar at 5 minutes <8	All	0.51	0.97	0.37	1	0.01	2.63 (1.26-5.46)
OR for other functional psychosis compared to siblings	Labour induced or c/s	All		2.73	1.04	1	<0.01	0.06 (0.00-0.51)
OR for siblings compared to sibling-controls	Mother Rhesus negative	All*	0.83	-1.25	0.35	1	<0.01	0.29 (0.14-0.57)
	Primiparity		0.83	-0.83	0.26	1	<0.01	0.44 (0.27-0.72)
	Labour induced or c/s		0.83	0.53	0.24	1	<0.05	1.69 (1.07-2.68)
	Low social class	Males	0.97	0.73	0.33	1	<0.05	2.08 (1.09-3.98)
	Primiparity	Females	0.42	-1.24	0.37	1	<0.01	0.29 (0.14-0.59)

* A similar finding for maternal Rhesus status was found in both genders separately

4.9 Comparisons between diagnostic groups

The index cases in each diagnostic group were compared to each other to ascertain if any individual OCs affected the risk for one condition over any other.

4.9.1 Demographics and obstetric variables by diagnosis

The 492 index cases were compared by diagnosis. Differences occur for the proportion of males in each diagnostic group, but no other demographic variables differs between those with schizophrenia, affective disorder or other functional psychosis. Of the obstetric complications, only bleeding in pregnancy differs between these three diagnostic groups, as this complication does not occur in any of the schizophrenic subjects.

Table 4.9.1 Demographics and obstetric variables by diagnosis

	Schizophrenia	Affective Disorder	Other functional psychosis	p
N (% male)	180 (68.3)	220 (31.8)	92 (51.1)	<0.01
Maternal age at delivery: Mean (s.d.)	26.33 (5.63)	25.29 (5.40)	26.00 (5.49)	n.s.
Mother not married: N (%)	8 (4.4)	6 (2.7)	2 (2.2)	n.s.
Low social class: N (%)	47 (26.1)	66 (30.0)	25 (27.2)	n.s.
Primiparity: N (%)	64 (35.6)	89 (40.5)	39 (42.2)	n.s.
Mother Rhesus negative: N (%)	31 (18.6)	48 (23.1)	12 (14.1)	n.s.
Pre-eclampsia: N (%)	5 (2.8)	4 (1.8)	2 (2.2)	n.s.
Bleeding in pregnancy: N (%)	0	11 (5.0)	3 (3.3)	<0.05
Prematurity: N (%)	6 (3.5)	8 (3.9)	5 (5.9)	n.s.
Labour induced or c/s: N (%)	56 (31.1)	60 (27.3)	16 (17.4)	n.s.
Non-OA presentation: N (%)	5 (3.0)	7 (3.4)	4 (4.9)	n.s.
Intervention delivery: N (%)	27 (15.0)	27 (12.3)	21 (22.8)	n.s.
Low birth weight: N (%)	5 (3.1)	3 (1.5)	1 (1.3)	n.s.
Apgar at 1 minute < 7: N (%)	25 (24.8)	29 (22.8)	13 (29.5)	n.s.
Apgar at 5 minutes < 8: N (%)	16 (15.8)	24 (18.9)	12 (27.3)	n.s.
Any OC: N (%)	109 (60.6)	133 (60.5)	50 (54.3)	n.s.

4.9.2 Crude odds ratios by diagnosis

The ORs for each demographic variable and obstetric complication were calculated for schizophrenia compared to affective disorder, schizophrenia compared to other functional psychosis, and affective disorder compared to other functional psychosis, and the results are shown in table 4.9.2. No single factor is associated with an increased odds ratio of schizophrenia compared to affective disorder when all cases are considered together or when males and females are considered separately. Induced labour or elective c/s is associated with an increased risk of schizophrenia compared to other functional psychosis in all cases and in females. Maternal Rhesus negative status is associated with an increased risk of affective disorder compared to other functional psychosis in females, but not in males or when all cases are considered together. Intervention delivery is associated with an increased risk of other functional psychosis compared to affective disorder in all cases, but not in either gender separately. Given the smaller numbers of index cases with other functional psychosis, these results must be interpreted with caution.

Table 4.9.2 Crude odds ratios and 95% C.I. by diagnosis

	Schizophrenia compared to affective disorder			Schizophrenia compared to other functional psychosis			Affective disorder compared to other functional psychosis		
	All	Males	Females	All	Males	Females	All	Males	Females
Mother not married	0.82 0.53-1.28	0.66 0.35-1.26	1.06 0.54-2.06	0.95 0.54-1.67	1.06 0.48-2.33	0.94 0.40-2.20	1.15 0.67-1.98	1.60 0.69-3.71	0.89 0.43-1.83
Low social class	1.66 0.56-4.87	1.44 0.27-7.63	2.03 0.44-9.36	2.09 0.44-10.06	0.95 0.18-5.09	*	1.26 0.25-6.37	0.66 0.09-4.87	*
Primiparity	0.81 0.54-1.22	0.75 0.41-1.38	0.99 0.53-1.84	0.75 0.45-1.25	0.62 0.31-1.23	1.01 0.46-2.25	0.92 0.56-1.51	0.83 0.39-1.74	1.03 0.52-2.03
Mother Rhesus negative	0.76 0.46-1.26	0.71 0.34-1.48	0.73 0.32-1.66	1.39 0.67-2.86	0.88 0.38-2.03	3.77 0.76-18.57	1.83 0.91-3.64	1.23 0.50-3.03	**5.14** **1.17-22.53**
Pre eclampsia	1.54 0.41-5.83	0.56 0.08-4.08	4.11 0.67-25.28	1.29 0.24-6.76	1.19 0.19-7.47	*	0.83 0.15-4.63	0.29 0.04-2.12	*
Bleeding in pregnancy	*	*	*	*	*	*	1.56 0.43-5.73	0.21 0.02-2.11	*
Prematurity	0.90 0.31-2.64	0.57 0.11-2.91	1.55 0.36-6.70	0.58 0.17-1.95	0.26 0.05-1.20	2.37 0.24-23.59	0.64 0.20-2.03	0.45 0.10-2.12	1.53 0.17-13.47
Labour induced or c/s	1.20 0.78-1.86	1.06 0.54-2.07	1.74 0.92-3.29	**2.15** **1.15-4.01**	1.55 0.68-3.55	**3.67** **1.40-9.63**	1.78 0.96-3.30	1.46 0.59-3.61	2.11 0.87-5.10
Non-OA presentation	0.86 0.27-2.76	0.54 0.13-2.22	0.89 0.09-8.74	0.60 0.16-2.29	0.68 0.12-3.85	0.39 0.03-4.48	0.70 0.20-2.45	1.27 0.22-7.26	0.44 0.07-2.73
Intervention delivery	1.26 0.71-2.24	1.24 0.53-2.91	1.20 0.49-2.93	0.60 0.32-1.13	0.60 0.26-1.38	0.57 0.20-1.59	**0.47** **0.25-0.89**	0.48 0.18-1.28	0.48 0.20-1.13
Low birth weight	2.04 0.48-8.66	*	*	2.45 0.28-21.36	1.87 0.21-16.50	*	1.20 0.12-11.75	*	*
Apgar at 1 minute < 7	1.11 0.60-2.05	0.93 0.38-2.28	1.36 0.52-3.56	0.78 0.36-1.73	1.08 0.38-3.12	0.54 0.15-1.93	0.71 0.33-1.52	1.17 0.37-3.71	0.40 0.13-1.19
Apgar at 5 minutes < 8	0.81 0.40-1.62	1.26 0.41-3.93	0.75 0.25-2.22	0.50 0.21-1.18	0.79 0.25-2.54	0.30 0.08-1.16	0.62 0.28-1.38	0.63 0.16-2.42	0.40 0.13-1.19
Any OC	1.00 0.67-1.50	0.83 0.46-1.51	1.44 0.76-2.76	1.29 0.78-2.14	0.98 0.50-1.93	2.07 0.92-4.65	1.28 0.79-2.10	1.18 0.56-2.50	1.43 0.73-2.80

* Odds ratio could not be calculated.

4.9.3 Logistic regression modelling by diagnosis

No single demographic variable or obstetric complication is associated with an increased crude OR for schizophrenia compared to affective disorder. In keeping with this finding, the logistic regression model also finds no variable to be associated with an increased or decreased risk of schizophrenia compared to affective disorder.

The risk of schizophrenia compared to other functional psychosis is increased by induced labour or elective c/s in the crude OR comparison above, but in the logistic regression model an increased risk of schizophrenia is found for intervention delivery, and this finding persists when all other OCs are included in the model (corrected OR 2.23, 95% C.I. 1.62-4.89), but does not persist when potential confounding factors of parity, socio-economic status and marital status are included. When genders are analysed separately, no OC or demographic variable alters the risk in male subjects, but in females, the risk of schizophrenia is increased by maternal Rhesus negative status and by induced labour or elective c/s in a model controlling for all other demographic and obstetric variables.

The crude ORs for the risk of affective disorder compared to other functional psychosis indicate maternal Rhesus negative status and intervention delivery as likely risks. In the logistic regression model, intervention delivery is associated with a decreased risk of affective disorder compared to other functional psychosis when all other variables are controlled for. In female subjects alone, the risk of affective disorder compared to other functional psychosis is increased by maternal Rhesus negative status.

Table 4.9.3 Logistic regression coefficients and corrected odds ratios by diagnosis

Comparison	Variable	Subgroup	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
OR for schizophrenia compared to affective disorder	No OC or demographic variable associated with increased risk of schizophrenia							
OR for schizophrenia compared to other functional psychosis	Mother Rhesus negative	Females	0.48	0.97	0.98	1	<0.05	7.18 (1.06-48.53)
	Labour induced or c/s		0.48	1.12	0.57	1	<0.05	3.07 (1.01-9.37)
OR for affective disorder compared to other functional psychosis	Intervention delivery	All	0.76	-0.91	0.41	1	<0.05	0.41 (0.18-0.90)
	Mother Rhesus negative	Females	0.15	1.77	0.77	1	<0.05	5.88 (1.29-26.77)

4.10 Comparisons using other diagnostic criteria

In order to test the effect of the diagnostic system used, comparisons were made on the basis of DSM-III-R and RDC criteria. As illustrated in figure 4.1, RDC criteria diagnosed 526 of the 627 potential index cases with a disorder, and produced the highest number of cases of schizophrenia (275), and lowest number of cases of other functional psychosis (26). By DSM-III-R there were 194 patients with schizophrenia. The numbers of patients with affective disorder was highest when DSM-III-R criteria were used, but are similar using ICD-9 and RDC criteria. By DSM-III-R criteria, there were 510 index cases who had 848 siblings, and each of these 1,358 had five controls, making a total of 8,148 births available for analysis. By RDC criteria, there were 526 index cases, 875 siblings and a total of 8,406 births available for analysis.

Tables 4.10.2 and 4.10.3 show the OCs and major confounding factors for all DSM-III-R and RDC diagnoses. Comparing these with table 4.5.1 the similarities are striking, and the only difference is in maternal marital status between groups using DSM-III-R criteria, which is not seen using ICD-9 or RDC criteria. This indicates that the diagnostic system used was unlikely to have a significant effect and therefore further comparisons using DSM-III-R and RDC diagnoses were not pursued.

Table 4.10.1 Demographics details and obstetric complications by DSM-III-R criteria

	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	510	2,550	848	4,240	
Maternal age at delivery: mean (s.d.)	26.0 (5.6)	26.2 (5.6)	26.0 (5.2)	26.0 (5.4)	n.s.
Mother not married: N (%)	17 (3.3)	161 (6.3)	44 (5.2)	222 (5.2)	<0.05
Low social class: N (%)	146 (28.6)	555 (21.8)	263 (31.0)	972 (22.9)	<0.01
Primiparity: N (%)	195 (38.2)	1,019 (40.0)	216 (25.5)	1,651 (38.9)	<0.01
Mother Rhesus negative N (%)	93 (19.6)	449 (19.5)	156 (19.4)	706 (19.1)	n.s.
Pre-eclampsia: N (%)	11 (2.2)	43 (1.7)	13 (1.5)	109 (2.6)	n.s.
Bleeding in pregnancy: N (%)	15 (2.9)	71 (2.8)	28 (3.3)	136 (3.2)	n.s.
Prematurity: N (%)	19 (4.0)	71 (3.0)	28 (3.6)	125 (3.1)	n.s.
Labour induced or c/s: N (%)	139 (27.3)	636 (24.9)	215 (25.4)	1,151 (27.1)	n.s.
Non-OA presentation: N (%)	18 (3.8)	100 (4.4)	26 (3.4)	140 (3.6)	n.s.
Intervention delivery: N (%)	80 (15.7)	404 (15.8)	80 (9.4)	665 (15.7)	<0.01
Low birth weight: N (%)	9 (2.0)	45 (2.0)	16 (2.2)	75 (2.0)	n.s.
Apgar at 1 minute < 7: N (%)	75 (26.4)	379 (26.7)	118 (25.7)	567 (24.7)	n.s.
Apgar at 5 minutes < 8: N (%)	55 (19.4)	258 (18.2)	87 (19.0)	380 (16.6)	n.s.
Any OC: N (%)	289 (56.7)	1,393 (54.6)	470 (55.4)	2,398 (56.6)	n.s.

Table 4.10.2 Demographics details and obstetric complications by RDC criteria

	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	526	2,630	875	4,375	
Maternal age at delivery: mean (s.d.)	25.9 (5.5)	26.2 (5.6)	26.0 (5.2)	26.1 (5.4)	n.s.
Mother not married: N (%)	17 (3.2)	161 (6.1)	47 (5.4)	232 (5.3)	n.s.
Low social class: N (%)	149 (28.3)	580 (22.1)	270 (30.9)	995 (22.7)	<0.01
Primiparity: N (%)	200 (38.0)	1,035 (39.4)	227 (25.9)	1,699 (38.8)	<0.01
Mother Rhesus negative N (%)	104 (21.1)	466 (19.6)	178 (21.3)	734 (19.4)	n.s.
Pre-eclampsia: N (%)	11 (2.1)	46 (1.7)	15 (1.7)	107 (2.4)	n.s.
Bleeding in pregnancy: N (%)	12 (2.3)	74 (2.8)	30 (3.4)	137 (3.1)	n.s.
Prematurity: N (%)	19 (3.8)	72 (2.9)	32 (4.0)	134 (3.2)	n.s.
Labour induced or c/s: N (%)	142 (27.0)	676 (25.7)	233 (26.6)	1,210 (27.7)	n.s.
Non-OA presentation: N (%)	19 (3.9)	107 (4.6)	32 (4.0)	148 (3.7)	n.s.
Intervention delivery: N (%)	84 (16.0)	414 (15.7)	82 (9.4)	717 (16.4)	<0.01
Low birth weight: N (%)	9 (1.9)	43 (1.8)	18 (2.4)	82 (2.1)	n.s.
Apgar at 1 minute < 7: N (%)	74 (25.0)	398 (26.9)	119 (24.3)	611 (25.0)	n.s.
Apgar at 5 minutes < 8: N (%)	54 (18.2)	273 (18.4)	87 (17.8)	410 (16.8)	n.s.
Any OC: N (%)	293 (55.7)	1,447 (55.0)	488 (55.8)	2,507 (57.3)	n.s.

4.11 Summary

Obstetric complications are not associated with an increased risk of schizophrenia compared to unrelated controls or to well siblings when confounding factors are controlled for in logistic regression models. First born female infants are at increased risk of schizophrenia compared to their sex-matched siblings. The risk of schizophrenia compared to other functional psychosis is increased by the mother being Rhesus negative and by induction of labour or elective caesarean section in female subjects only.

Being born to a mother of lower social class is associated with an increased risk of affective disorder in all subjects and in females. Bleeding in pregnancy and a low Apgar score 5 minutes after delivery are associated with an increased risk of affective disorder compared to controls after confounding variables are controlled for, but only in female subjects. A low Apgar score at 5 minutes is similarly associated with an increased risk of affective disorder compared to schizophrenia, also only in females. Having a Rhesus negative mother is associated with an increased risk of affective disorder compared to other functional psychosis, again only in females. Being born to a mother who was not married is associated with a decreased risk of affective disorder compared to normal controls.

A low Apgar score at 5 minutes is an apparent risk factor for other functional psychosis compared to normal controls. Intervention delivery by forceps, other instruments or emergency caesarean section is associated with an increased risk of other functional psychosis compared to affective disorder in the whole sample, but neither of these findings occurred separately by gender.

Initial differences between all subjects and their well siblings are not sustained when the confounding effects of maternal marital status, social class and parity, as well as the presence of other obstetric variables, are controlled for using conditional logistic regression techniques. Subjects with schizophrenia, affective disorder and other functional psychosis do not differ in their rates of OCs from their well siblings.

Chapter 5:

Season of birth, age of onset and family history

In order to explore whether OCs might be more relevant in particular subgroups of patients, rather than all subjects, the data were further explored with respect to three hypotheses; (1) that OCs may explain the apparent excess of winter / spring births seen in schizophrenic subjects, (2) that OCs may be associated with an earlier age of onset both in schizophrenia and in affective disorder, and (3) that OCs preferentially increase the risk of illness in those without a family history. For each of these analyses, the data are described and the method of dividing the group explained before the relationships with OCs are examined. The same technique of presenting the rates of OCs across groups, followed by calculation of crude ORs and the use of logistic or conditional logistic regression to control for confounding factors and calculate adjusted ORs is applied, but for these analyses tables showing crude odds ratios are not presented, but can be found in the Appendix.

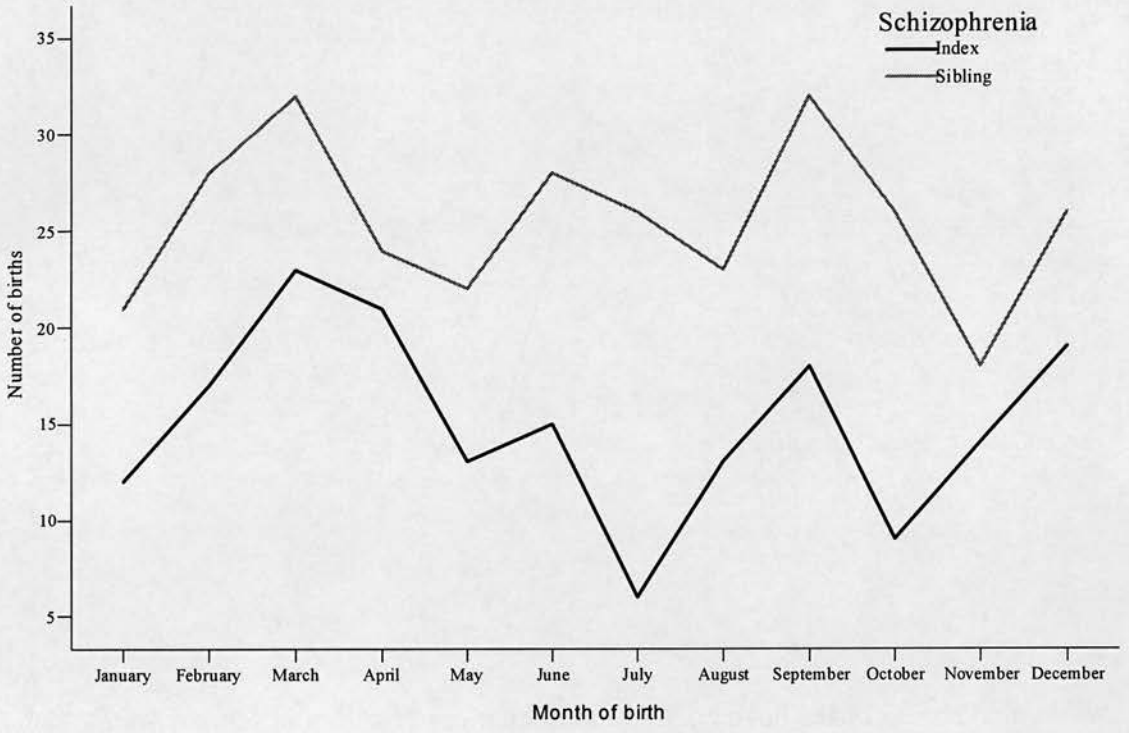
5.1 Season of birth in schizophrenic subjects

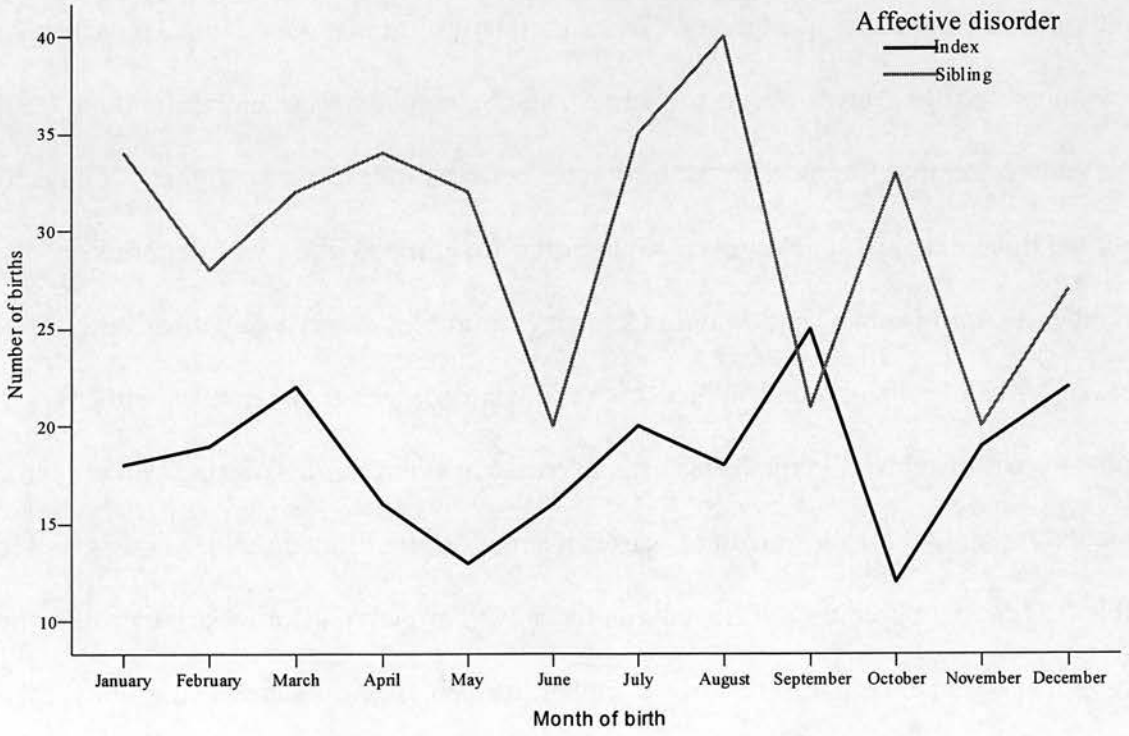
Before exploring whether increased OCs might explain an excess of births in winter or late spring in schizophrenic subjects, it was necessary to establish if there was any such seasonal pattern in schizophrenic births. As index cases and controls were matched on month of birth, the study design only allows for comparison of month of birth between index cases and their siblings. Figure 5.1 shows the number of index cases and well siblings born each month for each diagnostic group.

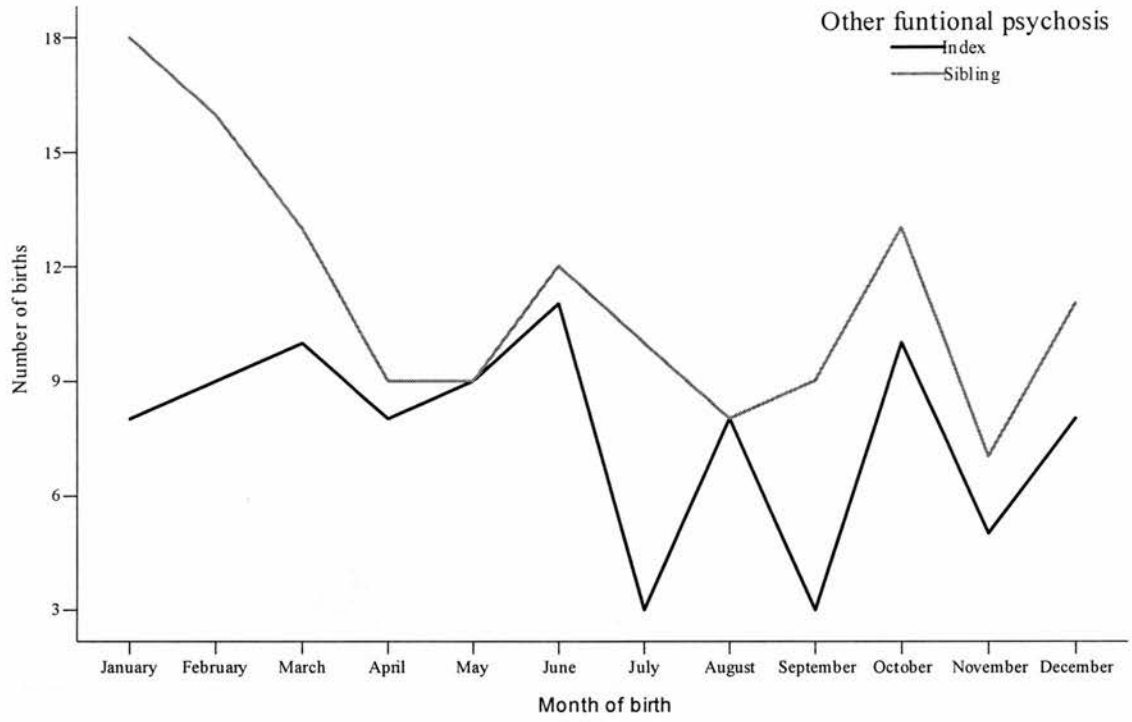
Visual inspection of the distribution of month of birth for schizophrenic subjects shows a peak number of births in March for both the subjects and their siblings. However, the siblings show a large decrease in births in April, whereas the numbers of schizophrenic patients born in April remains high. Both groups also tend to have a peak in births in September, but the schizophrenic subjects differ from their siblings in having their lowest number of births in July.

Patients with affective disorder and those with other functional psychosis also show high numbers of births in March and September, but also in December. There appear to be greater differences between these subjects and their siblings than those in seen in the schizophrenic subjects. None of these differences are statistically significant using Chi-squared tests (χ^2) as the numbers of index cases and siblings born per month are small.

Figure 5.1 Number of births by month







Late winter and spring births have been found to be more common in schizophrenia, but definitions of late winter / spring vary. When month of birth is grouped into January to April (late winter / spring), May to August (summer) and September to December (autumn / early winter), there are no differences in the birth rates between index cases and their siblings for any of the three diagnoses. However, when births are grouped into two categories, November to April (winter) and May to October (summer), there is a statistically significant excess of births of schizophrenic subjects born in winter, which may represent either a genuine excess of schizophrenic births, or a decrease in sibling births, during winter. No differences are found for those with affective disorder or other functional psychosis, as seen in table 5.1. Schizophrenic subjects, but not those with affective disorder or other functional psychosis, show an excess of births in November to April. For the sake of simplicity, this period will be referred to as 'winter' and May to October as 'summer' hereafter. Having established a greater rate of schizophrenic births in winter, the question of whether those

schizophrenic subjects born in winter have a higher rate of OCs in comparison to those born in summer is addressed.

Table 5.1 N (%) of births by season

		All psychoses		Schizophrenia		Affective		Other psychoses	
		Index cases	Siblings	Index cases	Siblings	Index cases	Siblings	Index cases	Siblings
Three season model	Jan – Apr	230 (36.7)	377 (36.0)	73 (40.6)	105 (34.3)	75 (34.1)	128 (36.0)	35 (38.0)	56 (41.5)
	May – Aug	186 (29.7)	355 (33.9)	47 (26.1)	99 (32.4)	67 (30.5)	127 (35.7)	31 (33.7)	39 (28.9)
	Sep – Dec	211 (33.7)	315 (30.1)	60 (33.3)	102 (33.3)	78 (35.5)	101 (28.4)	26 (28.3)	40 (29.6)
Two season model	Nov – Apr	339 (54.1)	519 (49.6)	106* (58.9)	149* (48.7)	116 (52.7)	175 (49.2)	48 (52.2)	74 (54.8)
	May – Oct	288 (45.9)	528 (50.4)	74* (41.1)	157* (51.3)	104 (47.3)	181 (50.8)	44 (47.8)	61 (45.2)

* χ^2 $p<0.05$

5.2 OCs and season of birth in schizophrenia

Date of birth was available for all subjects, and the 180 schizophrenic subjects were divided into those born in winter (November – April) and those born in summer, and compared to normal controls and siblings. While the normal controls were matched on month of birth, the siblings were not. Subjects were therefore compared only with siblings born in the same season. As apparent differences between index cases and siblings may be due to differences between these siblings and sibling-controls, the comparison between winter-born and summer-born subjects was conducted in a similar fashion to that of the total schizophrenic group (see 4.6). As bleeding in pregnancy did not occur in any of the schizophrenic subjects, this comparison is excluded from table 5.2 which shows the frequency of each OC and demographic variable of interest.

Schizophrenics born in winter are more often male. Those born in summer have mothers who were older at delivery compared to their siblings. Schizophrenic subjects and their siblings are more likely to be of lower social class than controls, but this reaches statistical significance only for those born in summer. Winter-born schizophrenics and their siblings are less likely to have been born to primiparous women, but the reverse is seen in those born in summer. Winter-born schizophrenics show a trend towards a lower Apgar score 5 minutes after delivery in comparison to their siblings, but the difference between the groups just fails to reach statistical significance. The groups differ significantly in their rates of intervention delivery and of any obstetric complication, with the difference appearing to be due to low rates in the siblings. Summer-born schizophrenics show no tendencies towards similar differences.

Table 5.2.1 Comparison of winter and summer birth in schizophrenia

	Winter births					Summer births				
	Index cases	Controls	Siblings	Sibling-controls	p	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	106 (71.7)	530 (71.7)	149 (48.3)	475 (48.3)	<0.01	74 (63.5)	370 (63.5)	157 (56.7)	785 (56.7)	n.s.
Maternal age at delivery: mean (s.d.)	26.4 (5.72)	26.0 (5.75)	25.9 (4.70)	26.1 (5.41)	n.s.	26.3 (5.53)	26.8 (5.49)	25.2 (5.09)	25.8 (5.08)	<0.01
Mother not married: N (%)	5 (4.7)	38 (7.2)	11 (7.4)	35 (4.7)	n.s.	3 (4.1)	21 (5.7)	10 (6.4)	38 (4.8)	n.s.
Low social class: N (%)	25 (23.6)	108 (20.4)	37 (24.8)	166 (22.3)	n.s.	22 (29.7)	78 (21.1)	52 (33.1)	182 (23.2)	<0.01
Primiparity: N (%)	34 (32.1)	215 (40.6)	35 (23.5)	269 (36.1)	<0.01	30 (40.5)	135 (36.5)	46 (29.3)	325 (41.1)	<0.05
Mother Rhesus negative: N (%)	15 (14.9)	83 (16.7)	23 (16.2)	134 (20.6)	n.s.	16 (24.2)	62 (19.2)	29 (19.2)	136 (20.6)	n.s.
Pre-eclampsia: N (%)	2 (1.9)	15 (2.8)	3 (2.0)	14 (1.9)	n.s.	3 (4.1)	5 (1.4)	2 (1.3)	17 (2.2)	n.s.
Prematurity: N (%)	4 (4.0)	14 (2.8)	7 (5.0)	27 (3.8)	n.s.	2 (2.8)	7 (2.0)	5 (3.6)	29 (3.9)	n.s.
Labour induced or c/s: N (%)	34 (32.1)	140 (26.4)	29 (19.5)	203 (27.2)	n.s.	22 (29.7)	88 (23.8)	41 (26.1)	203 (25.9)	n.s.
Non-OA presentation: N (%)	4 (4.2)	22 (4.7)	6 (4.3)	26 (3.8)	n.s.	1 (1.4)	13 (4.0)	3 (2.1)	27 (3.8)	n.s.
Intervention delivery: N (%)	18 (17.0)	18 (16.4)	10 (6.7)	123 (16.5)	<0.05	9 (12.2)	57 (15.4)	19 (12.1)	109 (13.9)	n.s.
Low birth weight: N (%)	4 (4.2)	7 (1.5)	2 (1.5)	15 (2.3)	n.s.	1 (1.5)	6 (1.8)	3 (2.3)	14 (2.0)	n.s.
Apgar at 1 minute < 7: N (%)	17 (25.4)	95 (28.4)	16 (18.8)	94 (22.1)	n.s.	8 (23.5)	50 (29.4)	23 (33.8)	89 (26.2)	n.s.
Apgar at 5 minutes < 8: N (%)	12 (17.9)	67 (20.0)	13 (15.3)	54 (12.7)	n.s. =0.054	4 (11.8)	33 (19.4)	33 (19.4)	59 (17.4)	n.s.
Any of the above OCs: N (%)	66 (62.3)	309 (58.3)	67 (45.0)	417 (56.0)	<0.01	43 (53.8)	199 (53.8)	89 (56.7)	443 (56.4)	n.s.

Calculation of crude ORs for schizophrenia, stratified by season of birth, indicates that no demographic or obstetric variable is associated with an increased risk of schizophrenia compared to normal controls in those born either in winter or summer (full table shown in Appendix). However, in comparison with well siblings, an increased risk of schizophrenia was found in winter-born subjects following induced labour or elective c/s (OR 1.95, 95% C.I. 1.10-3.47), intervention delivery (OR 2.84, 95% C.I. 1.25-6.44) and any OC (OR 2.02, 95% C.I. 1.20-3.36). Visual inspection of the data suggests that this may be due to fewer OCs in the siblings, rather than an increased rate of complications in the subjects. This possibility was explored in a logistic regression model which controlled for mother's marital status, social class and parity, as shown in table 5.2.2.

As expected, no variable is associated with an increased risk of schizophrenia in winter-born infants compared to controls. The comparison between subjects and siblings using conditional logistic regression also found no variable to be associated with an increased risk of schizophrenia in those born in winter. When siblings are compared to controls, primiparity, intervention delivery and any OC are associated with a reduced risk, which suggests that the crude OR findings may be due to differences between siblings and sibling-controls, and it would seem likely that the apparent differences between schizophrenic subjects and their siblings are related to the siblings having lower rates of primiparity, intervention delivery and any OC than their matched controls.

Table 5.2.2 Winter births. Logistic regression coefficients for schizophrenia

Comparison	Variable	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
OR for schizophrenia compared to controls	No OC or demographic variable associated with risk of schizophrenia						
OR for schizophrenia compared to Siblings	No OC or demographic variable associated with risk of schizophrenia						
OR for siblings compared to sibling-controls	Primiparity	0.08	-0.52	0.21	1	<0.05	0.60 (0.39-0.91)
	Intervention delivery	0.08	-0.80	0.35	1	<0.05	0.45 (0.22-0.89)
	Any OC	0.58	-0.40	0.18	1	<0.05	0.67 (0.47-0.96)

5.3. Age of onset in diagnostic groups

Age of onset was recorded as age in whole years at first admission in data collected from case notes and was available for 583 of the 627 potential index cases (93.0%). Age of onset ranged from 5 to 40 with mean (s.d.) of 23.8 (5.7). There is a significant difference in mean age of onset between diagnostic groups; patients with schizophrenia are two years younger at first admission than those with affective disorder. Subjects with other functional psychosis have an age of onset between these two other conditions, numbers in this group are already small, so no comparison of younger with older onset cases in this group is undertaken. Median age of onset was used to divide the other two diagnostic groups into younger and older onset cases; younger age of onset in schizophrenia is defined as before the 22nd birthday, younger age of onset in affective disorder is defined as age up to the 25th birthday.

Table 5.3 Mean and median age of onset by diagnosis.

	Schizophrenia	Affective Disorder	Other functional psychosis	p
Range	8-40	13-38	5-38	
Mean (s.d.)	22.58 (5.43)	25.02 (5.83)	23.06 (6.39)	<0.001*
95% C.I. for mean	21.77 - 23.39	24.31 - 25.73	21.72 - 24.39	
Median	22	24	23	<0.001**

* by ANOVA ** by Kruskal-Wallis

5.4 OCs and age of onset in schizophrenia

Using the same method as for the comparison between winter-born and summer-born schizophrenic subjects, demographic and obstetric variables were compared between groups for younger and older onset subgroups for schizophrenia as shown in table 5.4.1. Schizophrenic subjects with an older age of onset are more often male and show differences in maternal age at delivery, social class and gestational age which are not seen in those of younger age of onset, and which require to be explored further. Both older and younger onset groups show lower rates of primiparity in siblings of schizophrenic subjects.

Crude odds ratios for schizophrenia were calculated for younger and older onset subgroups. In comparison with controls increased risk for younger onset schizophrenia was found following induced labour or elective c/s (OR 1.81, 95% C.I. 1.11-2.93) and low birth weight (OR 3.97, 95% C.I. 1.04-15.12) but there is no association between these complications and the risk of older onset schizophrenia. No demographic or obstetric variables are associated with an increased risk of either younger or older onset schizophrenia in comparison with well siblings. The differences between siblings and sibling-controls on parity and social class are similar to what has previously been found for schizophrenia (full ORs are shown in the Appendix).

Table 5.4.1 Comparison of younger and older age of onset in schizophrenia

	Age of onset ≤ 21				p	Age of onset ≥ 22				p
	Index cases	Controls	Siblings	Sibling-controls		Index cases	Controls	Siblings	Sibling-controls	
N: (% male)	87 (58.6)	435 (58.6)	143 (54.5)	390 (54.5)	n.s.	**88 (78.4)**	**440 (78.4)**	**156 (50.6)**	**395 (50.6)**	**<0.01**
Maternal age at delivery: mean (s.d.)	26.77 (5.64)	26.06 (5.57)	26.27 (5.12)	25.80 (5.05)	n.s.	**25.78 (5.68)**	**26.64 (5.79)**	**24.82 (4.64)**	**26.19 (5.42)**	**<0.01**
Mother not married: N (%)	4 (4.6)	35 (8.0)	12 (8.4)	34 (4.8)	n.s.	4 (4.5)	24 (5.5)	9 (5.8)	37 (4.7)	n.s.
Low social class: N (%)	18 (20.7)	88 (20.2)	29 (20.3)	157 22.0%	n.s.	**27 (30.7)**	**96 (21.8)**	**57 (36.5)**	**183 (23.5)**	**<0.01**
Primiparity: N (%)	**31 (35.6)**	**155 (35.6)**	**37 (25.9)**	**279 (39.0)**	**<0.05**	**31 (35.2)**	**179 (40.7)**	**42 (26.9)**	**296 (37.9)**	**<0.05**
Mother Rhesus negative: N (%)	16 (20.0)	75 (19.3)	25 (18.2)	127 (21.3)	n.s.	13 (15.9)	66 (16.2)	27 (18.1)	139 (20.2)	n.s.
Pre-eclampsia: N (%)	4 (4.6)	14 (3.2)	3 (2.1)	15 (2.1)	n.s.	1 (1.1)	5 (1.1)	2 (1.3)	15 (1.9)	n.s.
Prematurity: N (%)	1 (1.2)	11 (2.7)	3 (2.3)	32 (4.8)	n.s.	**5 (6.0)**	**10 (2.4)**	**9 (6.3)**	**24 (3.2)**	**<0.05**
Labour induced or c/s: N (%)	33 (37.9)	110 (25.3)	37 (25.9)	199 (27.8)	n.s.	21 (23.9)	111 (25.2)	31 (19.9)	204 (26.20	n.s.
Non-OA presentation: N (%)	2 (2.5)	15 (3.9)	4 (3.1)	27 (4.2)	n.s.	3 (3.6)	19 (4.9)	5 (3.4)	25 (3.5)	n.s.
Intervention delivery: N (%)	10 (11.5)	63 (14.5)	12 (8.4)	104 (14.5)	n.s.	16 (18.2)	74 (16.8)	16 (10.3)	121 (15.5)	n.s.
Low birth weight: N (%)	4 (5.1)	5 (1.3)	3 (2.4)	16 (2.6)	n.s.	1 (1.3)	8 (2.0)	2 (1.5)	12 (1.7)	n.s
Apgar at 1 minute < 7: N (%)	12 (22.6)	74 (27.9)	19 (24.4)	91 (23.3)	n.s	13 (27.1)	71 (29.6)	20 (27.0)	91 (24.6)	n.s.
Apgar at 5 minutes < 8: N (%)	9 (17.0)	59 (21.3)	17 (21.8)	59 (15.1)	n.s.	7 (14.6)	41 (17.1)	14 (18.9)	53 (14.3)	n.s.
Any OC: N (%)	58 (66.7)	246 (56.6)	77 (53.8)	416 (58.2)	n.s.	48 (54.5)	250 (56.8)	77 (49.4)	431 (55.3)	n.s.

The logistic regression analysis is shown in table 5.4.2. Both induced labour or elective c/s and low birth weight remain as risk factors for younger onset schizophrenia compared to controls, but are not associated with an increased risk for older onset schizophrenia, and no differences remain when cases are compared to siblings.

Table 5.4.2 Logistic regression coefficients for schizophrenia by age of onset

	Comparison	Variable	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
Younger onset	Schizophrenia compared to controls	Labour induced or c/s	0.92	0.58	0.29	1	<0.05	1.80 1.11-2.93
		Low birth weight	0.92	1.41	0.69	1	<0.05	4.08 1.06-15.72
	Schizophrenia compared to siblings	No OC or demographic variable associated with risk of schizophrenia						
	Siblings compared to sibling-controls	Mother not married	0.80	0.76	0.39	1	<0.05	2.14 1.00-4.55
		Primiparity	0.80	-0.65	0.22	1	<0.01	0.52 0.34-0.81
Older onset	Schizophrenia compared to controls	No OC or demographic variable associated with risk of schizophrenia						
	Schizophrenia compared to siblings	No OC or demographic variable associated with risk of schizophrenia						
	Siblings compared to sibling-controls	Low social class	0.63	0.57	0.20	1	<0.05	1.76 1.20-2.59
		Primiparity	0.63	-0.48	0.21	1	<0.05	0.63 0.42-0.95

5.5 OCs and age of onset in affective disorder

Table 5.5.1 shows the rates of OCs in index cases of affective disorder and their comparison groups, stratified by age of onset. In subjects with affective disorder, the younger age of onset subgroup contains a greater proportion of males than the older onset group, the previously found differences in social class and parity (see table 4.7.2) occur in both older and younger onset subgroups. Intervention delivery also differs between groups in both younger and older onset subgroups. The siblings of subjects with affective disorder of older onset appear to have higher rates of maternal Rhesus negative status and of low birth weight.

Crude ORs for affective disorder in younger and older onset groups indicate that lower social class (OR 1.85, 95% C.I. 1.19-2.88) and premature delivery (OR 2.86, 95% C.I. 1.03-7.91) are associated with an increased risk of younger onset affective disorder compared to controls, but no effect is seen for older onset cases. Being born to an unmarried mother is associated with a decreased risk of affective disorder compared to controls for younger onset cases only (OR 0.21, 95% C.I. 0.05-0.89). Primiparity is associated with an increased risk of both younger and older onset affective disorder compared to siblings, but intervention delivery is associated with an increased risk in younger onset subjects only (OR 2.15, 95% C.I. 1.00-4.62). Differences between siblings and controls are apparent for social class, parity and intervention delivery in both groups, and for Rhesus negative status and low birth weight in older onset affective disorder. The full ORs are shown in the Appendix.

Table 5.5.1 Comparison of younger and older age of onset in affective disorder

	Age of onset ≤ 24				p	Age of onset ≥ 25				p
	Index cases	Controls	Siblings	Sibling-controls		Index cases	Controls	Siblings	Sibling-controls	
N: (% male)	**112 (36.6)**	**560 (36.6)**	**169 (52.7)**	**845 (52.7)**	**<0.01**	**108 (26.9)**	**540 (26.9)**	**187 (51.9)**	**485 (51.9)**	**<0.01**
Maternal age at delivery: mean (s.d.)	24.8 (5.19)	25.8 (5.51)	25.1 (5.19)	25.8 (5.39)	n.s.	25.79 (5.59)	26.41 (5.36)	26.45 (5.26)	26.0 (5.37)	n.s.
Mother not married: N (%)	2 (1.8)	44 (7.9)	10 (5.9)	48 (5.7)	n.s.	4 (3.7)	30 (5.6)	9 (4.8)	52 (5.6)	n.s.
Low social class: N (%)	**37 (33.0)**	**118 (21.1)**	**59 (34.9)**	**191 (22.6)**	**<0.01**	**29 (26.9)**	**105 (19.4)**	**61 (32.6)**	**215 (23.0)**	**<0.01**
Primiparity: N (%)	**47 (42.0)**	**231 (41.3)**	**45 (26.6)**	**339 (40.1)**	**<0.01**	**42 (38.9)**	**211 (39.1)**	**46 (24.6)**	**368 (39.4)**	**<0.01**
Mother Rhesus negative: N (%)	25 (24.3)	96 (18.4)	39 (23.8)	151 (20.2)	n.s.	**23 (21.9)**	**109 (22.6)**	**46 (25.8)**	**151 (20.2)**	**<0.05**
Bleeding in pregnancy: N (%)	5 (4.5)	12 (2.1)	3 (1.8)	31 (3.7)	n.s.	6 (5.6)	16 (3.0)	6 (3.2)	37 (4.0)	n.s.
Pre-eclampsia: N (%)	2 (1.8)	10 (1.8)	2 (1.2)	24 (2.8)	n.s.	2 (1.9)	5 (0.9)	4 (2.1)	22 (2.4)	n.s.
Prematurity: N (%)	6 (5.7)	11 (2.1)	3 (2.0)	18 (2.2)	n.s.	2 (2.0)	19 (3.8)	7 (4.0)	29 (3.3)	n.s.
Labour induced or c/s: N (%)	36 (32.1)	153 (27.3)	47 (27.8)	244 (28.9)	n.s.	24 (22.2)	124 (23.0)	43 (23.0)	265 (28.3)	n.s.
Non-OA presentation: N (%)	4 (3.8)	25 (5.1)	6 (3.9)	31 (4.0)	n.s.	3 (3.1)	17 (3.7)	10 (5.8)	41 (4.9)	n.s.
Intervention delivery: N (%)	**17 (15.2)**	**98 (17.5)**	**13 (7.7)**	**162 (19.2)**	**<0.01**	**10 (9.3)**	**68 (12.6)**	**15 (8.0)**	**163 (17.4)**	**<0.01**
Low birth weight: N (%)	2 (2.1)	14 (2.8)	0	18 (2.4)	n.s.	**1 (1.0)**	**6 (1.3)**	**10 (6.2)**	**15 (1.8)**	**<0.01**
Apgar at 1 minute < 7: N (%)	13 (17.3)	92 (24.5)	25 (21.2)	150 (25.4)	n.s.	16 (30.8)	80 (30.8)	24 (24.2)	127 (25.7)	n.s.
Apgar at 5 minutes < 8: N (%)	9 (12.0)	62 (16.5)	15 (12.7)	107 (18.1)	n.s.	15 (28.8)	65 (25.0)	19 (19.2)	91 (18.4)	n.s.
Any OC: N (%)	69 (61.6)	326 (58.2)	102 (60.4)	512 (60.6)	n.s.	64 (59.3)	297 (55.0)	110 (58.8)	538 (57.5)	n.s.

The logistic regression analysis is shown in table 5.5.2. Low social class and prematurity remain associated with an increased risk of younger onset affective disorder, but when potential confounding factors were included no effect is seen in the older onset group. Being born to a mother who was not married is associated with a decreased risk of younger onset affective disorder compared to controls. No obstetric complication or demographic variable is associated with an increased risk of affective disorder, either of younger or of older onset, when index cases are compared to their siblings.

Table 5.5.2 Logistic regression coefficients for affective disorder by age of onset

	Comparison	Variable	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
Younger onset	Affective disorder compared to controls	Mother not married	0.45	-1.62	0.74	1	<0.05	0.20 0.05-0.84
		Low social class	0.45	0.58	0.23	1	<0.05	1.79 1.15-2.81
		Gestation < 37 weeks	0.45	1.12	0.54	1	<0.05	3.05 1.06-8.80
	Affective disorder compared to siblings	No OC or demographic variable associated with risk of affective disorder						
	Siblings compared to sibling-controls	Low social class	0.87	0.57	0.18	1	<0.01	1.77 1.24-2.53
		Primiparity	0.87	-0.43	0.20	1	<0.05	0.65 0.44-0.96
		Intervention delivery	0.87	-0.87	0.31	1	<0.01	0.42 0.23-0.79
Older onset	Affective disorder compared to controls	No OC or demographic variable associated with risk of affective disorder						
	Affective disorder compared to siblings	No OC or demographic variable associated with risk of affective disorder						
	Siblings compared to sibling-controls	Low social class	0.25	0.48	0.19	1	<0.05	1.62 1.12-2.34
		Primiparity	0.25	-0.57	0.19	1	<0.05	0.56 0.38-0.83
		Mother Rhesus negative	0.25	0.60	0.21	1	<0.05	1.81 1.21-2.71
		Intervention delivery	0.25	-0.92	0.37	1	<0.05	0.40 0.19-0.83
		Low birth weight	0.25	1.37	0.46	1	<0.01	3.93 1.59-9.71

5.6. Family history of psychiatric disorder

It has been suggested that OCs are more common in schizophrenic subjects without a family history (non-familial cases) than in those who do have family history (familial cases). The study aimed to test this by examining whether OCs occurred more frequently in those without a relevant family history. Information on family history, as recorded in the case notes, showed that 43.5 % of the 627 potential index cases had a family history of psychiatric illness recorded as a narrative description. This was transcribed and categorised by type of condition described (psychosis, affective disorder, substance misuse, learning disability, suicide, other/unspecified) and is shown in table 5.6.1. Data were categorised by the type of condition rather than by degree of relatedness, which was usually also recorded. A family history of psychosis was deemed to be present if a first or second degree relative was recorded as having schizophrenia, schizoaffective disorder, delusional disorder or any other non-affective psychosis. Differences between diagnostic groups are seen for a family history of schizophrenia, affective disorder and any condition. As this study explores both affective disorder and non-affective psychosis, a family history of either of these conditions is used in the following analyses.

Table 5.6.1 Prevalence of family history in index cases by diagnosis

Family history of:	All potential index cases N=627	Schizophrenia N=180	Affective Disorder N=220	Other functional psychosis N=92	p
Psychosis	63 (10.0)	33 (18.3)	13 (5.9)	10 (10.9)	<0.01
Affective disorder	106 (16.9)	22 (12.2)	56 (25.5)	14 (15.2)	<0.01
Substance misuse	45 (7.2)	14 (7.8)	18 (8.2)	2 (2.2)	n.s.
Suicide	21 (3.3)	3 (1.7)	13 (5.9)	2 (2.2)	n.s.
Learning disability	4 (0.6)	2 (1.1)	1 (0.5)	1 (1.1)	n.s.
Other condition	80 (12.8)	22 (12.2)	32 (14.5)	11 (12.0)	n.s.
Any condition	273 (43.5)	87 (48.3)	108 (49.1)	37 (40.2)	<0.01

5.7 OCs and family history in schizophrenia

The frequency of demographic and obstetric variables in schizophrenic subjects and their comparison groups, stratified by family history, is presented in table 5.7.1. The non-familial subgroup has a higher proportion of male subjects than the familial subgroup. Both groups show a trend for subjects and their siblings to have higher rates of lower social class than controls, this is statistically significant only for those without a family history. Both groups show lower rates of primiparity in the siblings compared to index cases and controls. Two obstetric complications are of interest; intervention delivery in those without a family history, and induced labour or elective c/s in those with a family history. As has been the case in previous analyses, visual inspection of the data indicates this may be due to lower rates of these complications in siblings rather than higher rates in schizophrenic subjects.

Crude ORs for demographic and obstetric variables for schizophrenia indicate that induced labour or elective c/s is associated with an increased risk of familial schizophrenia compared to normal controls (OR 1.98, 95% C.I. 1.06-3.70) and to their siblings (OR 2.66, 95% C.I. 1.25-5.66). Intervention delivery is associated with an increased risk of non-familial schizophrenia in comparison with siblings (OR 2.24, 95% C.I. 1.13-4.43).

Table 5.7.1 Comparison between schizophrenic subjects with and without a family history

	Non familial schizophrenia					Familial schizophrenia				
	Index cases	Controls	Siblings	Sibling-controls	p	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	127 71.7%	635 71.7%	209 49.3%	1045 49.3%	<0.01	53 60.4%	265 60.4%	97 59.8%	485 59.8%	n.s.
Maternal age at delivery: mean (s.d.)	25.98 5.72	26.32 5.62	25.25 5.00	25.91 5.24	n.s.	27.19 5.34	26.29 5.76	26.14 4.68	26.15 5.25	n.s.
Mother not married N (%)	4 3.1%	42 6.6%	15 7.2%	56 5.4%	n.s.	4 7.5%	17 6.4%	6 6.2%	17 3.5%	n.s.
Low social class: N (%)	34 26.8%	128 20.2%	60 28.7%	227 21.7%	<0.05	13 24.5%	58 21.9%	29 29.9%	121 24.9%	n.s.
Primiparity: N (%)	48 37.8%	250 39.4%	60 28.7%	418 40.0%	<0.05	16 30.2%	100 37.7%	21 21.6%	176 36.3%	<0.05
Mother Rhesus negative: N (%)	22 18.8%	98 17.1%	38 19.2%	191 21.8%	n.s.	9 18.0%	47 19.1%	14 14.7%	79 18.2%	n.s.
Pre-eclampsia: N (%)	3 2.4%	15 2.4%	4 1.9%	26 2.5%	n.s.	2 3.8%	5 1.9%	1 1.0%	5 1.0%	n.s.
Prematurity: N (%)	4 3.3%	16 2.7%	8 4.2%	41 4.2%	n.s.	2 3.9%	5 2.0%	4 4.3%	15 3.2%	n.s.
Labour induced or c/s: N (%)	36 28.3%	166 26.1%	52 24.9%	272 26.0%	n.s.	20 37.7%	62 23.4%	18 18.6%	134 27.6%	<0.05
Non-OA presentation: N (%)	3 2.5%	27 4.8%	4 2.2%	37 3.9%	n.s.	2 4.0%	8 3.4%	5 5.3%	16 3.6%	n.s.
Intervention delivery: N (%)	21 16.5%	105 16.5%	17 8.1%	160 15.3%	<0.05	6 11.3%	39 14.7%	12 12.4%	72 14.8%	n.s.
Low birth weight: N (%)	4 3.5%	8 1.4%	4 2.3%	19 2.1%	n.s.	1 2.0%	5 2.2%	1 1.1%	10 2.3%	n.s.
Apgar at 1 minute < 7: N (%)	14 20.6%	89 26.2%	23 24.0%	110 22.9%	n.s.	11 33.3%	56 33.9%	16 28.1%	73 25.6%	n.s.
Apgar at 5 minutes < 8: N (%)	8 11.8%	59 17.4%	19 19.8%	65 13.5%	n.s.	8 24.2%	41 24.8%	12 21.1%	48 16.8%	n.s.
Any OC: N (%)	78 61.4%	352 55.4%	107 51.2%	581 55.6%	n.s.	31 58.5%	156 58.9%	49 50.5%	279 57.5%	n.s.

Logistic regression models which included all variables implicated in the crude OR calculations were fitted for both familial and non-familial schizophrenia and are shown in table 5.7.2. For those without a family history, no OC or confounding variable is associated with an altered risk compared to normal controls or to well siblings. For those with a family history, induced labour or elective c/s remains a risk factor when potential confounding factors are controlled for.

Table 5.7.2 Logistic regression coefficients for schizophrenics by family history

Family History	Comparison	Variable	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
Non-familial	Schizophrenia compared to controls	No OC or demographic variable associated with risk of schizophrenia						
	Schizophrenia compared to siblings	No OC or demographic variable associated with risk of schizophrenia						
	Siblings compared to sibling-controls	Low social class	0.97	0.35	0.17	1	<0.05	1.42 1.01-1.98
		Primiparity	0.97	-0.42	0.17	1	<0.05	0.66 0.47-0.92
		Intervention delivery	0.97	-0.56	0.27	1	<0.05	0.57 0.33-0.97
Familial	Schizophrenia compared to Controls	Labour induced or c/s	0.53	0.70	0.32	1	<0.05	2.02 1.08-3.78
	Schizophrenia compared to siblings	No OC or demographic variable associated with risk of schizophrenia						
	Siblings compared to sibling-controls	Primiparity	1.00	-0.76	0.27	1	<0.01	0.47 0.28-0.79

5.8 OCs and family history in affective disorder

Table 5.8.1 shows the frequency of demographic and obstetric variables in affective disorder stratified by family history. Both subgroups contain a lower proportion of males than sibling comparison groups, and subjects and their siblings are more often of lower social class than controls in both subgroups. Maternal age at delivery is younger in subjects and siblings compared to controls only for those with a family history. Primiparity tends to occur less often in the siblings compared to index cases and controls; this is statistically significant only for those without a family history. Two OCs, bleeding in pregnancy and intervention delivery appear to differ between index cases, siblings and controls only in those without a family history. Of these, intervention delivery appears to occur less often in siblings of patients with non-familial affective disorder, but the increased rates of bleeding in pregnancy appear to be due to an increase in the rate of this complication in index cases.

Calculation of crude ORs for affective disorder for subjects with and without a family history indicates a number of associations. In non-familial cases, lower social class (OR 1.50, 95% C.I. 1.01-2.23) and bleeding in pregnancy (OR 2.60, 95% C.I 1.19-5.68) are associated with an increased risk of affective disorder compared to controls. In comparison with well siblings, primiparity (OR 2.51, 95% C.I 1.63-3.87) and bleeding in pregnancy (OR 4.31, 95% C.I 1.33-13.98) are associated with an increased risk. For familial cases low social class (OR 2.16, 95% C.I 1.23-3.81) is associated with an increased risk, but OCs are not. A decreased risk was found in association with being born to a mother who was not married (OR 0.07, 95% C.I. 0.01-0.56). The full table of crude ORs is shown in the Appendix.

Table 5.8.1 Comparison between affective disorder subjects with and without a family history

	Non-familial					Familial				
	Index cases	Controls	Siblings	Sibling-controls	p	Index cases	Controls	Siblings	Sibling-controls	p
N: (% male)	154 35.1%	770 35.1%	252 53.6%	1260 53.6%	<0.01	66 24.2%	330 24.2%	104 49.0%	520 49.0%	<0.01
Maternal age at delivery: mean (s.d.)	25.64 5.81	26.23 5.41	26.44 5.46	26.07 5.46	n.s.	24.47 4.22	25.83 5.53	24.33 4.42	25.51 5.17	<0.05
Mother not married: N (%)	5 3.2%	53 6.9%	15 6.0%	73 5.8%	n.s.	1 1.5%	21 6.4%	4 3.8%	27 5.2%	n.s.
Low social class: N (%)	42 27.3%	154 20.0%	78 31.0%	285 22.6%	<0.01	24 36.4%	69 20.9%	42 40.4%	121 23.3%	<0.01
Primiparity: N (%)	66 42.9%	301 39.1%	58 23.0%	489 38.8%	<0.01	23 34.8%	141 42.7%	33 31.7%	218 41.9%	n.s.
Mother Rhesus negative: N (%)	33 22.8%	144 20.7%	58 24.3%	202 18.4%	n.s.	15 23.8%	61 19.7%	27 26.2%	88 18.5%	n.s.
Pre-eclampsia: N (%)	3 1.9%	11 1.4%	4 1.6%	34 2.7%	n.s.	1 1.5%	4 1.2%	2 1.9%	12 2.3%	n.s.
Bleeding in pregnancy: N (%)	10 6.5%	20 2.6%	4 1.6%	53 4.2%	<0.05	1 1.5%	8 2.4%	5 4.8%	15 2.9%	n.s.
Prematurity: N (%)	8 5.4%	20 2.8%	6 2.6%	37 3.1%	n.s.	0 .0%	10 3.2%	4 4.2%	10 2.0%	n.s.
Labour induced or c/s: N (%)	45 29.2%	191 24.8%	62 24.6%	364 28.9%	n.s.	15 22.7%	86 26.1%	28 26.9%	145 27.9%	n.s.
Non-OA presentation: N (%)	4 2.8%	29 4.3%	11 4.8%	47 4.2%	n.s.	3 4.8%	13 4.5%	5 5.2%	25 5.3%	n.s.
Intervention delivery: N (%)	20 13.0%	111 14.4%	19 7.5%	234 18.6%	<0.01	7 10.6%	55 16.7%	9 8.7%	91 17.5%	n.s.
Low birth weight: N (%)	1 0.7%	10 1.5%	8 3.7%	26 2.3%	n.s.	2 3.6%	10 3.4%	2 2.4%	7 1.5%	n.s.
Apgar at 1 minute < 7: N (%)	19 24.1%	109 27.6%	32 22.5%	182 25.6%	n.s.	10 20.8%	63 26.3%	17 22.7%	95 25.3%	n.s.
Apgar at 5 minutes < 8: N (%)	18 22.8%	80 20.3%	24 16.9%	127 17.9%	n.s.	6 12.5%	47 19.6%	10 13.3%	71 18.9%	n.s.
Any OC: N (%)	98 63.6%	429 55.7%	147 58.3%	749 59.4%	n.s.	35 53.0%	194 58.8%	65 62.5%	301 57.9%	n.s.

Once again, there are differences between siblings and their controls which may partly explain any differences between the subjects and their siblings and which are explored in the logistic regression model shown in table 5.8.2. This indicates that for both groups, lower social class is a risk factor for affective disorder. In those without a family history, bleeding in pregnancy remains a risk factor for affective disorder when subjects are compared to normal controls and to well siblings.

Table 5.8.2 Logistic regression coefficients for affective disorder by family history

	Comparison	Variable	Hosmer & Lemeshow	β	SE	d.f.	p	OR (95% C.I.)
Non familial	Affective disorder compared to controls	Low social class	0.50	0.43	0.20	1	<0.05	1.54 1.03-2.29
		Bleeding in pregnancy	0.50	0.92	0.40	1	<0.05	2.51 1.15-5.50
	Affective disorder compared to siblings	Primiparity	N/A	-0.44	0.20	1	<0.05	1.54 1.04-2.27
		Bleeding in pregnancy	N/A	-1.88	0.71	1	<0.01	6.67 1.04-25.00
	Siblings compared to sibling-controls	Low social class	0.87	0.36	0.16	1	<0.05	1.43 1.04-1.97
		Primiparity	0.87	-0.64	0.17	1	<0.01	0.53 0.38-0.74
		Intervention delivery	0.87	-0.84	0.26	1	<0.01	0.43 0.26-0.72
Familial	Affective disorder compared to controls	Low social class	0.37	0.79	0.29	1	<0.01	2.20 1.24-3.90
	Affective disorder compared to siblings	No OC or demographic variable associated with risk of schizophrenia						
	Siblings compared to sibling-controls	Low social class	0.65	0.77	0.23	1	<0.01	2.16 1.38-3.38

5.9 Summary

Schizophrenic subjects have higher rates of birth in winter months than do other diagnostic groups, but OCs are not associated with an increased risk of schizophrenia in those born in winter. Two OCs, induced labour or elective c/s and low birth weight, emerge as risk factors for early onset schizophrenia compared to controls. Contrary to the hypothesis that OCs may be more aetiologically important in non-familial schizophrenia, induced labour or elective c/s is associated with an increased risk of schizophrenia in those with a family history of psychosis or affective disorder compared to normal controls, but no OCs are associated with an increased risk of non familial schizophrenia.

Being of lower social class and being born at less than 37 weeks gestation is associated with an increased risk of younger onset affective disorder. Being born to an unmarried mother is associated with a decreased risk of younger onset affective disorder compared to controls. Bleeding in pregnancy emerges as a risk factor for non-familial affective disorder compared to both siblings and to controls.

Chapter 6:

Summary of findings and critique

6.1 Findings in relation to research questions

The findings of the study are considered with reference to the research questions posed in 3.1.

6.1.1 Are OCs more common in schizophrenic subjects compared to controls?

One of the primary aims was to determine if OCs occur more often in the birth histories of patients with schizophrenia compared to normal controls and if so, to assess the risk associated with OCs for the development of schizophrenia. Before controlling for confounding factors, it appears that induced labour or elective c/s and the presence of any OC are associated with an increased risk of schizophrenia compared to controls in female subjects only. The effect size is modest, with ORs of less than 2.0.

6.1.2 Are OCs more common in subjects with other disorders compared to controls?

Before confounding factors are taken into account, bleeding in pregnancy is associated with an increased risk of affective disorder in female subjects compared to controls, with an odds ratio of 2.61 (95% C.I. 1.20-5.69). An Apgar score of <8 at 5 minutes is associated with an increased risk of other functional psychosis, both in the total group and in females alone, and a low Apgar score at 1 minute is associated with an increased risk in females.

6.1.3 Are OCs confounded by demographic factors?

OCs are significantly associated with maternal marital status, social class and parity. Parity may itself be regarded as an obstetric variable, if not an obstetric complication as primiparity is associated with an increased rate of pre-eclampsia, prematurity, induced labour or elective c/s, abnormal fetal presentation and intervention delivery. In comparison with control subjects, the use of logistic regression models causes the parity effect to diminish, but both low social class and maternal marital status remain associated with the risk of illness. Low social class remains associated with an increased risk of affective disorder in all cases and in females alone, the same occurs in the 'all psychoses' group, which may reflect the findings for affective disorder. Being born to an unmarried mother is associated with a decreased risk of affective disorder, when all subjects are considered together, and with a decreased risk of psychosis in females.

6.1.4 Do OCs increase risk once confounding factors are controlled for?

When the risk of illness compared to unrelated controls is recalculated using logistic regression models controlling for maternal marital status, social class, parity and other OCs, no obstetric complication is associated with an increased risk of schizophrenia. Bleeding in pregnancy is associated with a three-fold increase in the risk of affective disorder for female subjects. An Apgar score of <8 at 5 minutes is associated with a similar increase in risk of any psychosis and of affective disorder, again only in females, and is associated with an increased risk of other functional psychosis in all subjects.

6.1.5 Is any increased risk following OCs specific to schizophrenia?

Of the three diagnostic groups compared to unrelated controls, two OCs, bleeding in pregnancy and a low Apgar score at 5 minutes, are related to the risk of affective disorder and a low Apgar score at 5 minutes is related to the risk of other functional psychosis. No OC is related to the risk of schizophrenia, indicating not only that the risk following OCs is not specific to schizophrenia, but that it may be of more importance in other diagnostic groups.

6.1.6 Do OCs increase the risk in cases compared to their well siblings?

Before demographic differences are controlled for, induced labour or elective c/s, instrumental delivery or emergency c/s and any OC are associated with an increased risk of schizophrenia compared to siblings. Intervention delivery by forceps or emergency caesarean section is associated with an increased risk of affective disorder and induced labour or elective c/s, intervention delivery and low Apgar score at 5 minutes are associated with an increased risk of other functional psychosis. After controlling for interactions by social class, parity and maternal marital status, no OC is associated with an increased risk of psychoses, schizophrenia, affective disorder or other functional psychosis compared to siblings. However, being first born remained a significant risk factor for schizophrenia in females subjects compared to their siblings and for non-familial affective disorder in both male and female subjects compared to their siblings. Throughout these analyses more differences have been found between siblings and sibling-controls than between index cases and their controls. The siblings of index cases are less often born to primiparous women. These siblings are thus more likely to be the younger siblings of the cases, rather than the older siblings. This may have occurred for one of two reasons, either the ascertainment of the siblings was biased

towards finding younger rather than older siblings, or schizophrenic subjects are more likely to be the first birth to that mother and therefore the eldest child in the family. The index cases were born between 1954 and 1970, the AMNDB began in 1950, and for the subjects born close to the beginning of the study period there may have been some older siblings, born prior to 1950, who were not ascertained. However, this should not have affected sibling ascertainment for those born later in the 20 year study period, and 115 (11%) of the 1,047 siblings found were born between 1950 and 1953. The sibling group is larger than the group of index cases and therefore better powered to find differences between siblings and sibling-controls than is the index group compared to their controls, which may account for the greater number of findings in these comparisons.

6.1.7 Do OCs increase the risk for winter-born schizophrenics?

The study found no evidence of an association between OCs and winter birth in schizophrenia.

6.1.8 Do OCs increase the risk of earlier onset illness?

Two OCs, a low birth weight and an induced labour or elective c/s are associated with an increased risk of earlier onset schizophrenia. Of these, low birth weight is associated with a four-fold increase in risk, but the effect size for induced labour or elective c/s was smaller. Prematurity is associated with a three-fold increase in the risk of early onset affective disorder.

6.1.9 Do OCs increase the risk of non-familial illness?

After controlling for confounding factors, an induced labour or elective c/s is associated with a doubling of the risk of schizophrenia in familial, rather than non-familial cases. Bleeding in pregnancy is associated with a two-fold increase in the risk of non-familial affective disorder compared to unrelated controls and a six-fold increase in risk compared to well siblings.

6.2 Specific findings by diagnosis

6.2.1 All psychoses

When schizophrenia, affective disorder and other functional psychosis are examined together, the findings are similar to those found for affective disorder. More cases had a diagnosis of affective disorder than of schizophrenia or other functional psychosis, and it is likely this influenced the findings in the total group. Lower social class, in all cases and in females, and low Apgar score at 5 minutes in females are associated with an increased risk of psychosis compared to controls when confounding factors had been controlled for. Being born to a mother who was not married is associated with a decreased risk of psychosis in females compared to normal controls and in all cases compared to their siblings, but this is not due to unmarried women being of lower social class.

6.2.2 Schizophrenia

The findings for schizophrenia are largely negative. No OC is associated with an increased risk of schizophrenia compared to normal controls or to well siblings when the total group was examined together or separately by gender, but being born to a primiparous woman is associated with an increased risk of schizophrenia in females compared to their well siblings. Schizophrenic subjects show higher rates of birth in winter months in comparison to their well siblings than do other diagnostic groups, but OCs are not associated with an increased risk of schizophrenia for those born in winter. When subgroups of those with earlier and later onset, and those with and without a family history of psychosis or affective disorder were

considered separately, two OCs emerge as risk factors for schizophrenia. Induced labour or elective c/s is associated with an increased risk of earlier onset schizophrenia and of schizophrenia in those with a family history, with an approximate doubling of risk. Low birth weight is associated with a four-fold increase in risk of earlier onset schizophrenia. When index cases of each diagnosis of interest are compared with each other, no OC is associated with an increased risk of schizophrenia compared to affective disorder, but the risk of schizophrenia compared to other functional psychosis is significantly increased by the mother being Rhesus negative and to a lesser extent by labour being induced or delivery by elective caesarean section, but both findings are restricted to females.

6.2.3 Affective disorder

Low social class is a risk factor for affective disorder compared to controls in all subjects and in females alone, for both familial and non-familial affective disorder and for earlier onset affective disorder in all subjects. Being born to a mother who was not married is associated with a decreased risk of affective disorder in the whole group and in younger onset cases. Bleeding in pregnancy is associated with an increased risk of affective disorder compared to normal controls in females, and of non-familial affective disorder in all subjects compared to normal controls and to well siblings, once confounding variables are controlled for. Premature birth, before 37 completed weeks of gestation, is associated with an increased risk of younger onset affective disorder compared to normal controls. A low Apgar score at 5 minutes is associated with an increased risk of affective disorder compared to controls and compared to schizophrenia in females. Having a Rhesus negative mother is also associated with an increased risk of affective disorder compared to other functional psychosis, again this was limited to females.

6.2.4 Other functional psychosis

A low Apgar score at 5 minutes is identified as a risk factor for other functional psychosis compared to controls once confounding factors are controlled for. Intervention delivery is associated with an increased risk of other functional psychosis compared to affective disorder when diagnostic groups are considered as a whole, but neither of these findings occurs in males or females separately. Numbers in this diagnostic group were small, and separate analysis of those with younger and older onset, or those with and without a family history, was not undertaken. However in this diagnostic group, a measure of neonatal well-being, and possibly of asphyxia, is associated with an increased risk of illness.

6.2.5 Gender effects

It is striking that where an effect is seen for gender, it is exclusive to females. None of the corrected ORs indicate an increased risk in male subjects alone. 48.8% of the 492 cases examined were male, but there was a higher proportion of males (68.3%) in the schizophrenic group and a lower proportion in the affective disorders group (31.8%). Relatively few findings occur in the schizophrenic group and no demographic or obstetric variables are associated with an increased risk of schizophrenia in the total group compared to normal controls or to siblings. However, for affective disorder several OCs are associated with an increased risk, after controlling for confounding factors, and as this diagnostic group is predominantly female, it is likely that the female subgroup will show differences that are too small to be seen in the male subgroup. Males show a non-significant trend in crude ORs in the same direction as the significant findings for females in social class, parity and maternal marital status, but not always for OCs. The risk associated with bleeding in pregnancy for

affective disorder appears to be confined to females, with no tendencies for the male subjects to show a difference, but as numbers of male subjects with affective disorder are small, this should be interpreted cautiously.

6.2.6 Relationships between subgroups

Generally speaking, and particularly for schizophrenia, the effect of OCs on the risk of illness was greater when age of onset and family history were taken into account than when the diagnostic groups were examined as a whole. This raises the issue of whether there is a relationship between age of onset and family history. No significant difference is found between the proportion of younger and older onset cases having a relevant family history when all psychoses are examined together, or for schizophrenia or affective disorder examined separately. For schizophrenic subjects, there is similarly no difference in the proportion of younger and older onset subjects, or those with and without a family history of psychosis or affective disorder in those born in winter (November – April) compared to those born in summer.

6.2.7 Summary

Table 6.2.7 summarises the corrected odds ratios for demographic and obstetric variables that are associated with risk of illness, at least in one of the subgroup analyses. Several different demographic factors and obstetric complications appear to be potentially important in different conditions.

Low social class is associated with an increased risk of any psychosis and of affective disorder. In contrast, being born to an unmarried mother is associated with a decreased risk of any psychosis or affective disorder.

Maternal Rhesus negative status is associated with an increased risk of both schizophrenia and affective disorder in comparison to other functional psychosis, probably because few index cases of other functional psychosis are born to a Rhesus negative mother. Although being born to a Rhesus negative mother was not a risk for schizophrenia or affective disorder per se, it is possible that this complication may influence the type of illness that develops in vulnerable individuals and increase the risk of symptoms common to both conditions.

Premature birth is associated with an increased risk of younger onset affective disorder compared to controls, but appears unrelated to schizophrenia or to other functional psychosis. An induced labour or elective caesarean section is associated with an increased risk of younger onset and of familial schizophrenia compared to normal controls, and with an increased risk of schizophrenia compared to other functional psychosis in females. Instrumental delivery or emergency caesarean section is associated with a risk of other functional psychosis compared to affective disorder only.

Low birth weight is associated with an increased risk of younger onset schizophrenia compared to controls. A low Apgar score at five minutes after delivery is a risk factor for any psychosis compared to controls, for affective disorder compared to controls, for affective disorder compared to schizophrenia in female subjects, and for other functional psychosis compared to controls, but does not appear to be related to the development of schizophrenia.

The results indicate different obstetric risk factors for the main diagnoses of interest. Induced labour or elective c/s appears to be related to schizophrenia. Bleeding in pregnancy is related to affective disorder and a low Apgar score at 5 minutes is related both to affective disorder and to other functional psychosis. The relationship between OCs and affective illness is stronger than that for schizophrenia and probably influences the results when all psychoses are examined together.

Table 6.2.7 Summary of demographic variables and OCs associated with risk

Variable	Corrected OR (95% C.I.)	Subgroup	For	Compared to
Low social class	1.36 (1.09-1.71)	All	Any psychosis	Normal controls
	1.64 (1.19-2.26)	Females	Any psychosis	Normal controls
	1.60 (1.14-2.24)	All	Affective disorder	Normal controls
	1.61 (1.06-2.44)	Females	Affective disorder	Normal controls
	1.79 (1.15-2.81)	Younger onset	Affective disorder	Normal controls
	1.54 (1.03-2.29)	Non-familial	Affective disorder	Normal controls
	2.20 (1.24-3.90)	Familial	Affective disorder	Normal controls
Mother not married	0.40 (0.16-0.96)	All	Any psychosis	Well siblings
	0.41 (0.18-0.92)	Females	Any psychosis	Normal controls
	0.41 (0.17-0.98)	All	Affective disorder	Normal controls
	0.20 (0.05-0.84)	Younger onset	Affective disorder	Normal controls
Primiparity	3.57 (1.15-11.1)	Females	Schizophrenia	Well siblings
	1.54 (1.04-2.27)	Non familial	Affective disorder	Well siblings
Mother Rhesus negative	7.18 (1.06-48.53)	Females	Schizophrenia	Other functional psychosis
	5.88 (1.29-26.77)	Females	Affective disorder	Other functional psychosis
Bleeding in pregnancy	3.73 (1.56-8.94)	Females	Affective disorder	Normal controls
	2.51 (1.15-5.50)	Non familial	Affective disorder	Normal controls
	6.67 (1.04-25.00)	Non familial	Affective disorder	Well siblings
Prematurity	3.05 (1.06-8.80)	Younger onset	Affective disorder	Normal controls
Labour induced or c/s	3.07 (1.01-9.37)	Females	Schizophrenia	Other functional psychosis
	1.80 (1.11-2.93)	Younger onset	Schizophrenia	Normal controls
	2.02 (1.08-3.78)	Familial	Schizophrenia	Normal controls
	0.06 (0.00-0.51)	All	Other functional psychosis	Well siblings
Intervention delivery	2.44 (1.11-5.56)	All	Other functional psychosis	Affective disorder
Low birth weight	4.08 (1.06-15.72)	Younger onset	Schizophrenia	Normal controls
Low Apgar score at 5 minutes	2.62 (1.06-6.49)	Females	Any psychosis	Normal controls
	3.77 (1.02-13.88)	Females	Affective disorder	Normal controls
	9.09 (1.09-100.00)	Females	Affective disorder	Schizophrenia
	2.63 (1.26-5.46)	All	Other functional psychosis	Normal controls

6.3 Confounding factors

The finding that lower social class is a risk factor for affective disorder, and for all psychoses, is not surprising, as previous studies have found socio-economic disadvantage to relate to the risk of depression and other illnesses in adults, as is considered in chapter 7. However, the finding that being born to a mother who is not married is associated with a reduced risk of these conditions is unexpected and more difficult to understand. The finding is due to index cases having fewer unmarried mothers than controls or siblings. The vast majority of mothers in this study (94.5%) were married when the subjects were born, and only 16 index cases (8 with schizophrenia, 6 with affective disorder and 2 with other functional psychosis) were born to unmarried mothers. In other words, subjects were more often born to married women than were controls or siblings, and the result might be expressed in terms of an increased risk of affective illness or any psychosis in the offspring of married women. The low numbers of births to unmarried mothers overall, and the low numbers of index cases born to unmarried mothers suggest that this may simply be a chance finding. Unmarried status at delivery is highly correlated with primiparity, but index cases and controls did not differ on primiparity and this does not seem adequate to explain the finding. Maternal marital status correlated with a number of OCs, including non-OA presentation, intervention delivery, Apgar scores at 1 and 5 minutes after delivery and any OC. When confounding factors were controlled for in the logistic and conditional logistic regression analyses, there was no effect for non-OA presentation or for Apgar score at 1 minute. Intervention delivery was associated only with a risk of other functional psychosis compared to affective disorder when index cases were compared by diagnosis, it did not contribute to the risk compared to controls or to siblings for any of the three conditions of interest either in total group or subgroup analyses. The Apgar score at 5 minutes was a significant risk factor for other functional psychosis (in

all cases) and for any psychosis and for affective disorder (in females) compared to controls, and a risk for affective disorder compared to schizophrenia in female index cases. However, in each of these cases the low Apgar score increased the risk of illness, while having a mother who was not married at the time of the subject's birth decreased the risk in similar comparison groups. Given that such relationships between risk factors do not offer an explanation, the conclusion that this is simply a chance finding, given the small numbers involved is more likely than the possibility that women who are not married at the time a subject is born differ from married mothers in a way that confers some protection to their infant against the later development of illness, particularly affective disorder. The index cases and control subjects in this study were born between 1954 and 1973, when attitudes to single mothers were different to what they are today. It remains difficult to see how offspring of such pregnancies could be advantaged.

The correlations between marital status, social class, parity and obstetric complications explain many of the differences between the crude and adjusted ORs. Many variables which appear to confer a risk when crude ORs are calculated disappear when the OR is corrected for the demographic confounders and for other OCs, as what appeared to be a correlation between a particular OC and illness was an artefact of the relationships between marital status, social class, parity and the OC in question. The subjects of this study were born over two decades during which there were significant changes in obstetric practice and maternal health, as well as social and demographic changes such as increasing urbanisation, which may also influence the rate of schizophrenia. It is not possible to exclude the possibility OCs are related to schizophrenia but that improving obstetric care, resulting in fewer complications for those born later in the study period, has been offset by an increase in other environmental risk factors for schizophrenia, such as increasing urbanisation and substance

misuse, and that this has contributed to the study not finding any OC to be a risk factor for the total group of schizophrenic subjects.

6.4 Limitations of the study

Although the OPCRIT procedure allowed reliable lifetime diagnoses, it was necessary to classify the different diagnoses into schizophrenic, affective disorder and other functional psychosis, and in doing so, subjects with schizoaffective disorder were included with schizophrenia, in keeping with most other studies. Not all the subjects with an affective disorder had a psychotic condition. Separating psychotic from non-psychotic affective disorder was not practical as none of the three diagnostic classifications distinguished between psychotic and non-psychotic bipolar disorder, so the complete affective disorder group were analysed together. Numbers of subjects were not sufficient to examine unipolar and bipolar disorder separately.

The selection of siblings as births to the same mother as index cases is routinely used (e.g. Kläning *et al,* 2004) but may have included half-siblings, although the impact such a bias might have is unclear and no previous study has taken measures to avoid this. It has been assumed that siblings not having a diagnosis of psychotic illness in the GPCR are unaffected, but the possibility that they, or the normal control subjects have presented to psychiatric services elsewhere and been diagnosed with a psychotic illness cannot be discounted. These factors are difficult to control for and limit most research efforts in this area. However, the geographical stability of the population of North East Scotland is good; in a study of children born in the 1950s, 73% were still living in the Aberdeen area in 1998 (Batty *et al,* 2004) and follow-up of a population born in Aberdeen in 1921 traced almost 80% (Whalley & Deary, 2001).

While the use of as comprehensive and enduring a data base as the AMNDB is an advantage of this study, there remains a possibility that some home births and births in rural areas in the early years of the study were missed. The study is limited to the analysis of data routinely recorded in the AMNDB, which did not lend itself to application of a standard OC scale. The inclusion of any of the ten complications examined is a crude measure which does not quantify the degree of risk, but has similarities with the approach used by the Lewis & Murray scale (Lewis *et al,* 1989). Data on maternal compliance with antenatal care is not recorded in the AMNDB. While most of the OC complications of interest are well recorded, one of the main OCs which appears to contribute to risk, Apgar score at 5 minutes, was available only for 55.4% of the sample. Rhesus incompatibility could not be ascertained as the AMNDB records only maternal, and not infant, blood groups. The analysis of only maternal Rhesus status, and therefore potential Rhesus incompatibility, may be seen as an equivocal, rather than a definite OC, but has been examined in previous studies (Sacker *et al,* 1995). Maternal cigarette smoking is a risk for premature delivery, IUGR and increased perinatal mortality (Morrow *et al,* 1988), and it is unfortunate that the AMNDB data on maternal smoking were insufficient to include this behaviour as a potentially important confounder.

The analysis of age of onset is based on age at first admission, which is likely to be later than symptom onset. DeLisi *et al* (1987) found a mean age at first admission of 21.5 (s.d. 6.6), which was well correlated with a mean age at symptom onset of 19.9 (s.d. 5.8) as reported by the patients. Other studies have often used age at first admission to define age of onset (Smith *et al,* 1995; Smith *et al,* 1998; Thomas *et al,* 2001) and this has been found to produce similar findings to the use of age at first symptoms to define onset (Könnecke *et al,* 2000).

The assessment of family history was from information routinely recorded in the case notes, based on standard clinical interview, and was therefore not in accordance with any validated system of recording such information. This is likely to have resulted in information being missed, and may have tended to underestimate the proportion of cases with a family history. It is a weakness of the study that the mothers' psychiatric status was not known.

The most significant limitation is the power of the study to find small differences and this is more problematic when numbers in comparative groups are small, such as for other functional psychosis and for schizophrenia and affective disorder subgroups stratified by season of birth, age of onset and family history. The frequency of OCs within the control groups was considerably less than the estimate of 7% for pre-eclampsia (1.3-2.4%), bleeding in pregnancy (2.8-3.3%), prematurity (2.9-4.1%), low birth weight (1.9-2.8%) and non-OA presentation (3.5-4.5%). Numbers required to detect a two-fold increase in risk for an OC with a 2% population frequency compared to controls, using this design would have been 795, for an OC with a 4% population frequency, 384 cases would have been required. None of the individual diagnostic groups approached these numbers, and the study is underpowered to find differences in risk for these OCs. The main findings were largely limited to the more common complications; differences in rarer complications may have failed to reach significance because of insufficient power. Conversely, some of the findings may have occurred by chance, particularly as multiple comparisons have been made. Although the use of conditional logistic regression for the comparisons between index cases and siblings was required as these two groups are not independent, conditional logistic regression is a more conservative model than standard logistic regression which was used for the other comparisons. Differences between index cases and siblings may have failed to reach significance in this more stringent comparison where a similar difference between index

cases and controls might have remained significant after controlling for maternal marital status, parity and SES in a logistic regression model. The sibling group is much smaller than the control group and it is likely the comparison between index cases and siblings is underpowered to find small differences. Power was a problem in the subgroup analyses which split diagnostic groups by gender, season of birth, age of onset and family history. It is likely many of these analyses were underpowered.

6.5 Strengths of the study

This study has a number of strengths in its design. The control subjects were randomly selected same-sex births in the same month, which avoids selection biases when matching is to the next / previous birth registered, which has previously led to false positive results (Kendell *et al,* 2000). The comparison with siblings, as well as normal control subjects, allows examination of hypotheses relating to how OCs may interact with genetic liability to illness. In contrast to studies which have used psychiatric registers and nationally collected statistics to select cases (Hultman *et al,* 1999; Bain *et al,* 2000; Browne *et al,* 2000), this study used case record derived information and a validated diagnostic system generating lifetime, rather than single episode, diagnoses. The validity of case register diagnoses has been poorly investigated, despite their widespread use. Scandinavian registers have been most often studied and show good reliability for both schizophrenia and affective disorder (Kessing, 1998; Dalman *et al,* 2002; Byrne *et al,* 2005). The correlation between the GPCR diagnosis and that based on a standardised review of case notes using the OPCRIT analysis to generate lifetime diagnoses, as in the present study, has been found to be only moderate (kappa = 0.58) suggesting that, at least for the GPCR, the case register diagnosis should be supplemented by other diagnostic procedures (McConville & Walker, 2000).

Previous studies have used maternal recall to assess OCs (Verdoux & Bourgeois, 1993a; Marcelis *et al,* 1998; Kinney *et al,* 1998b), but the obstetric data used in this study is drawn from contemporaneous records and not subject to recall bias. Numbers of patients with each condition are reasonably large and the use of five controls per subject improves the power of the study to find differences that do exist. The index cases were selected within a time frame that ensured the subjects had passed through at least a significant part of their period of risk.

At the time of ascertainment, the index subjects were between 25 and 46 years of age, the median ages of onset ranged from 22 for schizophrenia to 24 for affective disorder, therefore all subjects had passed through at least 50% of the period of risk.

The comprehensive nature of the AMNDB allows analyses to be controlled for parity, socio-economic status, maternal marital status, age at delivery and other obstetric complications. The ten obstetric complications examined have been clearly defined and all represent at least a potential hazard. The classification of social class on the basis of husband's occupation, although no longer the current standard, was appropriate to the era, and the vast majority of women in the study were married.

The method of data analysis is clearly described and the study specifies the methods of logistic and conditional logistic regression analyses used, the software programs employed and the goodness of fit of the models, as recommended by Bender & Grouven (1996).

Chapter 7:

Relevance of the findings

While there is little doubt that genetic factors play an important role in the aetiology of schizophrenia, bipolar disorder and probably most other major mental illness, the concordance in genetically identical twins is no higher than 50% (Portin & Alanen, 1997) and non-genetic factors are therefore implicated. Of these, obstetric complications have been perhaps most intensively studied as potential environmental risk factors, with at times intriguing, although inconsistent, results. This study has identified a number of OCs and demographic variables associated with psychosis and affective disorder, some of which are likely to be related to each other. These need to be considered in light of the relevant literature and put into context for the diagnoses examined. OCs of interest which emerge from this study occur in pregnancy (antepartum haemorrhage, prematurity and maternal Rhesus negative status), labour and delivery (induction of labour or elective c/s, instrumental delivery or emergency c/s) and in the neonatal period (a low Apgar score at five minutes). Parity is a significant confounder, but did not contribute to the risk of any of the conditions examined when other factors were controlled, although social class and maternal marital status were strongly related to the risk of affective disorder and to the risk when all diagnoses were considered together. The main findings of the study are compared to the literature and their potential aetiological importance is then considered.

7.1 Social class, parity and maternal marital status

7.1.1 Social class

Lower social class in childhood has been found to be associated with an increased risk of developing schizophrenia in later life in a large Swedish cohort (Wicks *et al,* 2005). Sørensen *et al* (2003) found SES at 1 year of age to be associated with schizophrenia. Harrison *et al* (2001) found social class IV and V, based on paternal occupation at birth, to increase the risk of schizophrenia and of other non-schizophrenic (mainly affective) psychosis, although the result only reached statistical significance when the two diagnostic groups were combined into an all psychoses category. This is similar to the findings of this study that low social class, defined in the same way, is a risk factor for all psychosis and for affective disorder. Lower household income assessed at birth was found not to be associated with any emotional or nervous condition in young adults, but a lower household income at age seven and in adulthood were associated with non-specific measures of mental distress (Fan & Eaton, 2001) suggesting that social class findings may not be specific to schizophrenia. Apparent differences between schizophrenic subjects and controls can be due to social class differences. Foerster *et al* (1991) found a lower birth weight in schizophrenic subjects compared to those with affective disorder which was confounded by race and social class and did not persist once these factors were controlled for.

However, an association between risk of illness and measures of social class is by no means invariable. Several studies have found no differences in socio-economic status between subjects with schizophrenia and controls (Günter-Genta *et al,* 1994; Jones *et al,* 1998; Byrne

et al, 2000; Dalman *et al,* 2001). Sacker *et al* (1995) found no relationship between social class and either schizophrenia or affective disorder in the BPMS study, and Buka *et al* (2000) also found no relationship between social class and later psychosis.

Many studies of OCs and schizophrenia, particularly those with small numbers, have not controlled for social class; this study illustrates the importance of doing so. In this study, there was no evidence of a relationship between low social class and schizophrenia or other functional psychosis, but low social class at birth was clearly associated with an increase in the risk of affective disorder. A relationship between social class and depression is already well established. Minor affective disorders are more common in adults of lower social class, although it remains unclear if this is due to increased rates of adversity in this group, or differences in coping styles which make it more likely that an individual of lower social class will develop symptoms of illness in response to life events, compared to an individual of higher social class (Bebbington *et al,* 1986; Wainwright & Surtees, 2004). This study suggests that social class at birth, which is likely to be related to social class later in life, may also increase the risk of affective disorder. Social class may act as a proxy indicator of nutrition, lifestyle and physical environment, as well as affecting access to health care (Power, 1994) and is known to relate to overall mortality (Morris, 1979).

7.1.2 Parity

Investigations of the relationship between schizophrenia, parity and birth order have resulted in conflicting findings. Schizophrenic subjects have been found to be more likely to be first-born (Rosso *et al,* 2000; Ichiki *et al,* 2000) and less likely to be first-born (Hultman *et al,* 1999; Kawai *et al,* 2004) than controls. Preti *et al* (2000) found OCs were more common in first births and more OCs were found in first-born infants who later developed schizophrenia than in first-born infants who did not (Cantor-Graae *et al,* 1997). In this study, primiparity was not a risk for any diagnosis compared to unrelated controls, but was initially associated with an increased risk in comparison with siblings for all three diagnostic groups considered separately or together, when crude ORs were calculated. In the conditional logistic regression models, being first-born was a risk factor only for female schizophrenic subjects and for those with non-familial affective disorder, compared to their siblings. The effects of parity were largely non-significant when social class and maternal marital status were considered. The selection of siblings found fewer individuals who were first-born than in either the index cases or the control groups, as have previously been found by Rosso *et al* (2000).

7.1.3 Maternal marital status

While the finding of a relationship between the risk of psychoses and maternal marital status was not surprising in itself, the direction of the association was. It is important to bear in mind social norms pertaining to the period when the individuals were born as well as the culture of the area. Grampian region is a large area which, prior to the discovery of oil off the Scottish coast in 1971, relied on fishing, shipbuilding, textiles and papermaking as its

major industries and had a high geographical stability (Batty *et al,* 2004). Giving birth without being married was a relatively rare event, and while a proportion of those classed in this study as not married were widowed, divorced or separated, the majority were single, which would be reasonably expected to be less than fully accepted at the time. Maternal marital status was included in this study as a potential confounder, but it was expected to be outweighed by the effect of social class, particularly given the relatively small proportion of women who were not married at the time of the birth. Unmarried women are more likely to be primiparous, but do not differ in social class from married women. The effect of primiparity is in the wrong direction to be an explanation of this finding that being born to an unmarried mother was associated with a decreased risk of affective disorder. However, the women who were not married were younger at delivery than those who were married, which may have been associated with a lower frequency of OCs in this group. The Copenhagen High Risk study of mothers with schizophrenia found them to be more often unmarried compared to controls (Mednick & Schulsinger, 1968). In the Swedish register study crude ORs for schizophrenia were increased following pre-eclampsia, bleeding in pregnancy, threatened premature delivery, short gestation, prolonged labour, uterine inertia, vacuum extraction, low ponderal index, respiratory infection and congenital malformations, and were confounded by parity. Of these, only pre-eclampsia was significantly associated with an increased risk of schizophrenia when other factors were controlled for. Interestingly, the effect of parity also disappeared, but there was an increased risk for schizophrenia if the mother's marital status was unknown (Dalman *et al,* 1999).

7.2 Gender

Gender differences in OCs have been frequently reported without any consensus being achieved; increased OCs have been found to be specific to male (O'Callaghan *et al,* 1992; Byrne *et al,* 2000; Rosso *et al,* 2000) and to female cases (Verdoux & Bourgeois, 1993a; McCreadie *et al,* 1994; Kunugi *et al,* 1996). This study found, where there was a sex difference, that findings were exclusive to female subjects, both for schizophrenia and for affective disorder. However, although within the 492 cases considered together, and within the other functional psychosis group, there were approximately equal numbers of males and females, this was not the case for schizophrenia, which showed a marked male predominance, or for affective disorder, which showed a marked female predominance. Since many of the study findings relate to affective disorder, in which numbers of male cases were small, it would be inappropriate to conclude that the risks found are risks only for females, it may well be the case that the number of male subjects with affective disorder was too low for the findings seen in the total group and in females to be significant in males. This argument does not, however, apply to schizophrenia, where females were in the minority. Relatively fewer sex differences were found for schizophrenia, and the increased risk of schizophrenia compared to other functional psychosis in females for two OCs, maternal Rhesus negative status and induced labour or elective c/s is based on small numbers of female schizophrenic cases. It would seem reasonable to conclude that risks for schizophrenia compared to controls did not differ by gender, and that the findings in affective disorder may reflect the relatively low proportion of male cases with this condition.

7.3 Complications of pregnancy

Pregnancy complications including bleeding, diabetes, Rhesus incompatibility, pre-eclampsia and abnormal fetal growth or development have been supported as associated with an increased risk of schizophrenia in two recent reviews (McNeil *et al,* 2000a; Mueser & McGurk, 2004) and a meta-analysis (Cannon *et al,* 2002a). Three complications of pregnancy were found to be relevant to the risks of schizophrenia and of affective disorder in the current study. Being born to a Rhesus negative mother was associated with an increased risk of schizophrenia and of affective disorder compared to other functional psychosis in females. Rhesus incompatibility has been found to be more common in schizophrenic subjects than their siblings (DeLisi *et al,* 1987) and associated with an increased risk for schizophrenia in males (Hollister *et al,* 1996). A recent meta-analysis concluded an approximate two-fold increase in risk of schizophrenia following Rhesus incompatibility (Cannon *et al,* 2002a). The relationship between Rhesus incompatibility and the risk of schizophrenia does not appear to be due to a genetic linkage or association, which further suggests the effect may be obstetric in nature (Palmer *et al,* 2002). Having a Rhesus negative mother was associated with an increased risk of affective disorder in the BPMS study (Sacker *et al,* 1995). Rhesus incompatibility may be related to the risk of both schizophrenia and affective disorder. Increased risks for both conditions, compared to other functional psychosis, were found for those born to Rhesus negative mothers in the current study.

The two other complications, antepartum haemorrhage (bleeding in pregnancy) and premature birth, were both associated with an increased risk of affective disorder, with the stronger effect being seen for antepartum haemorrhage. Bleeding in pregnancy has been associated with an increased risk of schizophrenia in a number of studies (Lewis & Murray,

1987; DeLisi *et al,* 1987; Sacker *et al,* 1995; Hultman *et al,* 1999; Boog, 2004) and has also been associated with an increased risk of neurosis (Done *et al,* 1991). It has also been found more commonly in the pregnancies of schizophrenic and bipolar women than in those of controls (Jablensky *et al,* 2005). One of the few 'positive' findings of the British Perinatal Mortality Survey (BPMS) study was that prematurity was a risk factor for affective disorder (Done *et al,* 1991). To my knowledge, this is the first study that has replicated that finding, although only in younger onset cases.

7.4 Complications of labour and delivery

Induction of labour is undertaken for a number of reasons including Rhesus sensitisation, pre-eclampsia, growth restriction, placental abnormalities, polyhydramnios, diabetes mellitus, unstable lie, prolonged pregnancy, feto-pelvic disproportion, ruptured membranes and multiple pregnancy (Lampe, 1996; Mackenzie, 2006). Although in recent years, non-medical indications such as maternal comfort and convenience have led to an increasing rate of induction of labour (Rayburn & Zhang, 2002), this is unlikely to have been an indication at the time of the births in this study. Many of the indications for induction of labour are OCs in themselves and may reflect an already compromised fetus. Similar considerations apply to elective c/s which is indicated for severe pre-eclampsia, antepartum haemorrhage and IUGR (Francome & Savage, 1993) but has also increased in frequency in recent years for non-medical reasons (Paul & Miller, 1995). The increased risk found in this study for younger onset and for familial schizophrenia associated with induction of labour or elective c/s suggests that at least for these subgroups, fetal maldevelopment may be implicated.

Byrne *et al* (2000) found delivery by caesarean section to be more common in male schizophrenic subjects than in controls, and the use of forceps was also found to be more common in male schizophrenics compared to controls by Günter-Genta *et al* (1994). Instrumental delivery has been found to be more common in schizophrenia than in other psychiatric disorders (Lewis & Murray, 1987) and in schizophrenic compared to bipolar subjects (Schwarzkopf *et al,* 1989). An increased rate of non-spontaneous delivery has also been found in those with affective psychosis compared to controls (Sacker *et al,* 1995). Bain *et al* (2000) considered delivery by emergency caesarean section to be associated with earlier onset of schizophrenia. Kendell *et al* (1996) found non-spontaneous delivery (forceps, c/s,

manipulation) to be more common in schizophrenia than in controls in a national sample of Scottish young adults, but later retracted the finding, due to an unrepresentative control group having been inadvertently chosen. When this cohort was re-examined using appropriate controls, no significant differences between schizophrenic subjects and controls were found, but in a second cohort, emergency c/s, prolonged labour and fetal malpresentation were associated with an increased risk of schizophrenia compared to controls. When both cohorts were first examined subjects were 18-22, and by definition had a young age of onset of schizophrenia. There are similarities between the findings in the initial studies which are both suggestive of labour complications related to poor fetal position. This study did not find any increased risk for schizophrenia following instrumental delivery, but did find an increased risk of other functional psychosis compared to affective disorder if labour was induced or delivery was by elective c/s.

7.5 Birth weight

Decades of research into the role of perinatal factors in the development of psychiatric disorders began with observations that schizophrenics were of lower birth weight than non-schizophrenics, but the relationship between schizophrenia and low birth weight remains controversial. Lane & Albee (1966) found schizophrenics to be lighter than their siblings, but Woerner *et al* (1971) found they were not. Lower birth weight has been associated with an increased risk of schizophrenia compared to controls (McNeil *et al,* 1993), but Gunnell *et al* (2005) found no relationship between low birth weight and later schizophrenia in a study of Swedish conscripts. Foerster *et al* (1991) found that an apparent lower birth weight in schizophrenic subjects compared to those with affective disorder was explained by racial and social class differences when these factors were included in a logistic regression model. However, Rifkin *et al* (1994) found low birth weight to be a risk factor for schizophrenia even after low social class was controlled for. Yun *et al* (2005) found a higher birth weight in schizophrenic subjects than in controls. By 1995, of 12 studies to have addressed this question, eight found no relationship (McNeil, 1995), but when six studies defining low birth weight as <2,500g and comparing schizophrenic subjects only to normal controls were aggregated, low birth weight was found to be a significant predictor of schizophrenia with a pooled odds ratio of 2.6 (95% C.I. 2.0-3.3) (Kunugi *et al,* 2001). Of the existing studies to have specifically examined low birth weight, none has stratified the sample by age of onset, although studies that have found low birth weight to be a risk for schizophrenia have not been confined to younger adult samples (McNeil *et al,* 1993; Rifkin *et al,* 1994). The current work found low birthweight, adjusted for gestational age, parity, sex and maternal height, was a risk factor for younger onset schizophrenia compared to normal controls once social class and other factors were controlled for.

7.6 Neonatal complications

Apgar scores were developed by an obstetric anaesthetist in 1952 in an attempt to identify which infants were most at risk of death and in need of resuscitation (Apgar, 1952). Although the initial intention was to use the scale to assess the condition of the infant at one minute after birth (Apgar *et al,* 1958), its use at 5 minutes after delivery is probably a more accurate predictor of the risk of neonatal death (Papile, 2001). The Apgar score at 5 minutes after delivery correlates poorly with later neurological outcomes (American Academy of Pediatrics, 2006). A poor Apgar score at 5 minutes has been found to be more common in schizophrenic subjects than in controls (Wright *et al,* 1995; Preti *et al,* 2000). Four population based cohort studies have reported a trend towards an increased frequency of low Apgar scores in patients who later developed schizophrenia (Dalman *et al,* 1999; Hultman *et al,* 1999; Bain *et al,* 2000; Dalman *et al,* 2001) although none found this to be statistically significant.

This study found no association between Apgar scores and schizophrenia, but did find a low Apgar score at 5 minutes was associated with an increased risk of affective disorder and of other functional psychosis compared to controls. Although Apgar scores were not intended to be a measure of neonatal asphyxia, a low Apgar score at 5 minutes is frequently taken to indicate hypoxia, which may have a number of underlying causes largely to do with impaired placental functioning and likely to result in intra-uterine growth retardation (IUGR). Levy *et al* (1998) found that delivery of such growth retarded infants by caesarean section decreased the risk of an Apgar score of <7 at five minutes and IUGR infants are increasingly likely to be delivered early, either through induction of labour or elective c/s (Chammas *et al,* 2000). The association found in this study suggests that infants who show evidence of hypoxia, at

least as far as is indicated by a low Apgar score at 5 minutes, or who have higher rates of bleeding in pregnancy, are at greater risk of affective disorder.

7.7 Diagnostic specificity of OCs

Few other studies have compared multiple diagnoses in cases and unrelated controls; but that of Hultman *et al* (1999) used a nested case-control design to compare subjects with early onset (before age 21) schizophrenia, affective disorder and reactive psychosis to controls from the same birth cohort using five controls per case. The numbers of schizophrenic and affective psychosis subjects (167 and 198 respectively) are comparable to the numbers in each of these diagnostic groups in the current study. The risk of schizophrenia was increased by multiparity, bleeding during pregnancy and birth in late winter. In male subjects the risk was increased by bleeding in pregnancy and low birth weight for gestational age. The authors suggested that bleeding during pregnancy could impair placental functioning leading to poor fetal growth as a mechanism in male subjects. The risk of affective disorder was increased by uterine atony and late winter birth. Although this provides some evidence that different OCs may have some diagnostic specificity with regard to their risk, as does this work, the findings of Hultman *et al* are opposed to what has been found in the current study; that bleeding in pregnancy is a risk for affective disorder rather than schizophrenia.

Of the many studies of OCs and psychiatric disorder, the majority have assessed composite measure of OCs rather than individual complications. In those that have assessed individual complications multiple findings have been reported. These include increased risks of schizophrenia compared to unrelated controls in association with pregnancy complications of hypertension or pre-eclampsia (McNeil & Kaij, 1978; Dalman *et al,* 1999; Sørensen *et al,* 2003), prematurity (McNeil & Kaij, 1978; Ichiki *et al,* 2000; Kotlicka-Antczak *et al,* 2001; Dalman *et al,* 2001) and bleeding in pregnancy (Hultman *et al,* 1999). Labour and delivery complications associated with schizophrenia include prolonged labour (Cantor-Graae *et al,*

1994b; Kendell *et al,* 2000), inertia of labour (McNeil & Kaij, 1978), fetal distress (O'Callaghan *et al,* 1992), atypical presentation (Günter-Genta *et al,* 1994), cord knotting (Günter-Genta *et al,* 1994) and caesarean section (Byrne *et al,* 2000; Kendell *et al,* 2000). Low birth weight or other markers of poor fetal growth such as reduced head circumference (McNeil *et al,* 1993; Hultman *et al,* 1997; Dalman *et al,* 2001; Gunnell *et al,* 2005) and a low Apgar score at five minutes (Preti *et al,* 2000) have also been associated with the risk of schizophrenia.

In affective disorder there are fewer studies of individual complications available but prematurity (Øgendahl *et al,* 2006), low birthweight (Thompson *et al,* 2001; Øgendahl *et al,* 2006) and abnormal presentation or artificial rupture of the membranes to induce labour have been found (Bain *et al,* 2000). In a cohort study of singleton births followed up at the age of 20 to 25, Batstra *et al* (2006) found a relationship between poor obstetric optimality scores and depression, phobia, nicotine dependence and multiple psychiatric morbidity, although the study was confined to non-psychotic conditions. The authors suggest that patients with more severe psychiatric illness frequently meet diagnostic criteria for multiple diagnoses and that OCs may correlate with severity as indicated by multiple diagnoses. However, the optimality score used in the study includes multiple measures of social status, previous obstetric history and family history, as well as somatic OCs. Although largely ignored in the discussion of findings, maternal marital status was associated with both phobia and somatisation disorder, and parental socio-economic status at the time of birth with somatisation disorder and substance use. Low birth weight and a low Apgar score at 3 minutes after delivery were associated with an increased risk of substance use. Prematurity and an Apgar score of <7 at 5 minutes were found to be associated with depression in a birth cohort follow-up study (Fan & Eaton, 2001). The findings from the current study do not immediately clarify the situation, in

that a stronger relationship was found between OCs and affective disorder than schizophrenia, with the main obstetric risks for affective disorders being a low Apgar score at 5 minutes and bleeding in pregnancy for females and those without a family history, while the main risk for schizophrenia was induced labour or elective c/s in younger onset cases and in those with a family history.

7.8 Winter birth, age of onset and family history

7.8.1 Winter birth

Birth in winter was more common in schizophrenic subjects compared to their well siblings, which was not found by DeLisi *et al* (1987). However, OCs did not occur more commonly in those born in winter, as has been previously reported (O'Callaghan *et al,* 1992; Wright *et al,* 1995; Hultman *et al,* 1997). In contrast, Takagai *et al* (2006) found a eight-fold increase in the risk conferred by OCs on male subjects born in winter, but, as this study divided 90 schizophrenic subjects by gender and by season of birth, numbers in each group were small, with only 19 male schizophrenics born in winter. McNeil *et al* (1997) found winter-born schizophrenic subjects to have had more OCs on McNeil-Sjöström scale but not on the Parnas or Lewis & Murray scales. In those born during the rest of the year, schizophrenic subjects had more definite OCs than controls only on the Lewis & Murray scale. Kinney *et al* (1994a) also found more OCs in schizophrenic subjects who were not born in winter.

7.8.2 Age of onset

OCs have been found to be more common in schizophrenic subjects with an early age of onset (Smith *et al,* 1998). Könnecke *et al* (2000) found OCs to be the strongest predictor of age of onset of schizophrenia after family history. A linear relationship, in which the number of OCs was correlated with earlier age of onset, has also been found (Kelly *et al,* 2004). Byrne *et al* (2000) found more OCs in male schizophrenics with onset by age 30, but the

mean age of onset of schizophrenia is not reported, and is usually significantly before this age. However several studies have found no relationship between OCs and age of onset (Thomas *et al,* 2001; Ordonez *et al,* 2005). With regard to individual complications, birth asphyxia has been related to early onset schizophrenia in males only (Rosso *et al,* 2000).

7.8.3 Family history

A similar lack of convergence of findings with regard to family history has been found in the literature. No relationship between OCs and family history has been found (McCreadie *et al,* 1992; O'Callaghan *et al,* 1992), but several studies have found more OCs in non-familial schizophrenics (Lewis & Murray, 1987; Schwarzkopf *et al,* 1989; Dassa *et al,* 1996) and in familial schizophrenics (Walshe *et al,* 2005). With regard to specific complications, a smaller head circumference in non-familial schizophrenic subjects has been found compared to controls (McNeil *et al,* 1993). The current study found an increased risk for familial schizophrenia compared to normal controls if labour was induced or an elective c/s was performed, but an increased risk for non-familial affective disorder compared to controls following bleeding in pregnancy.

7.9 Aetiological considerations

Schizophrenia is increasingly conceptualised as a disorder of neurodevelopment which is manifest by subtle impairments in motor, cognitive and emotional performance which are evident prior to the onset of specific symptoms (Kelly *et al,* 2003; Rapoport *et al,* 2005). However, the neurodevelopmental hypothesis is not universally accepted (Gross & Huber, 1997) and as with many findings in the history of schizophrenia research, such mechanisms may not be specific to schizophrenia and may be related to other conditions. Cerebral palsy was once thought to be caused by birth injuries, particularly those resulting in asphyxia, but as the incidence of cerebral palsy has not declined as obstetric care has improved, its aetiology has been reconsidered. Complications arising during pregnancy, such as fetal malformation and growth retardation, rather than complications of delivery, are found to be associated with cerebral palsy, but may indicate markers of aberrant development rather than accidents which happen to otherwise normal fetuses (Nelson & Ellenberg, 1986).

Data from the AMNDB showed no decrease in the rates of pre-eclampsia, antepartum haemorrhage, prematurity or low birth weight between 1950 and 1964, but interpretation of this finding in the light of a decline in new presentations with schizophrenia in the Aberdeen area is not straightforward. It is possible that improved obstetric care results in the survival of infants with more severe complications who would previously have died. If OCs do have an aetiological role in the development of schizophrenia, this improvement in obstetric care could increase the rates of schizophrenia (Eagles *et al,* 1996). However, better obstetric care may have ameliorated the effects of other OCs by interventions such as induction of labour and elective c/s, but the effect of this been compensated for by higher rates of exposure to

other potentially important factors such as cannabis consumption, thus making it difficult to attribute causality to any change in the incidence of schizophrenia.

Neuroimaging techniques have revealed that cerebrovascular events in newborn infants, once thought uncommon, are quite frequent, often small and associated with a relatively good short term outcome. Intraventricular haemorrhage (IVH) is the most common of these events among premature infants, and involves bleeding into the highly cellular, richly vascularised primitive tissue of the subependymal germinal matrix, causing destruction of glial precursor cells which are in the process of migrating to cortical layers (Vohr & Ment, 1996; Volpe, 1997). Even when uncomplicated by parechymal involvement or hydrocephalus, such IVH is associated with reduced cortical volume in premature infants (Vasileiadis *et al,* 2004). IVH has been associated with a five-fold increase in the risk of white matter disorders in premature infants (Kuban *et al,* 1999). Such white matter injury has been shown to be associated with abnormal neurodevelopmental outcome manifest in motor, cognitive and visual deficits (Perlman, 1998). In infants who are not premature, the primary cause of IVH is hypoxia which may occur acutely at birth, but is more commonly due to placental insufficiency, maternal illness or antepartum haemorrhage (Lewis, 1989). Zornberg *et al* (2000b) found that such 'hypoxic-ischaemic' OCs doubled the risk of any psychotic disorder (schizophrenia or affective psychosis) even when the confounding factors of familial risk, gender, age, prenatal care and socio-economic status at birth were controlled for, but did not clearly specify which OC were included in the definition of hypoxic-ischaemic complications. The current study found premature birth, antepartum haemorrhage and a low Apgar score at 5 minutes after birth to be associated with an increased risk of affective disorder compared to normal controls, and suggests that hypoxic-ischaemic mechanisms, liable to increase the risk of small IVHs, are possible mechanisms.

Obstetric complications have been found to cluster in families with schizophrenia, especially in those with multiple affected individuals (Walshe *et al,* 2005), suggesting that a predisposition to OCs, as well as a predisposition to schizophrenia, may be genetic in origin (Preti, 2005). A recent study found that when mothers and their offspring had the same human leucocyte antigen (HLA-B) and therefore the mother did not make antibodies to fetal HLA-B, there was an increased risk of schizophrenia in female subjects (Palmer *et al,* 2006). It has been suggested that maternal sensitisation to fetal HLA and other antigens may be important for the normal maintenance of pregnancy, and when this fails to occur adverse outcomes, including fetal loss, pre-eclampsia and low birth weight, are more common. In contrast, maternal-fetal Rhesus incompatibility has been associated with an increased risk of schizophrenia which does not reflect genetic linkage or association, but is likely to be mediated via the maternal immunological mechanisms associated with the incompatibility (Palmer *et al,* 2002).

A number of other research strands contribute to the idea that immunological mechanisms may be implicated. Prominent among these are the findings that prenatal exposure to viral infections, particularly influenza, may be associated with later schizophrenia. The autoimmune disorders of thyrotoxicosis and insulin-dependent diabetes mellitus (IDDM) have been found to be more common in the relatives of schizophrenic probands than controls (Gilvarry *et al,* 1996). Patients with a family history of schizophrenia in a first degree relative showed higher rates of IDDM in their relatives than those without a family history, suggesting that 'familial' schizophrenia and autoimmune disorders may be correlated, and possibly implicating autoimmune abnormalities in the aetiology of schizophrenia (Wright *et al,* 1996). An adverse effect of raised levels of glucocorticoid hormones has been suggested as a possible mechanism by which maternal infection or stress could affect fetal brain

development and increase the risk of schizophrenia (Koenig *et al,* 2002). In animal studies, exposure of pregnant mice to influenza influenced multiple gene expression in the offspring (Fatemi *et al,* 2005), and the induction of a maternal cytokine response in pregnant rats has been shown to result in apparently normal pups, which develop behavioural abnormalities as adults (Robertson *et al,* 2006).

Animal models have been used to assess the implications of other obstetric complications on later neurological development. Changes in dopaminergic functioning have been found in rodents exposed to hypoxia through ligation of the uterine artery during pregnancy, and in those exposed to acute birth hypoxia mediated via delivery of the term uterus into a saline bath for several minutes, with males showing more changes than females (Boksa & El Khodor, 2003). Prenatal stress, modelled by administration of glucocorticoids to pregnant rats, has been found to be associated with changes in dopamine and glutamine receptor levels in the hippocampus, prefrontal cortex and nucleus accumbens (Boksa, 2004). Pyramidal cell atrophy following prenatal exposure to influenza in mouse embryos has been found in two studies, (Fatemi *et al,* 2002; Shi *et al,* 2003), although a third investigation found no difference in pyramidal cell structure in the dorsal hippocampus between those exposed and controls (Cotter *et al,* 1995). Hippocampal functioning has been considered central to the pathophysiology and neuropathology of schizophrenia (Harrison, 2004). Experimental lesions of the rat hippocampus have been found to result in behavioural abnormalities and working memory deficits in adult animals (Robertson *et al,* 2006).

Theories of gene-environment interactions imply that sensitivity to environmental factors is genetically mediated or that environmental factors affect gene expression (Kendler & Eaves, 1986). The stress-vulnerability model proposes the former, i.e. that psychiatric disorder

occurs because genetically sensitive individuals are more likely to develop illness in response to environmental hazards than are those who are not genetically sensitive (Zubin & Spring, 1977). This hypothesis predicts that patients with a family history of schizophrenia, who have more genetic loading for the condition, should be more sensitive to environmental hazards than those without. The finding in this study that induced labour or elective c/s doubled the risk of schizophrenia in familial, but not in non-familial cases, is in keeping with this idea.

More recently it has been proposed that genetic factors may both influence sensitivity to environmental factors and determine those exposures, the genotype-environment correlation hypothesis. This hypothesis suggests that those with a higher genetic sensitivity to a particular environmental hazard are also genetically predisposed to experiencing that hazard. This may operate through higher risk individuals seeking out exposures such as consumption of cannabis and other substances, as well as being more likely to develop psychotic symptoms when exposed (van Os & Marcelis, 1998).

An alternative model proposed to explain the findings of increased risk of schizophrenia following OCs, maternal infection, stress or malnutrition, is that of a perturbation of insulin-like growth factors (IGF). IGF stimulates neuronal proliferation and inhibits apoptotic cell death: infants of low birth weight have lower levels of IGF, which may be associated with less optimal CNS development, and possibly with a poorer ability to compensate for other insults such as hypoxia (Gunnell & Holly, 2004).

Separating schizophrenia from affective disorder, particularly bipolar disorder, is not straightforward. Genetic studies indicate failure to 'breed true' with increased risk of bipolar

disorder, as well as of schizophrenia, in the relatives of schizophrenic subjects. Community based samples suggest psychotic symptoms occur in 4.2% of the general population, although fewer than half of this number met diagnostic criteria for a non-affective psychosis. Poor educational achievement, young age, living alone and lower income were associated with an increased risk of psychotic symptoms. The study suggests psychotic symptoms exist on a continuum within the general population and are not specific to diagnosis (van Os *et al,* 2000). Poor premorbid social functioning has been found to occur both in schizophrenia and in bipolar disorder (Cannon *et al,* 1997). The generally negative findings of previous studies of OCs in bipolar disorder have led to the suggestion that a common genetic liability to psychosis interacts with different environmental factors to produce either schizophrenia or affective disorder. OCs have been considered to be a risk factor for schizophrenia but not for bipolar disorder (Walker *et al,* 2002a).

Low social class was found in the current study to increase the risk for illness compared to controls and to increase the risk of being a sibling of an ill subject. This implies low social class is associated both with disease and with genetic loading for disease. Poorer socio-economic status has been associated with a number of findings that may relate to the development of schizophrenia and affective disorder. The current study assesses social class at the time of birth, but also reflects the socio-economic status of the mother during that pregnancy. Lower social class in pregnant women is associated with poorer nutrition and with cigarette smoking, which are related to low birth weight in the infant (van den Berg, 1981; Metcoff *et al,* 1981; Haste *et al,* 1990). The diet of UK residents of lower social class has been shown to be lower in essential minerals and vitamin C than those of higher social class (James *et al,* 1997). An ongoing study of individuals born in Aberdeen in the 1950s shows that rates of prematurity and low birth weight are associated with social class; the

highest rates of these complications are seen in the lower social classes. Similar relationships were also found for measures of childhood growth, intelligence and psychological disorder in childhood (Batty *et al,* 2004). Intelligence in childhood has been shown to be related to social class, with higher rates of low IQ in the lower social classes (Sameroff *et al,* 1987). Lower premorbid intelligence has been shown to be a risk factor for schizophrenia (Jones *et al,* 1994a; David *et al,* 1997; Russell *et al,* 1997) and for affective disorder (van Os *et al,* 1997). A decline in childhood IQ between the ages of 4 and 7 has been associated with a significantly increased risk of psychotic symptoms in adult life after controlling for the effect of social class (Kremen *et al,* 1998). A similar finding, that the increased risks of mortality related to lower social class was attenuated by controlling for IQ, has been found in the Scottish population (Batty *et al,* 2006).

Children of psychotic mothers have lower IQ in childhood, and this finding may be limited to males (Rieder *et al,* 1977; Gamer *et al,* 1977). Patients with affective disorder, particularly depression, have been found to be of lower IQ (Clark *et al,* 1985). These findings for IQ may not be disease specific. Mild cognitive impairment in childhood has been associated with increased rates of psychiatric problems (Chen *et al,* 2006). An increasing risk of contact with psychiatric services and lower IQ has also been found (Walker *et al,* 2002b).

An association between a gene on chromosome 8p, Neuregulin 1 (NRG1) and schizophrenia was recently identified in an Icelandic population by Stefansson *et al* (2002) as a candidate gene for schizophrenia. This finding has been replicated in studies in Scotland (Stefansson *et al,* 2003), the UK (Williams *et al,* 2003), The Netherlands (Bakker *et al,* 2004), the USA (Hashimoto *et al,* 2004), South Africa (Hall *et al,* 2004) and China (Zhao *et al,* 2004), although different haplotype abnormalities have been found in different populations. A

recent meta-analysis of these studies found significant heterogeneity between studies and no evidence that one particular haplotype was associated with an increased risk of schizophrenia. The heterogeneity is probably related to racial characteristics of the populations investigated. However, summing the data for haplotypes found to be associated with schizophrenia in individual studies confirmed the association between NRG1 and schizophrenia, although recent studies have found more modest ORs than initially reported (Munafo *et al,* 2006). While the precise function of NRG1 is not yet known, mediation of glutaminergic neurones may be implicated (Stefansson *et al,* 2002), but further research is needed to clarify possible roles for NRG1 in neurotransmission, glial differentiation and myelination, which may all be potentially important in the development of schizophrenia (O'Donovan *et al,* 2003; Owen *et al,* 2005; Harrison & Law, 2006). A recent investigation of the role of NRG1 in subjects at high risk of schizophrenia indicates that a variant in the promoter region of this gene is associated with decreased premorbid IQ, as well as with the development of psychotic symptoms and decreased activation of frontal and temporal regions on fMRI (Hall *et al,* 2006).

Abnormalities of fetal development are increasingly implicated in the relationship between OCs and psychotic illness. Complications which affect placental functioning, which may be mediated by immunological mechanisms or hypoxia, may influence neuronal proliferation and migration in the developing fetal brain. Fetuses with such neurodevelopmental abnormalities may be more likely to be at risk of further hypoxic injury during delivery, possibly intraventricular haemorrhage. However, these infants may also be more likely to have obstetric intervention, such as induction of labour or an instrumental or surgical delivery in an attempt to ameliorate these risks. Other markers of poor infant development, such as low birth weight, or poor Apgar scores may be seen as reflecting the underlying aberrant

neurodevelopment in such cases. Placental function is likely to be significantly affected by the mother's health, her diet and her behaviour including cigarette smoking and caring for herself during pregnancy, all of which are likely to be related to intelligence and social class.

7.10 Conclusions

Overall the results of this study do not support OCs as a significant aetiological factor for schizophrenia, although power limitations mean this cannot be confidently excluded. This is in accord with some recent large studies, which have also failed to confirm the earlier finding of increased OCs in schizophrenia (McCreadie *et al,* 1992; Buka *et al,* 1993; Marcelis *et al,* 1998; Gunduz *et al,* 1999; Nicolson *et al,* 1999; Byrne *et al,* 2000; Kendell *et al,* 2000). In studies calculating crude and then corrected ORs for schizophrenia, initial findings of increased risk have diminished as confounding factors have been controlled for. However, it would not be appropriate to conclude that OCs are unrelated to schizophrenia, as induced labour or elective c/s was associated with an increased risk of both early onset schizophrenia and familial schizophrenia, and low birth weight was associated with an increased risk of early onset illness. The results for schizophrenia are in keeping with the idea that OCs may be related to the age of onset of schizophrenia, and supports the idea that a genetic predisposition interacts with low birth weight to lower age of onset in vulnerable subjects.

Antepartum haemorrhage and low Apgar scores at 5 minutes may be associated with an increased risk of affective disorder, at least in female subjects, but the findings of this study require to be replicated. Both complications may be related to placental insufficiency resulting in an hypoxic infant who is more likely to experience subtle CNS injury, possibly intraventricular haemorrhage. Previous studies have implicated similar processes in schizophrenia; this study suggests such obstetric risks are not specific to schizophrenia and may also apply to affective disorder.

Complications of pregnancy, birth and early life are implicated in the aetiology of major psychiatric disorder, but so far, individual complications have not proved specific to any one condition (Verdoux, 2004). The balance of evidence remains in favour of OCs having some role in the aetiology of major mental illnesses, possibly through mechanisms that involve the efficiency of the placenta to provide for normal fetal growth. The number of studies finding such associations, despite their heterogeneity of findings, suggests that specific OCs do contribute to the risk, at least in certain subgroups, rather than supporting the conclusion of Crow (2003) that OCs are not a risk factor for psychosis. The conclusion of Pasamanick & Knobloch (1960) that 'there exists a continuum of reproductive insult, at least partially socioeconomically determined, resulting in a continuum of reproductive casualty' implicated in the later development of serious mental illness, remains valid.

Investigating the relationships between OCs and psychotic illness is not easy. The exposures of interest occur over twenty years before the development of symptoms and therefore relationships are likely to be confounded by other factors operating during some or all of that period which may be reflected in measures of socio-economic deprivation, urban dwelling and substance misuse. There is no agreed consensus as to which OCs may be of greatest importance, different complications are ascertained and found relevant in different studies. Standard obstetric practice changes over time, this may not affect the incidence of complications such as antenatal haemorrhage or pre-eclampsia, but there are clear trends over time in rates of induction, use of forceps and other instruments and both elective and emergency caesarean sections. Rates of maternal viral infection vary annually and some OCs show seasonal variation.

Obstetric complications may not be related to the risk of illness per se, but may be important only for certain subgroups. It is possible that obstetric adversity influences the age of onset, and, perhaps, severity of the illness, rather than the type of disorder manifest. Serious psychiatric disorder is not always easy to classify, and dimensional, rather than categorical, approaches may clarify relationships with OCs.

In terms of further research, despite the strengths of cohort studies being able to examine large numbers and to use prospectively collected obstetric data, these studies are too insensitive to potentially important clinical variables, such as age of onset and family history, to be likely to easily investigate relationships in these subgroups. Cohort studies are often disadvantaged by relying on case register diagnoses, which are less robust than those made by case note analysis or at interview. Cohort studies depend on awaiting the development of illness in individuals, and differing results are likely with time as the birth cohort progresses through the major period of risk. Definitive results only become available after at least thirty years and, because the entire cohort is born at the same time, seasonal and annual influences cannot be assessed.

Case-control studies, on the other hand, are limited by the type of obstetric information available, which does not always lend itself to examining modern hypotheses. However, useful and consistent measures of neonatal well being, the Apgar scores, are in widespread use and the recording of birth weight and gestational age is likely to be universal. Birth weight, appropriately adjusted for maternal parity and physique, gestational age and infant sex, and Apgar scores, should be studied further. Similarly data on maternal cigarette smoking, compliance with antenatal care, parity, socio-economic and marital status should be included as potential confounding factors. Complications of pregnancy such as pre-

eclampsia, maternal diabetes and antepartum haemorrhage are also likely to be readily available and increasingly operationally defined. Maternal malnutrition may be inferred from routinely recorded height and weight measurements at specific gestations. However, the situation for complications of labour and delivery is less straightforward. While the use of induction of labour, forceps, Venteuse extraction or caesarean section is highly likely to be recorded, the indication for such procedures, which is likely to be as important, may not be. Such interventions are increasingly undertaken in order to lessen the risk of adverse fetal outcomes and may reduce the likelihood of OCs that would otherwise be expected. For example, a fetus with borderline IUGR, which if left to its own devices may be at greater risk of low birth weight, is now likely to be delivered earlier to avoid the effects of further placental decompensation. Such infants may be born at a time when they remain just within the normal weight for gestational age range and the mode of delivery by caesarean section may result in them having better neonatal outcomes than they otherwise would. Further research therefore should include the indications for such interventions.

Ideally, index subjects should be interviewed and a family history ascertained using standardised methods. Proxy indicators of illness severity, perhaps as measured by earlier age of onset, longer duration of in-patient care, use of compulsory treatment or need for higher doses of antipsychotic medication, may help to delineate in which types of patients OCs may play a role. Research should not be limited to schizophrenia, further assessment of the role of OCs in affective disorder, particularly unipolar depression, should be considered. Comparison groups in case-control studies should include both same-sex siblings and unrelated controls. It may be useful to specifically examine first and subsequent births separately where siblings are included, as siblings cannot be matched to index cases on parity. Another potential strategy would be to examine only first and second born same-sex

pairs discordant for illness, matched with control first and second born pairs with no illness. Births examined should occur throughout the year and preferably over several years to allow seasonal factors to be investigated. Case-control studies cannot however be expected to clarify other potentially important risks such as maternal viral infections, as routinely collected obstetric data is unlikely to record minor illnesses or adequately differentiate between the infectious agents responsible. As knowledge has advanced, obstetric complications have become seen less as discrete events which simply happen to an otherwise normally developing fetus, but as a complex array of conditions pertaining to an underlying biological impairment of the fetus and the modern obstetric responses to these conditions. As obstetric care has developed, it has become more interventional, for both medical and non-medical reasons. Future research will have to contend with this development and consideration of more precise measures of fetal growth occurring prior to the onset of labour, as well as the traditional measures of birth weight and length, appropriately corrected, may be useful.

As research into the relationship between OCs and psychotic illness has developed over the past four decades, the focus has shifted from concepts of damage at birth to earlier in the prenatal period. At the same time, the design of studies investigating this relationship has been improved by the inclusion of larger numbers of subjects, the assessment of obstetric data from unbiased and reliable sources and by controlling for important socio-demographic and parity influences. As this has occurred, the size of the effect of OCs on the risk of psychosis has diminished. Although this has been interpreted as evidence of no relationship between OCs and psychosis, it is perhaps more likely that OCs are related to the development of psychosis in some individuals but not in others, and that OCs may influence clinical manifestations of illness, such as the age of onset.

As research into the aetiology of schizophrenia and major affective disorder develops, studies of obstetric adversity which assess individual complications, and not only composite scores, have the potential to advance understanding of the mechanisms which predispose individuals to a higher risk of illness. Although the effect of obstetric complications on the risk of psychosis is small, further research is important to clarify possible mechanisms which may contribute to the development of psychotic illness.

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Appendix

Table A1 Winter and summer births. Crude odds ratios and 95% C.I. for schizophrenia

	Winter-born			Summer-born		
	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls
Mother not married	0.64 0.25-1.67	0.62 0.21-1.84	**0.39** **0.19-0.79**	0.70 0.20-2.42	0.62 0.17-2.33	1.34 0.65-2.74
Low social class	1.21 0.73-1.98	0.93 0.52-1.67	1.15 0.76-1.74	1.58 0.91-2.77	0.85 0.47-1.56	**1.64** **1.13-2.38**
Primiparity	0.69 0.44-1.08	1.54 0.88-2.68	**0.54** **0.36-0.82**	1.19 0.71-1.98	1.65 0.92-2.93	**0.59** **0.40-0.85**
Mother Rhesus negative	0.87 0.48-1.58	0.90 0.44-1.83	0.74 0.46-1.21	1.35 0.72-2.52	1.35 0.67-2.69	0.92 0.59-1.43
Pre-eclampsia	0.66 0.15-2.93	0.94 0.15-5.70	1.07 0.30-3.78	3.08 0.72-13.20	3.27 0.54-20.03	0.58 0.13-2.55
Prematurity	1.44 0.47-4.48	0.79 0.22-2.77	1.31 0.56-3.07	1.30 0.26-6.39	0.78 0.15-4.14	0.91 0.35-2.39
Labour induced or c/s	1.32 0.84-2.07	**1.95** **1.10-3.47**	0.65 0.42-1.00	1.36 0.78-2.36	1.20 0.65-2.21	1.01 0.69-1.50
Non-OA presentation	0.90 0.30-2.67	0.97 0.27-3.55	1.13 0.46-2.79	0.33 0.04-2.60	0.64 0.07-6.30	0.55 0.16-1.84
Intervention delivery	1.04 0.60-1.82	**2.84** **1.25-6.44**	**0.36** **0.19-0.71**	0.76 0.36-1.61	1.01 0.43-2.34	0.85 0.51-1.44
Low birth weight	2.88 0.83-10.05	2.83 051-15.76	0.66 0.15-2.92	0.82 0.10-6.93	0.65 0.07-6.34	1.15 0.03-4.06
Apgar at 1 minute < 7	0.86 0.47-1.56	1.47 0.68-3.18	0.82 0.45-1.47	0.74 0.31-1.74	0.60 0.24-1.54	1.44 0.83-2.52
Apgar at 5 minutes < 8	0.87 0.44-1.72	1.21 0.51-2.85	1.24 0.64-2.39	0.55 0.18-1.68	0.37 0.11-1.20	1.71 0.93-3.15
Any OC	1.18 0.77-1.81	**2.02** **1.21-3.36**	**0.64** **0.45-0.92**	1.19 0.72-1.98	1.06 0.61-1.85	1.01 0.72-1.43

Table A2 Younger and older age of onset. Crude odds ratios and 95% C.I. for schizophrenia

	Age of onset ≤ 21			Age of onset ≥ 22		
	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls
Mother not married	0.55 0.19-1.59	0.53 0.16-1.69	1.83 0.92-3.63	0.83 0.28-2.44	0.78 0.23-2.60	1.23 0.58-2.60
Low social class	1.03 0.58-1.82	1.03 0.53-1.98	0.90 0.58-1.41	1.59 0.96-2.63	0.77 0.44-1.34	**1.88** **1.30-2.71**
Primiparity	1.00 0.62-1.62	1.59 0.89-2.82	**0.55** **0.36-0.82**	0.79 0.49-1.28	1.48 0.84-2.59	**0.60** **0.41-0.88**
Mother Rhesus negative	1.05 0.57-1.91	1.12 0.56-2.25	0.83 0.51-1.33	0.98 0.51-1.87	0.85 0.41-1.76	0.87 0.55-1.38
Pre-eclampsia	1.45 0.47-4.51	2.25 0.49-10.30	1.00 0.29-3.50	1.00 0.12-8.67	0.89 0.08-9.90	0.66 0.15-2.93
Prematurity	0.43 0.06-3.41	0.52 0.05-5.06	0.47 0.14-1.54	2.63 0.88-7.92	0.95 0.31-2.93	2.02 0.92-4.44
Labour induced or c/s	**1.81** **1.11-2.93**	1.75 0.99-3.10	0.91 0.60-1.36	0.93 0.54-1.59	1.26 0.67-2.37	0.70 0.46-1.07
Non-OA presentation	0.63 0.14-2.81	0.79 0.14-4.44	0.74 0.25-2.14	0.73 0.21-2.53	1.06 0.25-4.54	0.98 0.37-2.60
Intervention delivery	0.77 0.38-1.56	1.42 0.59-3.44	0.54 0.29-1.01	1.10 0.61-2.00	1.94 0.92-4.11	0.62 0.36-1.08
Low birth weight	**3.97** **1.04-15.12**	2.15 0.47-9.88	0.94 0.27-3.28	0.63 0.08-5.14	0.83 0.07-9.32	0.89 0.20-4.02
Apgar at 1 minute < 7	0.76 0.38-1.52	0.91 0.40-2.07	1.06 0.60-1.87	0.88 0.44-1.77	1.00 0.44-2.27	1.14 0.65-2.00
Apgar at 5 minutes < 8	0.71 0.33-1.55	0.73 0.30-1.80	1.56 0.85-2.86	0.83 0.35-1.98	0.73 0.27-1.97	1.40 0.73-2.67
Any OC	1.54 0.95-2.49	1.71 0.99-2.98	0.84 0.58-1.20	0.91 0.58-1.44	1.23 0.73-2.08	0.79 0.56-1.11

Table A3 Younger and older age of onset. Crude odds ratios and 95% C.I. for affective disorder

	Age of onset ≤ 24			Age of onset ≥ 25		
	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls
Mother not married	**0.21** **0.05-0.89**	0.29 0.06-1.35	1.04 0.52-2.11	0.65 0.23-1.90	0.76 0.23-2.53	0.86 0.42-1.77
Low social class	**1.85** **1.19-2.88**	0.92 0.56-1.52	**1.84** **1.29-2.62**	1.52 0.94-2.45	0.76 0.45-1.28	**1.62** **1.15-2.28**
Primiparity	1.03 0.68-1.55	**1.99** **1.20-3.31**	**0.54** **0.37-0.78**	0.99 0.65-1.52	**1.95** **1.17-3.25**	**0.50** **0.35-0.72**
Mother Rhesus negative	1.42 0.86-2.35	1.03 0.58-1.83	1.23 0.83-1.84	0.96 0.58-1.60	0.80 0.45-1.43	**1.58** **1.08-2.30**
Pre-eclampsia	1.00 0.22-4.63	1.52 0.21-10.94	0.41 0.10-1.75	2.02 0.39-10.54	0.86 0.16-4.79	0.91 0.31-2.66
Bleeding in pregnancy	2.13 0.74-6.18	2.59 0.61-11.04	0.47 0.14-1.57	1.93 0.74-5.04	1.77 0.56-5.65	0.80 0.33-1.93
Prematurity	**2.86** **1.03-7.91**	2.95 0.72-12.07	0.90 0.26-3.10	0.51 0.12-2.21	0.48 0.10-2.34	1.23 0.53-2.86
Labour induced or c/s	1.26 0.81-1.95	1.23 0.73-2.07	0.95 0.66-1.37	0.96 0.58-1.57	0.96 0.54-1.69	0.78 0.54-1.12
Non-OA presentation	0.74 0.25-2.16	0.97 0.27-3.51	0.97 0.40-2.35	0.84 0.24-2.93	0.51 0.14-1.91	1.20 0.59-2.45
Intervention delivery	0.84 0.48-1.48	**2.15** **1.00-4.62**	**0.35** **0.19-0.63**	0.71 0.35-1.42	1.17 0.51-2.70	**0.41** **0.24-0.72**
Low birth weight	0.72 0.16-3.23	*	*	0.80 0.10-6.74	0.16 0.02-1.24	**3.51** **1.55-7.96**
Apgar at 1 minute < 7	0.64 0.34-1.23	0.78 0.37-1.64	0.79 0.49-1.27	1.00 0.52-1.91	0.39 0.66-2.93	0.93 0.56-1.53
Apgar at 5 minutes < 8	0.69 0.33-1.45	0.94 0.39-2.26	0.66 0.37-1.17	1.22 0.63-2.36	1.71 0.78-3.73	1.05 0.61-1.83
Any OC	1.15 0.76-1.75	1.05 0.65-1.72	0.99 0.71-1.39	1.19 0.78-1.81	1.02 0.63-1.65	1.05 0.77-1.45

* OR cannot be calculated as no subjects have the complication

Table A4 Family history. Crude odds ratios and 95% C.I. for schizophrenia

	No family history of psychosis or affective disorder			Family history of psychosis or affective disorder		
	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls
Mother not married	0.46 0.16-1.30	0.42 0.14-1.30	1.36 0.76-2.46	1.19 0.38-3.69	1.24 0.33-4.60	1.82 0.70-4.73
Low social class	1.45 0.93-2.24	0.91 0.55-1.49	**1.45** **1.04-2.03**	1.16 0.58-2.31	0.76 0.36-1.63	1.28 0.79-2.08
Primiparity	0.94 0.63-1.39	1.51 0.95-2.41	**0.60** **0.44-0.84**	0.71 0.38-1.35	1.56 0.73-3.35	**0.49** **0.29-0.81**
Mother Rhesus negative	1.12 0.67-1.87	0.98 0.54-1.75	0.85 0.58-1.26	0.93 0.42-2.04	1.27 0.51-3.18	0.66 0.35-1.28
Pre-eclampsia	1.00 0.29-3.51	1.24 0.27-5.63	0.76 0.26-2.21	2.04 0.38-10.80	3.76 0.33-42.52	1.00 0.12-8.66
Prematurity	1.25 0.41-3.81	0.77 0.23-2.63	1.02 0.47-2.20	2.00 0.38-10.61	0.90 0.16-5.08	1.36 0.44-4.20
Labour induced or c/s	1.12 0.73-1.71	1.19 0.73-1.96	0.94 0.67-1.33	**1.98** **1.06-3.70**	**2.66** **1.25-5.66**	0.60 0.34-1.03
Non-OA presentation	0.52 0.15-1.74	1.19 0.26-5.40	0.54 0.19-1.53	1.18 0.24-5.72	0.75 0.14-4.01	1.50 0.54-4.20
Intervention delivery	1.00 0.60-1.67	**2.24** **1.13-4.43**	**0.49** **0.29-0.83**	0.74 0.30-1.85	0.90 0.32-2.57	0.81 0.42-1.56
Low birth weight	2.56 0.76-8.67	1.56 0.38-6.37	1.11 0.37-3.31	0.94 0.11-8.21	1.79 0.11-29.29	0.49 0.06-3.88
Apgar at 1 minute < 7	0.73 0.39-1.38	0.82 0.39-1.75	1.06 0.63-1.77	0.97 0.44-2.15	1.28 0.51-3.23	1.13 0.60-2.14
Apgar at 5 minutes < 8	0.64 0.29-1.40	0.54 0.22-1.32	1.58 0.89-2.77	0.97 0.41-2.31	1.20 0.43-3.33	1.32 0.65-2.67
Any OC	1.28 0.87-1.89	1.52 0.97-2.38	0.84 0.62-1.13	0.98 0.54-1.79	1.38 0.70-2.71	0.75 0.49-1.17

Table A5 Family history. Crude odds ratios and 95% C.I. for affective disorder

	No family history of psychosis or affective disorder			Family history of psychosis or affective disorder		
	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls	Index cases compared to controls	Index cases compared to siblings	Siblings compared to controls
Mother not married	0.45 0.18-1.15	0.53 0.19-1.49	1.03 0.58-1.83	**0.07** **0.01-0.56**	0.38 0.04-3.52	0.73 0.25-2.13
Low social class	**1.50** **1.01-2.23**	0.84 0.54-1.30	**1.53** **1.14-2.07**	**2.16** **1.23-3.81**	0.84 0.45-1.59	**2.23** **1.44-3.47**
Primiparity	1.17 0.82-1.66	**2.51** **1.63-3.87**	**0.47** **0.34-0.65**	0.72 0.41-1.24	1.15 0.60-2.21	0.64 0.41-1.01
Mother Rhesus negative	1.13 0.73-1.73	0.92 0.56-1.50	**1.42** **1.02-1.98**	1.28 0.67-2.43	0.88 0.43-1.82	1.56 0.95-2.57
Pre-eclampsia	1.37 0.38-4.97	1.23 0.27-5.58	0.58 0.20-1.65	1.25 0.14-11.40	0.78 0.07-8.83	0.83 0.18-3.77
Bleeding in pregnancy	**2.60** **1.19-5.68**	**4.31** **1.33-13.98**	0.37 0.13-1.02	0.62 0.08-5.04	0.30 0.03-2.67	1.70 0.60-4.79
Prematurity	2.01 0.87-4.67	2.13 0.72-6.27	0.84 0.35-2.02	*	*	2.15 0.66-6.99
Labour induced or c/s	1.25 0.85-1.84	1.27 0.81-1.98	0.80 0.59-1.10	0.83 0.45-1.56	0.80 0.39-1.64	0.95 0.59-1.53
Non-OA presentation	0.65 0.22-1.87	0.58 0.18-1.85	1.16 0.59-2.28	1.08 0.30-3.91	0.93 0.21-4.02	0.99 0.37-2.66
Intervention delivery	0.89 0.53-1.48	1.83 0.94-3.55	**0.36** **0.22-0.58**	0.59 0.26-1.37	1.25 0.44-3.54	0.45 0.22-0.92
Low birth weight	0.48 0.06-3.77	0.19 0.02-1.50	1.62 0.72-3.62	1.07 0.23-5.01	1.51 0.21-11.05	1.62 0.33-7.95
Apgar at 1 minute < 7	0.83 0.47-1.46	1.09 0.57-2.08	0.84 0.55-1.30	0.74 0.35-1.57	0.90 0.37-2.17	0.86 0.48-1.56
Apgar at 5 minutes < 8	1.16 0.65-2.08	1.45 0.73-2.88	0.93 0.58-1.51	0.59 0.24-1.46	0.93 0.31-2.75	0.66 0.32-1.35
Any OC	1.39 0.97-1.99	1.25 0.83-1.89	0.96 0.73-1.26	0.79 0.47-1.35	0.68 0.36-1.27	1.21 0.79-1.87