THE COMPARISON OF OBSTETRIC COMPLICATION HISTORIES
OF INDIVIDUALS WITH
CHILDHOOD-ONSET SCHIZOPHRENIA VS. ADULT-ONSET SCHIZOPHRENIA:
A MULTI-SITE FEASIBILITY STUDY

by

Lorena Hsu

A thesis submitted in conformity with the requirements
for the degree of Master of Science
Graduate Department of Community Health
University of Toronto

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The Comparison of Obstetric Complication Histories of Individuals with Childhood-onset Schizophrenia vs. Adult-onset Schizophrenia:
A Multi-site Feasibility Study

Lorena Hsu, Master of Science (Epidemiology), 1999
Graduate Department of Community Health, University of Toronto

Abstract

The present study examined the feasibility of conducting a comparative study of obstetric complication (OC) histories among individuals with childhood-onset schizophrenia and adult-onset schizophrenia. Using a retrospective case-control design, subjects were identified from facilities in the Greater Toronto Area and their psychiatric charts and/or hospital birth records were examined with respect to diagnostic, demographic, and OC information. Research questions pertaining to issues of sample size requirements, data quality, and potential for measurement bias served to address the feasibility of the proposed study. The results showed that sample size requirements were met for the adult-onset schizophrenia group, but not for the childhood-onset schizophrenia group. The findings also demonstrated poor quality of OC data from psychiatric charts, difficulty in obtaining patient birth records, and the potential for bias with respect to the ascertainment of OC data in psychiatric charts and birth records, and in the reporting of OC information in the psychiatric charts. The findings suggest that based on the design and resources used in this study, the comparative study would not be feasible.
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I. INTRODUCTION

The present study is based on the concept that obstetric complications (OCs) may be associated with the subsequent development of schizophrenia. Over the past two decades, a large body of literature has accumulated to provide support for this view. While the majority of existing studies have examined the association between OCs and adults with schizophrenia, the relationship between OCs and children with schizophrenia has also been explored, although such studies are fewer and less systematic. A unique approach to the examination of the association of OCs and schizophrenia is to compare the OC histories of adults with schizophrenia vs. children with schizophrenia. It is proposed that such a design may help to further elucidate the nature of the relationship between OCs and schizophrenia.

The objective of the present study is to examine the feasibility of using psychiatric charts and hospital birth records to assess the OC histories among individuals with childhood-onset schizophrenia and adult-onset schizophrenia identified from various facilities in the Greater Toronto Area. The data collected from the psychiatric charts and birth records are analysed in order to determine whether it is practical to proceed with an actual comparative study of OC histories of childhood-onset vs. adult-onset schizophrenia based on the particular resources used for the present multi-site feasibility study.

In order to determine the feasibility of the comparative study, issues pertaining to sample size requirements, the quality of data in psychiatric charts and birth records, as well as the potential for bias are addressed. In addition, methodological issues related to the clinical records systems and ethical procedures of the various facilities provide further insight to the question of feasibility.
II. LITERATURE REVIEW

2.1 Introduction

Schizophrenia is the most persistent and debilitating of the major neuropsychiatric disorders. Due to the significant and long-lasting impairments resulting from this condition, and the need for hospital care, ongoing clinical care, rehabilitation, and support services, schizophrenia exacts enormous personal and economic costs worldwide. In Canada alone, almost three billion dollars is spent every year in health and social care for schizophrenia (Beiser & Iacono, 1990), making it a public health concern of major significance.

In spite of the progress made over the years toward understanding schizophrenia, there is currently no prevention for this condition. Thus, it is important for present research to focus on delineating the causes of schizophrenia so that efforts can be directed toward the prevention of this disease. Although the etiology of schizophrenia continues to evade researchers, there is increasing evidence to indicate that multiple factors are involved (Brixey et al., 1993). Genetic predisposition is the single most established risk factor for the disorder in some, if not all, cases. Twin, family, and adoption studies have consistently demonstrated that the familial aggregation of schizophrenia is largely accounted for by genetic factors (Sasaki & Kennedy, 1995). However, information concerning the mode of transmission for schizophrenia is lacking. Also, specific genes have not yet been implicated, and it is unclear how these genes contribute to pathophysiology, or whether the same or different genes are involved in all cases with a genetic etiology (Harris, 1995).

Since many identical twins are found to be discordant for schizophrenia, it is believed that some environmental factors must combine or interact with genetic predisposition to increase the
risk for the affected twins (Gottesman & Shields, 1972). Research over recent decades has focussed on a number of environmental and biological factors that may influence the development of schizophrenia. After many years of speculation that schizophrenia develops due to cerebral pathological events that occur or are expressed around early adulthood, recent evidence continues to point to events that occur long before the clinical onset of the illness. There is increasing support for the neurodevelopmental hypothesis of schizophrenia which contends that abnormalities occurring in fetal or immediate postnatal life critically disrupt the establishment of basic aspects of cerebral structure and function (O'Callaghan et al., 1992). It is currently believed that the psychotic symptoms of schizophrenia emerge only on the occurrence of maturational events triggered by the process of puberty (Galdos et al., 1993). While such a theory is compatible with the considerable increase in the incidence of schizophrenia seen around and after puberty (Galdos & van Os, 1995), it does not explain the occurrence of prepubertal schizophrenia and very late onset schizophrenia.

Based on the above presumptions, research in the past decade has focussed on potential sources of such early cerebral insults. One source which has received particularly widespread attention are complications experienced during gestation or delivery. Such obstetric complications (OCs) are increasingly considered to represent an important somatic environmental factor associated with the subsequent development of schizophrenia, and this is largely due to the accumulating evidence from a number of systematic investigations to support this contention. In the framework of the current theory of puberty, the study of OCs and their possible interactions with genetic predisposition may help to explain the onset of schizophrenia before and long after puberty.

The concept that OCs may be associated with the subsequent development of schizophrenia
in some cases forms the basis for the present feasibility study. However, unlike the majority of existing studies of OCs and schizophrenia that have compared persons with schizophrenia to non-schizophrenic groups, this study is uniquely based on the examination of the relationship between OCs and childhood-onset schizophrenia compared to adult-onset schizophrenia. It is thought that the examination of OCs in the context of such differences in the timing of onset of schizophrenia may provide clues as to the nature of the relationship between OCs and schizophrenia.

The following sections in this literature review examine epidemiological and related studies which are relevant to the issues of the present feasibility study. First, the historical background of childhood-onset schizophrenia as well as other relevant issues to describe the disorder are reviewed in some detail. The particular attention given to childhood-onset schizophrenia in this review is due to its more recent nature and relative obscurity in the general schizophrenia literature. A comparison of the characteristics of childhood-onset schizophrenia vs. adult-onset schizophrenia is also presented in order to address the relationship between the two forms of the disorder. The greater part of this review addresses the studies which investigate the association of OCs with childhood-onset and adult-onset schizophrenia, as well as the methodological approaches and issues related to such studies.

2.2 Childhood-onset Schizophrenia

2.2.1 Historical Background

In the early 20th century, DeSanctis recognized the onset of psychotic behaviour in childhood and introduced the term 'dementia praecocissima' (Hollis & Taylor, 1997). This was an extension
to Kraepelin's dementia praecox, used in the late 1800's to define a number of psychotic symptoms in adults (Harris, 1995). In 1919, Kraepelin observed that dementia praecox could begin during childhood and found that 3.5% of cases with dementia praecox had onsets before the age of 10, with another 2.7% of cases developing between 10 and 15 (Hollis & Taylor, 1997). Similarly, Bleuler estimated in 1911 that onsets of schizophrenia before age 15 made up 4% of all schizophrenic cases, while onsets of schizophrenia before age 10 comprised 0.5-1% of schizophrenic psychoses (Asarnow & Asarnow, 1994).

Up until the 1930s, schizophrenia in children and adults was recognized as essentially the same disorder with similar presentations (Hollis & Taylor, 1997). However, childhood psychoses began to be recognized as separate from adult psychoses in the 1930s, and investigators attempted to classify a broad range of childhood psychoses under the general term "childhood schizophrenia". Potter introduced the diagnosis of "infantile schizophrenia" in the prepubertal child. The symptoms included loss of interest in the environment, disturbances of thought, and lack of emotional rapport (Harris, 1995). According to DSM-IV criteria used today, Potter's criteria would have included not only children with schizophrenia, but autism, pervasive developmental disorder, and schizotypal personality disorder (Asarnow & Asarnow, 1994). In 1947, Bender distinguished between two groups of children with schizophrenia on the basis of age at onset (Asarnow & Asarnow, 1994), but her descriptions also encompassed a broad range of psychoses. To further complicate matters, Kanner identified the syndrome of early infantile autism in 1943, which he believed to be the earliest possible manifestation of childhood schizophrenia and thus did not discriminate between the two disorders. Subsequent to a follow-up study in 1949, however, Kanner changed his thinking and recognized the distinctiveness of autism and
schizophrenia in childhood (Beitchman, 1985). These broad definitions of schizophrenia in childhood were used up until the 1970s, and clearly had an influence on DSM-II which grouped all psychoses with onset in childhood under the category of "childhood schizophrenia" (Hollis & Taylor, 1997).

Since marked differences between subgroups of childhood psychoses existed, the grouping together of various childhood psychoses under the general rubric of "childhood schizophrenia" obscured any findings that may have been related to schizophrenia alone (Beitchman, 1985). This practice was eventually challenged in the 1970s, following the landmark study by Kolvin et al. (1971). This study compared childhood psychoses of early and late onset in terms of age of onset, phenomenology, and family history, demonstrating that autism and schizophrenia in childhood were essentially different disorders. Furthermore, the study found that children in the late onset (schizophrenic) group showed similarities with regard to symptoms experienced by adults with schizophrenia. Thus, it was also concluded that schizophrenia in adults and children were related and may therefore have similar etiologies (Kolvin et al., 1971). A number of reviews have credited the work of Kolvin and his colleagues as being the most influential in differentiating the various psychoses of childhood, and leading to changes in the diagnostic criteria of schizophrenia occurring in childhood (Rutter, 1972; Beitchman, 1985; Werry, 1992; Asarnow & Asarnow, 1994; Harris, 1995; Hollis & Taylor, 1997).

The findings of Kolvin et al. led to the abandonment of the term "childhood schizophrenia" and the introduction of DSM-III (APA, 1980) and ICD-9 (WHO, 1979) in which the diagnosis of schizophrenia in children was made using adult diagnostic criteria, with appropriate adjustments made for differences in the manifestations of symptoms in childhood (Asarnow & Asarnow,
1994). In DSM-III, infantile autism and pervasive developmental disorder (PDD) were distinguished from childhood-onset schizophrenia to describe infants in the first 30 months of life, and children with dysfunctional development and behaviour, respectively. The category of PDD included some children who in previous classification systems were diagnosed with schizophrenia (Harris, 1995). This practice of diagnosing childhood-onset schizophrenia continued in DSM-III-R (APA, 1987) and DSM-IV (APA, 1994) (see Appendix A). Research since the emergence of DSM-III has validated the use of adult criteria for diagnosing schizophrenia in children (Beitchman, 1985; Werry, 1992).

Although childhood-onset schizophrenia has been recognized since the beginning of the century, the studies available are limited in extent and methodology. Some methodological problems include the use of retrospective study designs, a lack of standardized tools for diagnosis, small sample sizes, and lack of control groups (Werry, 1992). In particular, reviewing the literature on childhood-onset schizophrenia is complicated by the varying concepts of the disorder at different periods of time. Since DSM-II aggregated all childhood psychoses under one category, the literature from about 1960 to the advent of ICD-9 and DSM-III in 1979/1980 did not distinguish between childhood-onset schizophrenia, autism, and other child psychoses. Thus, the findings from many of the studies in this period are questionable and difficult to interpret (Beitchman, 1985). The literature regarding childhood-onset schizophrenia before 1960 used diagnostic criteria similar to those in DSM-III, but due to crude methodology, the findings require replication (Werry et al., 1994). A review by Werry (1992) which examined studies in English since 1965 found that with two exceptions (Kolvin et al., 1971; Makita, 1966), only studies since 1975 were acceptable in terms of using modern diagnostic criteria for schizophrenia.
2.2.2 Epidemiology

Before reviewing the epidemiological data on schizophrenia occurring in childhood, it is relevant for comparative purposes to examine the epidemiology of the more common adult form of schizophrenia. The lifetime risk of schizophrenia occurring in adults is estimated at 1% of the general population and appears to be equal for both men and women (Jablensky, 1995), although a male to female ratio of 1.4:1 for the incidence of schizophrenia has been calculated (Beitchman, 1985). The prevalence among adults is on the order of 0.2%-0.5% and appears to be relatively stable across cultures (Coleman & Gillberg, 1996). Men tend to have an earlier age of onset with a peak risk around 20 years of age, while the peak incidence for women is around 30 years of age (Coleman & Gillberg, 1996).

While childhood-onset schizophrenia is known to be quite rare, almost no epidemiologic data on incidence and prevalence in large-scale population-based samples, using standard diagnostic criteria is available (Harris, 1995). Most investigators agree that the earliest age that schizophrenia has been diagnosed is 6 to 7 years, though there have been cases reported at 3 and 5.7 years of age (Green & Padron-Gayol, 1986). It is estimated that the prevalence rate for onset of schizophrenia before 13 years is less than one in 10 000 children (Burd & Kerbeshian, 1987). A close approximation to the treated prevalence of schizophrenia in children 15 years of age and under is less than 0.14 per 1000, which is almost 50 times less prevalent than schizophrenia with onset between 15 and 54 years of age (Beitchman, 1985). It is noted that due to the severity of schizophrenia in childhood, the treated prevalence likely approximates the true prevalence (Beitchman, 1985). It is also notable that the prevalence figures vary within different age groups. The diagnosis of childhood-onset schizophrenia has been found to increase significantly after 11
to 12 years of age (Harris, 1995), though there is a paucity of studies in the 13-15 age group (Werry, 1992). Furthermore, the rate of onset of schizophrenia appears to increase during adolescence to achieve adult rates of about 0.1% incidence per year (McClellan & Werry, 1992).

Data pertaining to the sex ratio of childhood-onset schizophrenia is shown to vary widely depending on the particular study examined (Beitchman, 1985). However, the male to female ratio is typically reported to be around 2:1 in schizophrenic patients with onset under 16 years of age (Coleman & Gillberg, 1996), except for two studies (Eggers, 1978; Russell, 1994). Beitchman (1985) counted the numbers of male to female cases in nine selected studies, and after excluding those cases that were not necessarily schizophrenia or had an onset before age 5, found a male to female ratio of 1.48:1. Findings of male to female sex ratios of 17:2 in children and 5:6 in adolescents (Cantor et al., 1982) and 4:1 in children/early adolescents vs. 2:1 in late adolescents (Thomsen, 1996), suggest a distinct age effect in that the sex ratio varies according to the age group under study. It is notable that the above sex ratios observed in adolescents approach the equal sex ratio seen in adults with schizophrenia.

2.2.3 Diagnostic Issues

Diagnostic Nomenclature

It is evident from studies of childhood-onset schizophrenia that there is much ambiguity in defining this disorder. Since the term "childhood schizophrenia" was previously used to refer to all forms of childhood psychoses, the use of this term in the present diagnostic nomenclature is discouraged. However, Beitchman (1985) argues for the reintroduction of the term "childhood schizophrenia" as it is useful in drawing attention to the fact that there may be real differences
between the child and adult forms. Werry (1992), on the other hand, argues for abandoning 'vague' terms of adolescent, childhood, and prepubertal schizophrenia and using age-related categories instead. These categories are "early-onset schizophrenia" (EOS) to describe children and adolescents under 16 or 17 years of age, and "very early onset schizophrenia" (VEOS) when onset is before the age of 13. He notes that this latter subgroup is usually referred to as "prepubertal"; however, since this terms refers to a biodevelopmental state which cannot be precisely defined by age, the use of the term VEOS does have a definite meaning. Yet another view is taken on by Cantor et al. (1982) who argue that signs and symptoms should define a disorder, and not age of onset. This approach, however, is not practical when children are very young as the evaluation of many of the critical symptoms of schizophrenia may be hampered by the level of language and emotional development in such children (Beitchman, 1985). Keeping in mind the above differing views, and following the tendency of more recent studies, the term "childhood-onset schizophrenia" will be used for the present study to describe schizophrenia with onset occurring in childhood.

Another source of ambiguity in studies of childhood-onset schizophrenia is the age cut-off used to define the disorder. For studies that define the age criteria used, there does not seem to be agreement on the upper and lower age limits of the disorder. Kolvin et al. (1971) defined his late onset psychosis group as having an onset at 5 to 15 years of age. In another study of diagnosis and phenomenology in children with schizophrenia, the age criteria used was 5 to 11 years (Spencer & Campbell, 1994). McKenna et al. (1994), in screening for childhood-onset schizophrenia patients included those with onset at or before 12 years of age. Similarly, studies looking at phenomenology by Green et al. (1992) and Russell et al. (1989) focussed on schizophrenia in
children under the age of 12. Hollis & Taylor (1997) chose to refer to childhood-onset schizophrenia as cases with onsets of 16 years or younger. They recognized that this was an arbitrary cut-off, but chose it to include those subjects usually excluded from adult-onset studies. This lack of consistency in defining age criteria makes valid comparisons across studies of childhood-onset schizophrenia rather difficult. Werry (1992) recognizes that the lower limit of onset of schizophrenia seems to be declining with increasing diagnostic sophistication, but suggests that with the scarcity of data on schizophrenia in children, it is premature to apply any age limitation to the diagnosis.

**Problems in Diagnosis**

Although the adopted nosology of separating the various childhood psychoses into different categories since DSM-III has improved the accuracy and consistency of diagnosis, the criteria must be followed closely with regard to type, number, duration, and combinations of symptoms to ensure a valid and reliable diagnosis (McClellan & Werry, 1992). There are a number of clinical features in children that may cause problems in the diagnosis of childhood-onset schizophrenia. As McClellan & Werry (1994) pointed out, one problem is making certain that a true psychotic state in the child exists, and that the peculiarities observed are not nonpsychotic thoughts and perceptions due to developmental delays, exposure to trauma, and/or overactive imagination. Similarly, the level of language and cognitive development in children may make it difficult to describe complex internal symptoms, such as loosening of associations (Russell, 1994).

The six month duration criterion of symptoms for schizophrenia may also be a potential
diagnostic problem since most children are brought to medical attention before their symptoms have persisted for that amount of time, and in some cases, symptoms have remitted before six months. The use of neuroleptics that successfully treat the symptoms before the duration criterion is met also adds to the problem of diagnosis. Not surprisingly, such diagnostic problems are also encountered in adults with schizophrenia. Another concern is the increased likelihood of patients being incorrectly diagnosed at onset due to an overlap in symptomatology in schizophrenia and affective psychoses. In fact, about 50% of adolescents with bipolar disorder may be originally misdiagnosed as having schizophrenia (Werry et al., 1991). Thus, it is necessary to follow cases longitudinally, with periodic reassessments, so that a confirmed diagnosis can be made (McClellan & Werry, 1994).

2.3 Comparison of Childhood-onset Schizophrenia and Adult-onset Schizophrenia

The practice of applying the same diagnostic criteria to schizophrenia regardless of age of onset since DSM-III in 1980 has led many researchers to address the issue of whether continuity exists between childhood-onset and adult-onset schizophrenia, or whether they are etiologically distinct phenocopies (Hollis & Taylor, 1997). Asarnow et al. (1994) proposed that childhood-onset schizophrenia is continuous with or similar to adult-onset schizophrenia but may be a more familial and severe form of the disorder. Comparisons made on a number of characteristics have supported this to some extent. In terms of symptomatology, a number of studies have demonstrated that adult-type characteristic symptoms of delusions, hallucinations, incoherence, catatonic behaviour, and flat/inappropriate affect can be found in children, with expected
developmental variations (Kolvin, 1971; Eggers, 1989; Green & Padron-Gayol, 1986; Volkmar et al., 1988; Werry et al., 1991; Russell et al., 1989). On the other hand, the typically reported gender ratio in young children with schizophrenia (see section 2.2.2) has been cited as a factor that distinguishes the childhood-onset and adult-onset forms of the disorder. Russell (1994) points out that this distinction may not be valid as several recent large-scale studies of schizophrenia in adults using similar diagnostic criteria have shown ratios similar to the childhood gender ratio, at least for those with onset under age 45.

Another difference that has been shown is a higher frequency of insidious onset in childhood-onset schizophrenics, as opposed to acute onset which is typical in adults with schizophrenia (McClellan & Werry, 1994). Since early onset and insidious onset are generally considered to be negative prognostic factors, these types of onset are consistent with the belief that schizophrenia occurring in childhood represents a more severe form of the disorder. In terms of premorbid functioning, a high percentage of patients with schizophrenia in childhood experience premorbid abnormalities; however, it is difficult to tell whether these abnormalities are more common in childhood-onset schizophrenics since direct comparison with properly matched adults has not been done (Werry, 1992). With regard to prognosis, several follow-up studies have shown a substantial number of schizophrenic patients with onset in childhood to show symptoms as they progress into adolescence and adulthood (Werry, 1992). It is often suggested that the outcome for childhood-onset schizophrenia is worse than that for adult-onset schizophrenia, but this is difficult to discern as outcome studies are limited (Werry, 1992). Thus, the above comparisons seem to indicate that schizophrenia in childhood may be similar or continuous to the adult form, apart from greater male predominance and type of onset, and that it is perhaps a more severe subtype of the disorder.
Based on the concept that continuity exists between the two, some studies suggest that findings pertaining to adult-onset schizophrenia can be reasonably extrapolated to schizophrenia in childhood, with developmental differences being taken into account (McClellan & Werry, 1994). Since the vast majority of literature on schizophrenia focuses on onset in adults, being able to extrapolate findings from adult studies can help to advance our understanding of schizophrenia in childhood, of which currently little is known, and can also be a basis for initiating further studies on this particular subtype. Keeping with the assumption of continuity between adult-onset and childhood-onset schizophrenia, extrapolating from childhood-onset schizophrenia data for the purposes of research on adults with schizophrenia is also advantageous. Research on vulnerability factors may be more useful when undertaken on children with schizophrenia since adults with schizophrenia may be subject to the distorting influences of long-term exposure to neuroleptics or institutionalization. Since schizophrenia in childhood may prove to be more homogeneous in etiology with less time for disruptions in brain function and structure (Werry, 1992), the study of this subgroup may make it easier to isolate etiologic risk factors for schizophrenia.

Based on the evidence that childhood-onset schizophrenia may be continuous with, but perhaps a more severe form of adult-onset schizophrenia, it is pertinent to examine the factors that may explain the "atypical" onset of schizophrenia in childhood. With the recent emergence of the neurodevelopmental model of schizophrenia, obstetric complications (OCs) as etiologic factors for schizophrenia have been the focus of a number of systematic studies. Although such studies have reported on the association between OCs and childhood-onset or adult-onset schizophrenia, potential differences in the OC histories among these two subgroups have not yet been evaluated.
The following sections review the evidence for the association between OCs and schizophrenia as well as the methodological approaches and issues involved in conducting the proposed comparative study.

2.4 Obstetric Complications and the Development of Schizophrenia

The concept that OCs may predispose the individual to schizophrenia later in life is not new. In 1934, Rosanoff and colleagues first hypothesized that some schizophrenic illnesses were the result of birth injury (Lewis et al., 1989). Over the past three decades, a growing body of epidemiological and neuropathological research has been carried out to examine the possibility that OCs are important environmental factors associated with the subsequent development of schizophrenia.

OCs may be defined as the wide range of somatic anomalies from a normal course of events and offspring development during pregnancy, labor/delivery, and the neonatal period (McNeil, 1988). OCs are often divided according to the phase of gestation in which they occur. Pregnancy complications (PCs) arise during the period from conception until the onset of labour, birth complications (BCs) occur during labour and delivery, and neonatal complications (NCs) cover the time from the moment of birth through the first one to four weeks post partum (McNeil, 1988). More current research tends to divide OCs into prenatal complications, which are experienced during the period before birth, and perinatal complications, which occur during the period shortly before and after birth (from the 28th week of gestation to 1-4 weeks after birth) (Brixey et al., 1993).
The question of whether OCs act separately or additively with genetic predisposition, or are actually caused by pre-existing fetal abnormality remains to be answered. A number of hypotheses have been suggested for the etiologic role of OCs in the development of schizophrenia in adults (McNeil & Kaij, 1978), although two competing hypotheses appear to be more accepted among researchers. The first is a diathesis-stress model which suggests that the phenotypic expression of the genetic predisposition for schizophrenia takes the form of a vulnerable brain which is especially susceptible to damage from OCs (Mednick & Hollister, 1995). According to this model, an infant who has a strong genetic predisposition and experiences severe OCs has a high risk of subsequently developing schizophrenia. The second hypothesis is a familial-sporadic model which posits that where genetic risk is high, some cases of schizophrenia may develop in the absence of other factors, while where genetic predisposition is low, OCs are necessary for the later development of schizophrenia (Lewis & Murray, 1987).

Systematic investigations of the relationship between OCs and schizophrenia have been carried out using samples of childhood-onset and adult-onset schizophrenics, high risk offspring, and schizophrenics within monozygotic twin pairs discordant for schizophrenia. The weight of the evidence suggests that an association exists between OCs and the later development of schizophrenia in the offspring.

2.4.1 Obstetric Complications and Childhood-onset Schizophrenia

During the last few decades, there have been a number of more or less systematic studies examining the relationship between OCs and childhood psychoses. Clinical findings of the frequency of OCs in a variety of childhood psychiatric conditions led Pasamanick and colleagues
(1956) to postulate the existence of a "continuum of reproductive casualty" ranging from neonatal deaths through varying degrees of neuropsychiatric impairment. As such, schizophrenia occurring in childhood was implicated as one of the neuropsychiatric entities of this continuum.

The majority of the studies which compared childhood-onset schizophrenics with controls found a significant increase on some summary OC variable for the childhood-onset schizophrenia group. A large proportion of these studies, however, were performed during the 1960's and early 1970's when differential diagnosis of childhood psychoses was fraught with difficulties. As noted by Beitchman (1985), the diagnostic criteria used in these studies either do not differentiate between a variety of childhood psychoses, or are not clearly specified; therefore, it cannot be unequivocally concluded that the results apply to children with schizophrenia, and not other disorders such as autism or organic diseases. As such, studies of childhood-onset schizophrenia and OCs that were conducted during the period of 1960 to 1970, inclusive, will be excluded from this review.

Kolvin et al.'s (1971) study examining cerebral dysfunction and childhood psychoses found a 12% incidence of OCs in schizophrenic children who were diagnosed using present-day criteria for schizophrenia. It is noted that the assessment of OCs as risk factors may not have been complete as subjects were classified according to the main OC experienced, and thus, the results did not take into account the frequency and severity of OCs. In a series of 100 cases of "childhood schizophrenics" described by Bender and Faretra (1972) which included autistic children, it was reported that abnormal pregnancies took place in 10% of the 41 schizophrenics with onsets over 3 years of age. It should be noted that selection bias may be present as the 100 cases were chosen because they had the most complete records. Although it is not clear whether modern-day
diagnostic criteria for schizophrenia was used, these results do appear to reflect the findings of Kolvin et al. (1971).

A study by Rutt & Offord (1971) found a 51% incidence of prenatal and perinatal complications in 33 childhood-onset schizophrenics which was significantly higher compared to their siblings. As pointed out by Beitchman (1985), this rate is much higher than that reported for childhood-onset schizophrenics in Kolvin et al.'s (1971) study. It is, however, more consistent with the 37% incidence of OCs and 50% of abnormal pregnancies found in Kolvin et al.'s (1971) and Bender and Faretra's (1972) samples of autistic children, respectively. Since the diagnostic criteria used for the Rutt & Offord (1971) study was not clearly specified, it is possible that the sample may have comprised a large number of autistic children.

Mura (1974) compared 74 child psychiatric inpatients, including 48 with schizophrenia, to their well siblings on a set of scale scores reflecting the frequency of OCs, severity of OCs, and OC of highest severity. It was found that the number of pregnancy complications, the severity of delivery complications, and the severity of all OCs combined, was significantly higher in the patient group. These results, however, should be interpreted with caution since the sample includes only children whose mothers visited them in the hospital, and maternal bias may be present in the reporting of OC data. Furthermore, the diagnostic criteria for schizophrenia was not clearly stated and it cannot be certain that the results apply only to children with schizophrenia.

A study by Torrey et al. (1975) used detailed and systematic OC data collected prospectively on 14 children with infantile autism and 6 children identified as psychotic, including those with schizophrenia. When matched to two control groups (one of normal-IQ children and the other of low-IQ children), it was found that maternal uterine bleeding during pregnancy was significantly
associated with the subsequent development of children with autism and other psychoses. It was also found that mid-trimester bleeding was especially prevalent among mothers of such children. Due to the small sample size involved, as well as the variety of childhood psychoses included in the sample, however, it is not possible to unequivocally apply the findings of this study to children with schizophrenia.

In a pilot study, Funderburk and colleagues (1983) found a statistically higher frequency of infertility and spontaneous abortion in the parents of a sample of patients which included 42 autistics and 5 childhood-onset schizophrenics when compared to three different control groups. The frequency of exposure to exogenous hormones was also significantly increased in patients compared to controls; however, since hormones were prescribed for parental reproductive problems in almost half of the exposed patients, it is not possible to discern whether hormonal exposure was causally related to the development of psychoses in these patients. Once again, due to the inclusion of autistics in the sample, it is not possible to know whether the results of this study apply to autistic or schizophrenic children.

It is reasonable to conclude that no studies unequivocally demonstrate that the rate of OCs is significantly higher in childhood-onset schizophrenics compared to a suitably matched control group. This is due to the inclusion of other childhood psychoses in study samples, lack of clearly specified diagnostic criteria, and the presence of bias in the OC data due to inadequate or inaccurate sources. Thus, the majority of the findings provide only suggestive evidence that a significantly increased frequency of OCs occurs in childhood-onset schizophrenics compared to control children. Further studies which use stringent diagnostic criteria for identifying subjects with childhood-onset schizophrenia, and which assess the quality of the OC data are required.
2.4.2 Obstetric Complications and Adult-onset Schizophrenia

The possibility that OCs could contribute to or even cause schizophrenia in adults has been the topic of a large number of epidemiological studies in recent years. In a meta-analysis of 18 studies by Geddes & Lawrie (1995), an overall odds ratio of 2.0 (95% confidence interval, 1.6-2.4) was found for the risk of schizophrenia subsequent to any kind of OC. These studies are varied in terms of the methodological approaches used, and tend to have relatively small sample sizes. Different studies have compared schizophrenics with a variety of groups, including delivery series matched controls, nonmatched population controls, mentally well and abnormal siblings, and patients with other psychiatric disorders (McNeil, 1995). Similar to the childhood-onset schizophrenia studies, OC information has been obtained from a number of sources, including prospectively recorded medical record information, routine hospital or midwife records, birth certificates, psychiatric records, and retrospective reports by parents, relatives, or the patients themselves (McNeil, 1995).

*OC Rates in Adult-onset Schizophrenics vs. Non-schizophrenic Controls*

The majority of investigations have found significantly increased rates of OCs among schizophrenics as compared to controls (Lewis & Murray, 1987; McNeil, 1995). The rates of OCs were typically measured by a total OC score or other type of summary score, depending on the OC scale employed. Studies using matched controls from the same delivery series found that schizophrenic patients were significantly more likely than controls to have experienced at least one OC (OR=2.4; 95% CI, 1.1-6.0) (O'Callaghan et al., 1992), and that schizophrenics had a non-significantly higher rate of OCs compared to controls (OR=1.3; 95% CI, 1.0-1.7) (Cantor-Graae
et al., 1994). Kendell et al. (1996) compared 115 closely matched schizophrenic/control pairs and found a highly significant excess of complications of both pregnancy and delivery in the schizophrenics (P<0.001). When compared to population controls, schizophrenic patients were either more likely to have experienced at least one OC (Jacobson & Kinney, 1980; Gunther-Genta et al., 1994), or did not differ significantly with respect to OCs (Done et al., 1991).

A number of studies compared schizophrenics to their normal siblings and demonstrated either significantly higher rates of OCs in schizophrenics compared to their siblings (Woerner et al., 1973; Eagles et al., 1990; McNeil et al., 1994), or did not find any significant differences in OC rates for the two groups (Pollack et al., 1966; DeLisi et al., 1987; McCreadie et al., 1992; Kunugi et al., 1996). Comparisons of schizophrenics with their ill siblings showed a higher rate of OCs for schizophrenics in one study (Heun & Maier, 1993), but no differences in OC rates in another (Gunther-Genta et al., 1994). The remainder of investigations compared schizophrenic patients with psychiatric controls and all demonstrated significantly higher rates of OCs in the schizophrenic groups (Lewis & Murray, 1987; Wilcox & Nasrallah, 1987; Schwarzkopf et al., 1989; Foerster et al., 1991; Verdoux & Bourgeois, 1993; Gureje et al., 1994). All of the studies with psychiatric controls used retrospectively reported OC information.

The association between OCs and age at onset of schizophrenia has also been examined. Lewis et al. (1989) found that the onset of schizophrenic patients with a history of OCs was on average 5 years earlier than those without such a history. A meta-analysis of individual patient data (Verdoux et al., 1997) found a significant linear trend in the association between age at onset and definite OCs, indicating that the earlier the age at onset, the more likely the history of OCs (odds ratio for linear trend=0.80, 95% CI, 0.67-0.97).
Specific OCs and Schizophrenia

Although many studies have found an increased incidence of OCs in schizophrenics compared to controls, there is no consensus on which specific complications are associated with schizophrenia. This is because studies commonly compare schizophrenics and controls on a global OC score which takes into account a broad range of OCs (Kendell et al., 1996). When specific OCs were reported to be significantly higher in schizophrenics than in controls, they have varied from study to study. These include prolonged labour (McNeil & Kajj, 1978; Jacobsen & Kinney, 1980), low birth weight (Lane & Albee, 1966; Rifkin et al., 1994), preeclampsia (McNeil & Kajj, 1978; Kendell et al., 1996, O’Dwyer, 1997), abnormal presentation of the fetus (Parnas et al., 1982; Gunther-Genta et al., 1994), fetal distress (O’Callaghan et al., 1992), premature rupture of the membranes (Eagles et al., 1990), umbilical cord complications (Gunther-Genta et al., 1994), small head circumference (Kunugi et al., 1996), and Rh incompatibility (Hollister et al., 1996). With the exception of preeclampsia, the fact that only one or two studies obtained significant results for each of these OCs suggests that some of the findings may be due to chance. Regardless, Kendell et al. (1996) point out that a common theme of fetal hypoxia exists among many of these OCs.

There are recent studies that focus on the association between specific OCs and schizophrenia. A study by Jones et al. (1998) examined the associations between schizophrenia and specific pregnancy, delivery, and neonatal conditions, and found that low birth weight (OR=2.6, 95% CI, 1.1-5.9) and the combination of low birth weight and short gestation (OR=3.4, 95% CI, 1.2-9.4) were more common in schizophrenics compared to normal controls. Dalman et al. (1999) examined specific OCs that were indicators of three proposed etiologic mechanisms of OCs and
schizophrenia. Preeclampsia, an indicator of fetal malnutrition, was the strongest individual risk factor after controlling for confounding (OR=2.1, 95% CI, 1.1-1.4), and there was also evidence of increased risk associated with the mechanisms of prematurity and hypoxia.

**High-Risk Offspring**

In 1970, Mednick compared OCs in the offspring of schizophrenic mothers, who were at heightened genetic risk, with low-risk offspring of normal control mothers. Follow-up at the mean age of approximately 20 years showed that there were significant differences between the high-risk and low-risk groups. At least one OC occurred among 70% of the high-risk subjects who later developed a mental illness, 15% of the high-risk subjects who remained well, and 36% of the low-risk controls. Also, the two specific types of OCs that were most discriminative of the sick compared to the well and/or control subjects were prolonged labor (32% versus 0% and 13%, respectively) and prematurity (21% versus 7% and 7%, respectively), which replicates findings seen in adult-onset schizophrenic samples (McNeil & Kaij, 1978; Jacobsen & Kinney, 1980). These results suggested that OCs tend to produce psychopathology in offspring at genetic risk and led to a renewed interest in the relevance of OCs in the development of schizophrenia (McNeil, 1988).

Parnas et al. (1982) used Mednick's high-risk sample followed up at 24 years to investigate the relationship between OC history and the development of schizophrenia versus the development of borderline schizophrenia (i.e. schizotypal personality disorder) versus no mental illness. The results of this study showed that schizophrenics had significantly higher values than the borderline subjects on three summary OC scores representing total number of OCs, total OCs weighted for
severity, and the greatest severity of any single OC that occurred. However, neither the schizophrenics nor the borderline subjects differed significantly from the well subjects, whose OC summary scores stood at an intermediate position between those of the schizophrenic and borderline groups. The possible interpretation of these findings was that OCs contribute to the later development of schizophrenia in the genetically predisposed individual, and since borderline subjects have an inherited genetic loading similar to that of schizophrenics, they remain borderline only when exposed to an unusually uncomplicated birth. An alternative interpretation of these results may be that since the subjects are not through their risk period by the follow-up of 24 years of age, the results to this time only demonstrate a relationship between OCs and age at onset of schizophrenia (i.e. the greater the number and severity of OCs, the earlier the onset of schizophrenia), which has been found in other research (McNeil, 1988). Subsequent follow-up of these subjects to see whether the borderline and normal high-risk subjects remain as they are should provide answers as to the correct interpretation of these findings.

**Monozygotic Twin Pairs Discordant for Schizophrenia**

The examination of OC differences within monozygotic twin pairs discordant for schizophrenia allows one to evaluate the effect that OCs have on the later development of schizophrenia while controlling for genetic influences. Since a pair of twins share not only all genetic influence, but also the same pregnancy, studies of OCs within twin pairs are typically limited to differences in OCs within pairs for BCs (i.e. birth complications) and NCs (i.e. neonatal complications). However, birth weight can be a reflection of potential differences in PCs (i.e. pregnancy complications) for the twin pair (McNeil, 1988).
Birth weight within twin pairs discordant for schizophrenia has been the subject of considerable study. In a well-known study by Pollin & Stabeneau (1968), history differences including birth weight, was collected for 100 monozygotic discordant twin pairs. It was found that 61 of these twin pairs demonstrated intra-pair differences on measures of birth weight. Furthermore, lower birth weight was found to be twice as frequent among the schizophrenics as compared to their co-twins. A study by Gottesman & Shields (1972), however, did not yield similar findings. Using combined samples that came from England, Finland, Norway, and Japan, they also analysed the birth weights for 81 monozygotic discordant twin pairs. It was found that lower birth weight was equally distributed among the schizophrenics and their co-twins.

There is greater agreement among studies concerning the significance of BCs in monozygotic twins discordant for schizophrenia. From Pollin & Stabeneau's (1968) 100 discordant pairs, it was found that 30 pairs showed within pair differences on any BC, and 15 pairs demonstrated intra-pair differences on asphyxia. Furthermore, both of these BCs were found to be four times more frequent among the schizophrenics as compared to their co-twins. McNeil & Kaij (1978) also performed an analysis of BCs in a sample of 39 discordant twin pairs. The results showed that in 72% of the twin pairs, the schizophrenics had significantly more BCs than did their co-twins. Therefore, the results from both studies indicate that BCs may be relevant in the development of schizophrenia.

In summary, the use of many different types of samples of individuals with schizophrenia to examine the association between OCs and the development of schizophrenia has provided much insight into this etiologically complex disorder. The evidence obtained for differing patient samples which come from a number of different countries, and experience a variety of prenatal
and obstetric care routines, is substantial to indicate that OCs are in some way related to the subsequent development of schizophrenia. However, additional studies are needed to confirm such findings and to further elucidate the nature of the relationship between OCs and schizophrenia.

2.4.3 Mechanism of OCs and the Development of Schizophrenia

Until recently, the idea of a causal link between an event at or even before birth and the development of a psychotic illness later in life has been neglected due to the absence of a plausible mechanism. The concept of a delayed expression of a biological determinant is now thought to establish such a mechanism; since the genetic hypothesis of schizophrenia involves the phenotypic expression of an abnormal gene or genes that can be delayed for many years, it is conceivable that other biological determinants, such as OCs might function in a similar time scale (Lewis et al., 1989). Furthermore, the onset of schizophrenia is often preceded by disturbances in cognition, affect, and social interaction. The concept of schizophrenia as a neurodevelopmental disorder, with premorbid personality disturbances lends further plausibility to the relevance of early risk factors (Lewis et al., 1989).

Structural Brain Changes in Schizophrenia

Over the past two decades, schizophrenia researchers have been increasingly investigating the structural brain changes associated with schizophrenia and their possible links to a neurodevelopmental origin. A number of recent post-mortem brain studies have provided evidence that abnormalities in brain structure and physiology are involved in schizophrenia. The findings suggest that the anomalies seen in the brains of schizophrenics are not due to a
progressive, degenerative brain disease, but rather reflect a disorder in which there is a disturbance of early brain development, possibly occurring in the prenatal or perinatal periods (Bogerts, 1991). Reports of reduced nerve cell numbers in regions of the post-mortem brains of schizophrenics are suggestive of a disruption of early brain development (Bogerts, 1991). McLardy (1974) found that 12 out of 30 brains of early-onset schizophrenics showed reduced nerve cell bodies in the dentate gyrus of the hippocampal formation. Benes et al. (1986) reported that neuronal density was significantly lower in regions of the prefrontal cortex, cingulate gyrus, and motor cortex in 10 schizophrenics. Further examinations of 13 schizophrenics by Falkai & Bogerts (1986) of the hippocampal formation, and by Falkai et al. (1988) of the entorhinal region showed that the number of nerve cells was reduced in hippocampal segments, the dentate gyrus, and the entorhinal cortex of such patients.

Findings of cellular disarray in certain regions of the brain have provided further evidence of a disruption of early brain development. A report by Kovelman and Scheibel (1984) based on the brains of 10 chronic schizophrenics indicated pyramidal cell disorientation in anterior and middle hippocampal regions. It was suggested that these structural alterations were indicative of defective patterns of neuronal migration into the hippocampus primordium during prenatal development of the brain. Jakob & Beckmann (1986) examined 64 schizophrenic brains and found that 20 of these showed cytoarchitectonic abnormalities with displacement of single pre-alpha cell groups in the upper layers of the rostral entorhinal region of the parahippocampal gyrus. The authors suggested that a disruption of neuronal migration during the second trimester of pregnancy was involved.

The recent introduction of neuroimaging techniques in the neonate has yielded increasing
knowledge of the structural brain changes associated with schizophrenia. It is estimated that up to one third of schizophrenics show evidence of abnormalities on computerized tomographic (CT) scanning (McNeil, 1988). The most consistent findings from CT research in adults with schizophrenia are enlargement of the lateral and third ventricles, and widening of the cortical sulci (McNeil, 1988). Recent neuroimaging studies of schizophrenia have also shown loss of volume in brain regions along with the absence of fibrillary gliosis or of reactive astrocytes, which suggests a fetal origin of brain abnormality (Harris, 1995). In magnetic resonance imaging (MRI) studies of childhood-onset schizophrenia, progressive increases in lateral ventricle volume (Rapoport et al., 1997) as well as progressive reductions of temporal lobe structures have been found to occur with ongoing illness.

OCs and Cerebral Insults

In light of the evidence that possibly links brain abnormalities found in schizophrenics to early neurodevelopmental insults, it becomes important to examine the pathological nature of OCs and their possible functional effects on the developing brain in relation to schizophrenia. It appears that the majority of specific OCs that frequently occur with excess in schizophrenic samples are linked with fetal hypoxia, a complication in which a deficient amount of oxygen reaches the body tissue (Brixey et al., 1993). For example, there are a number of studies of different adult-onset schizophrenic samples reporting the occurrence of prolonged labor (Mednick, 1970; McNeil & Kaij, 1978; Jacobsen & Kinney, 1980; Parnas et al., 1982), and the most likely negative consequence of prolonged labor is oxygen deprivation. Furthermore, different studies of childhood psychotics (most of whom were schizophrenics) found that toxemia, bleeding during
pregnancy/threatened spontaneous abortion, and asphyxia, all of which imply risk of oxygen deprivation, were the specific OCs most characteristic across these studies (McNeil, 1988). Thus, the evidence from the analysis of specific OCs across different studies strongly suggests that the type of OC especially relevant to schizophrenia concerns oxygen deprivation.

Although a specific pathologic mechanism between OCs and schizophrenia has not yet been established, the findings that many of the reported OCs can be associated with temporary hypoxia suggests that the general mechanism whereby OCs may alter brain development is diminished oxygen supply. Primary support for this oxygen-deprivation theory comes from findings that brain regions that are most frequently implicated as deviant in schizophrenia, such as the hippocampus, the cerebral cortex, and the basal ganglia, are among the areas in the developing brain that are most sensitive to the adverse effects of oxygen deprivation (Harris, 1995).

Much of the research examining the effects of hypoxia on the brain has looked at the hippocampus. Oxygen deficiency due to hypoxia is thought to result in severe hippocampal damage due to a loss of enzymes. There is also speculation that oxygen deprivation may have an effect on neurotransmitters. It has been shown in animal studies that the synthesis and turnover of neurotransmitters such as dopamine, noradrenalin, and serotonin diminishes dramatically at relatively moderate levels of hypoxia (McNeil, 1988). These findings suggest that OC-related hypoxia may prove to be relevant to the neurochemical contribution to schizophrenia.

In summary, substantial evidence exists that OCs are important in the subsequent development of schizophrenia. This is shown by the increased rates of OCs that have been found in a variety of samples of individuals with schizophrenia. The understanding of the pathological nature of OCs and their possible functional effects on the developing brain has increased with the help of
postmortem brain and neuroimaging studies, and provides a strong basis for future research. Particularly, there is a need for more studies to confirm the relationship of OCs to childhood-onset schizophrenia, as well as further studies to examine structural brain changes associated with childhood-onset schizophrenia. Findings from such studies may help to further elucidate the factors responsible for the differences in onset between children and adults with schizophrenia.

2.5 Methodological Issues Related to Studies of OCs and Schizophrenia

2.5.1 Potentially Confounding Factors

Socioeconomic Status

The association between schizophrenia and lower socioeconomic status (SES) has been repeatedly demonstrated in a vast number of studies conducted in different countries and using a variety of research methods (Dohrenwend & Dohrenwend, 1969; Kohn, 1973; Eaton, 1974; Holzer et al., 1986; Bruce, 1990). According to the social causation theory, poor living conditions are conducive to an increased morbid risk for schizophrenia either directly through psychosocial processes or indirectly through neurodevelopmental disorders arising from higher rates of perinatal complications (Hafner et al., 1995). Alternatively, the social drift theory asserts that cognitive and social impairments as a consequence of schizophrenia will lead to social decline (Hafner et al., 1995), while the social selection theory contends that an individual fails to ever achieve his/her expected social level due to personal characteristics or other impairments predisposing to the disorder (Dohrenwend, 1990).

The majority of SES studies tend to focus on adult-onset schizophrenia, while studies
examining the association between SES and childhood-onset schizophrenia are lacking. According to McClellan & Werry (1994), studies that provide data on childhood-onset schizophrenia and SES have a selection bias toward inpatient samples with inconclusive results; thus, it is not possible to say whether a relationship between childhood-onset schizophrenia and SES exists. A study by Makikyro et al. (1997) somewhat addressed this by examining social class in "early onset" cases of schizophrenia and finding the cumulative incidence of schizophrenia to be significantly higher among persons from the highest social class than among persons from lower social classes. These subjects, however, were between the ages of 16 and 23 and thus do not represent cases of childhood-onset schizophrenia.

Although it is not yet clear whether an association exists between childhood-onset schizophrenia and SES, the findings thus far do demonstrate an overall association between schizophrenia and SES. In terms of the association of SES with the exposure of interest (i.e. OCs), it has been well established that the incidence of poor perinatal outcomes, including low birth weight and prematurity, is significantly higher in lower SES groups (Emanuel, 1977; Dunn, 1984; Shah et al., 1984; Silins et al., 1985; Canadian Institute of Child Health, 1992). In particular, low level of maternal education which is often used as a proxy for SES has been shown to be a risk factor for low birthweight (Institute of Medicine, 1985; Canadian Institute of Child Health, 1992). Thus, it seems reasonable to consider SES as a potentially confounding variable for the relationship between OCs and childhood-onset schizophrenia vs. adult-onset schizophrenia. In most studies of OCs and schizophrenia that matched schizophrenics with controls on SES, the SES of origin (i.e. parental SES) was used rather than the current SES (i.e. subject's own SES).

Due to the fact that many schizophrenics tend to migrate into lower social classes as a result of
their illness, inconsistencies in matching could result from using current SES (LaFosse et al., 1994).

**Gender**

Since males have an earlier onset of illness, lower premorbid functional level, and poorer outcome than women (Dalman et al., 1999), it raises the question of whether there is a sex difference in the risk of schizophrenia following OCs. Several researchers have, in fact, found a higher prevalence of OCs among males compared to females (Wilcox & Nasrallah, 1987; Owen et al., 1988; Foerster et al., 1991). A history of OCs appears more likely in males with an early onset of illness (Lewis et al., 1989; Castle & Murray, 1991; O'Callaghan et al., 1992).

2.5.2 Risk Factors for OCs

In studies examining the relationship between OCs and schizophrenia, there are a number of variables that subjects are often matched on which have been shown to be associated with OCs, but not necessarily with schizophrenia. For the purposes of keeping with the literature, such risk factors for OCs will be examined. Since low birthweight and prematurity have been linked to a large number of medical and obstetric factors, and much of the literature has focussed on these two as poor perinatal outcomes, the following risk factors for obstetric complications or events will be discussed in terms of their associations with these two perinatal outcomes.

**Race**

Race has been shown to be a risk factor for low birth weight and prematurity. In particular, black neonates are at a higher risk of low birthweight compared to other nonblack neonates, with
an approximate black neonate to nonblack neonate low birthweight ratio of 2:1 (Institute of Medicine, 1985).

**Maternal Age**

Adolescent mothers, particularly those under age 15, have a significantly higher risk for poor perinatal outcomes, including low birth weight, prematurity, and intrauterine growth restriction (Canadian Institute of Child Health, 1992). The rate of low birthweight is shown to be highest at ages under 15, and to fall throughout the teenage years to reach its lowest point between 25 and 29 years of age. Thereafter, the risk of low birth weight is shown to increase for rising maternal age (Institute of Medicine, 1985).

**Maternal Parity**

The history of a mother's previous pregnancies is important in predicting the risk of low birthweight. Specifically, the risk of low birthweight increases if it is the woman's first pregnancy, or if she has had a history of more than 4 pregnancies (Institute of Medicine, 1985).

### 2.5.3 Time of Onset of Schizophrenia

The determination of the time of onset of schizophrenia is significant when trying to understand the etiologic factors involved with the disorder. This is currently a difficult issue in schizophrenia research as there is no fully operationalized method of assessing the time of onset of schizophrenia. The fact that many schizophrenics experience prodromal symptoms before the first psychotic episode has led some to question whether the onset of schizophrenia should be defined by the first appearance of prodromal symptoms, or the first occurrence of psychotic
symptoms. Even more problematic than determining which point in time defines the onset is the fact that the time of onset is most often assessed retrospectively. Thus, many studies use the first admission date for schizophrenia as an approximation of time of onset (Bromet et al., 1988). It has been shown that the onset of schizophrenia lies on average several years prior to first admission (Lindelius, 1970; Angermayer et al., 1990; Hafner et al., 1994).

Determining the time of onset can especially be difficult in childhood-onset schizophrenia. Since schizophrenia in childhood most often has an insidious onset, and in most cases, a history of behavioural, developmental, and personality anomalies, distinguishing between the premorbid state and the psychotic onset can be extremely difficult (McClellan & Werry, 1994). There is, however, assurance in the fact that symptoms such as hallucinations and delusions are necessary for the diagnosis and that the appearance of such symptoms usually results in a noticeable change in the child's mental state and level of functioning (McClellan & Werry, 1994).

2.5.4 Sources of OC Information: Medical Records vs. Retrospective Recall

The significance of studies examining OCs and schizophrenia is critically dependent on the reliability and accuracy of the source of obstetrical data. Sources of OC information include prospectively compiled records for research purposes, prospective hospital or midwife records, birth certificates, psychiatric records, and retrospective reports by parents, relatives, or the patients themselves (McNeil, 1995). In Scandinavian studies of OCs and schizophrenia, it has been possible to obtain systematic maternity hospital and midwifery records for a substantial portion of schizophrenic patients due to long-standing health-care practices (Parnas et al., 1982). In most other studies, however, obstetrical data has been obtained through the retrospective recall of the
patient and/or a relative of the patient (O'Callaghan et al., 1990).

A major concern has been whether OC information obtained through retrospective reporting is reliable and accurate. Possible sources of error in retrospective reports include memory deficits, ambiguity in questionnaires or interviews (Hewson & Bennett, 1987), and the fact that the biological mother may not have actually been made aware of the complications of her pregnancy and/or delivery (O'Callaghan et al., 1990). In studies of OCs and schizophrenia, there is a potential for recall bias since mothers of schizophrenic patients may have poorer recall in general, due to cognitive impairment (Harris et al., 1996), and/or may tend to falsely recall OCs (errors of commission) in order to 'explain' their offspring's illness (Cantor-Graae et al., 1998). It has been suggested that retrospective reports are more likely to lead to omissive errors than to commissive errors, with general omission tending to decrease and commission tending to increase schizophrenic-control differences with respect to OCs (McNeil, 1995). As a result of such potential for error in recall, it is often assumed that medical records are objective and more accurate as compared to recall, and therefore the more acceptable data source (Hewson & Bennett, 1987).

It has recently been shown that information obtained from medical records is not always more accurate and reliable than data from retrospective recall. In several studies, the reliability of retrospective reports has been investigated by a comparison with medical records. In a study of the effects of exposure to the hormone diethylstilbestrol (DES) during fetal life, Tilley et al. (1985) compared prenatal records with obstetric data from questionnaires given to mothers ten or more years after the birth of their daughters. Analyses of agreement between the records and the questionnaires using kappa statistics showed that, in general, the mothers' recall of obstetrical
history had good to excellent agreement with their medical records. Agreement was poor, however, for items concerning medical intervention such as drugs and x-rays. It is noted by the authors that for items with poor agreement, if one of the events is reported in the record, it can be assumed that the record is correct. However, a mother’s positive response for an item should not necessarily be classified as invalid when it is not reported in the record since it is possible that events may not always be recorded. The results of this study can be generalized to other studies involving retrospective recall of prenatal history, but not necessarily of birth history as there may be differences in the reliability of recall for the two reproductive phases.

Hewson and Bennett (1987) compared the agreement of medical records and maternal recall for information on pregnancy and birth in 397 low-risk, primiparous women who had given birth at one of five teaching hospitals. These women were interviewed, and their reports were compared to data from their medical records. Based on the authors’ assumption that agreement between medical records and women's reports indicated accuracy, it was found that the majority of variables from both data sources were accurate. It was also found that both medical records and maternal reports were subject to variation from the actual events represented. Recording errors, criteria differences for recording certain variables among the various hospitals, and abstraction errors were found to be error sources for medical records, while memory problems, and ambiguous questioning were possible sources of error in women's reports. It should be pointed out that the resulting agreement between the two data sources may be indicative of the fact that women were interviewed after a relatively short duration of three weeks after giving birth, and that a longer time duration may limit women's recall, and thus the reliability of OC data.

A study by O'Callaghan et al. (1990) was the first to systematically evaluate the validity of
maternal recall of OCs in relation to adult schizophrenic patients. OC information was obtained through semi-structured interviews with 21 biological mothers of 17 adult schizophrenic and four other patients, and was then compared to OC data relating to pregnancy and delivery from the maternity hospital records of these patients. It was found that in only two of the twenty-one subjects, there were inconsistencies of details between maternal recall and hospital records. The authors concluded that maternal recall can be an accurate source of obstetric information, even in adult schizophrenia research which involves the recall of events occurring decades before the typical adult patient is assessed. It should be pointed out that since the biological mothers were interviewed to some depth in a semi-structured manner, it may not be appropriate to generalize these findings to other forms of maternal recall (e.g. unstructured interview or questionnaire).

Cantor-Graae et al. (1998) took the study by O'Callaghan et al. one step further by examining whether obstetric recall differs in mothers of adult-onset schizophrenic patients vs. mothers of psychiatrically normal offspring. OC information obtained from structured maternal interviews was compared with OC data from hospital birth records in 45 patient mothers and 34 control mothers. Considerable discrepancies were found between maternal recall and birth records for both maternal groups, and no significant differences were found between patient and control mothers with respect to type of recall errors or recall for selected obstetric events. It was suggested that OC data from maternal recall has methodological problems and that medical records may in fact be preferable with respect to OC research.

In reviewing these studies on sources of OC data, there are a couple of issues that warrant consideration. First, in the studies of Hewson and Bennett (1987) and O'Callaghan et al. (1990), it is stated that the "validity" of retrospective reporting of OC data was evaluated by comparing
the agreement of medical records and women's reports. Since it has been suggested that medical records should not be regarded as definitive and always complete, they should not be used as a gold standard when comparing maternal reports. Therefore, in these studies, only the reliability, or the extent of agreement rather than the validity or accuracy of the OC data can be assessed, and the use of the words "validity" and "reliability" interchangeably should be discouraged.

Secondly, there have been no studies to date that examine the reliability of retrospective recall of OC history with medical records in relation to childhood-onset schizophrenia. It is likely that the results from the reliability of recall in relation to adult schizophrenics cannot be generalized to that of childhood schizophrenics since for the latter, less time has passed since the event, and thus recall for the mothers/relatives may be more reliable. Therefore, before comparing the obstetric histories between childhood-onset schizophrenics and adult-onset schizophrenics, it is necessary to examine whether there are differences in the degree of reliability of this data among the two groups.

2.5.5 OC Scoring Scales

Another methodological characteristic of studies of OCs and schizophrenia is the use of scales for sampling and scoring OCs. A number of different OC scales have been employed, with many researchers developing their own versions. The various scales used differ in terms of their comprehensiveness in sampling and representing OCs as well as to the extent to which prenatal versus perinatal OCs are represented (McNeil, 1995). Not surprisingly, the particular OC scale employed may be influential with respect to the results of such studies.

One of the most frequently used scales is that constructed by Lewis et al. (1989). This scale
constitutes a list of OCs taken from at least half of six other OC rating scales and was designed to score a limited range of OCs obtained from retrospective parental reports. The rating scale was developed in accordance to the authors' preferred definition of OCs which is "any factor in the prenatal or perinatal environment which increases the risk of fetal mortality" (Lewis et al., 1989). OCs that are present are divided into two groups: "definite OCs" and "equivocal OCs". In terms of scoring, OCs are neither weighted or added together; thus, if any one of the "definite OCs" is present, the case is given the highest possible score for the total reproduction, without further differentiation of the number of OCs for the total reproduction as well as during various gestational phases of the reproduction. According to McNeil et al. (1994), a major concern is the inconsistent use of the Lewis et al. scale across studies, with various researchers employing different combinations among the three scoring categories. Dalman et al. (1999) consider this scale to be nonspecific, thus providing little clue to the underlying cause of the disorder.

Another OC scale that is frequently used is that of Parnas et al. (1982). This scale represents a fairly limited range of OCs and uses three different global scores of OCs. These scores are: the frequency score, which indicates the number of distinct OCs reported; the severity score, which represents the weight of the single most severe complication experienced (graded on a 4-point scale of severity); and the total score, which is obtained by adding the individual weighted scores for all OCs experienced. Unlike the scale by Lewis et al. (1989), this scale provides a summary score for the total reproduction which takes into account total amount and severity of OCs.

According to McNeil et al. (1994), the two above scales are not optimally effective in representing the amount, severity, or timing of OCs in a sample. Thus, the McNeil-Sjostrom OC scale was developed for the purpose of providing a standardized, functional system for the scoring
and weighting of several hundred specific OCs and their treatments (McNeil & Sjostrom, 1995). The McNeil-Sjostrom OC scale is based on the principles that the effects of various OCs need to be summed together since many different kinds of specific OCs contribute to trauma in the offspring, and that different OCs have varying negative effects on the offspring, and thus should receive different weights. One of six severity levels which make up an ordinal scale is given to each OC and is intended to reflect the inferred probability of harm to the developing offspring, with special emphasis on central nervous system damage. The severity weights for the specific OCs are based on general obstetric and pediatric experience as well as previous studies of OCs as risk factors for schizophrenia. They are used to calculate separate summary scores for OCs during different gestational phases (i.e. pregnancy, labor-delivery, and neonatal periods), and for the total reproduction. Furthermore, the McNeil-Sjostrom scale is intended for application in a generally comparable manner to a variety of sources of OC information, such as retrospective parental recall, hospital records, population registers, and prospective research studies.

The sensitivity and summarizing effects of the McNeil-Sjostrom OC scale have been compared to those of the OC scales of Lewis et al. and Parnas et al. (McNeil et al., 1994). Among the three scales, the McNeil-Sjostrom scale consistently showed statistically significant differences between schizophrenics and controls in both singleton and twin samples, and thus was found to be the best in discriminating between the OC histories of schizophrenics and controls. This study indicates the relevance of the particular OC scale used with respect to the results obtained, with higher risk estimates from the use of a weighted scale, and may explain some of the inconsistencies in results obtained across various OC studies (McNeil & Sjostrom, 1995).
2.6 Summary

The lack of comparative studies between childhood and adult-onset schizophrenia does not allow one to make any inferences about whether OCs are more commonly found in childhood-onset schizophrenia (Hollis & Taylor, 1997). Thus, the main objective of the present study is to assess the feasibility of conducting a comparative study that examines the OC histories of childhood-onset vs. adult-onset schizophrenia. It is based on the hypothesis that childhood-onset schizophrenia is associated with higher rates and greater severity of OCs in comparison to adult-onset schizophrenia. The comparison of OC histories between these two subgroups represents a unique approach to understanding the nature of the relationship between OCs and schizophrenia, and may shed light on the underlying mechanisms that work to precipitate the onset of schizophrenia in childhood and adulthood.
III. OBJECTIVES OF THE STUDY

The objective of the present study is to determine the feasibility of conducting a comparative study of obstetric complication (OC) histories of childhood-onset schizophrenia versus adult-onset schizophrenia. This will be done through a retrospective review of psychiatric chart records from selected sites in the Greater Toronto Area (GTA), as well as hospital birth records.

The purpose of the proposed comparative study is to test the hypothesis that persons with childhood-onset schizophrenia have a higher rate and greater severity of OCs than do persons with adult-onset schizophrenia, and that there may be differences in the specific types of OCs and the gestational timing of OCs that occur between these two groups. A multi-site study is proposed where information pertaining to OC history will be retrospectively obtained either from psychiatric charts, birth records, or both. In order to evaluate and weight the OC histories for children and adults with schizophrenia, the revised McNeil-Sjostrom OC scale (McNeil & Sjostrom, 1995) would be employed.

The feasibility of the comparative study will be evaluated by addressing three main issues: sample size requirements, data quality, and potential for bias. A number of questions which address different aspects of these main issues are presented below.

Research Questions

1. Sample Size Requirements

a) Is it possible to ascertain the required number of cases and controls from the selected sites to answer the study question?
b) What is the response rate for subjects in providing consent to participate in the study?

c) Is it possible to obtain the required number of cases and controls all having useful data?

2. Data Quality

a) How accurate is the diagnostic information pertaining to the time of onset of schizophrenia?

b) What are the missing data rates for cases and controls in the charts? What are the missing data rates for potentially confounding variables and variables related to OC exposure?

c) What is the extent of agreement of the OC data in psychiatric charts vs. birth records?

3. Potential for Measurement Bias

a) Is the ascertainment of OC information from the psychiatric charts and birth records comparable for cases and controls?

i) Are there differences in the method used to elicit OC data from the psychiatric charts of cases compared to controls (e.g. interview vs. form)? What is the average number of questions asked and/or specific OCs listed from such methods for cases vs. controls?

ii) Are there differences in the elicitation of OC data in the birth records of cases compared to controls? What are the proportions of cases vs. controls with birth records that request general OC information? What is the average number of particular OC items elicited from the birth records of cases vs. controls?

b) Are exposures equally likely to be reported for both cases and controls (e.g. recall bias)?

With respect to the issue of sample size, three components were considered to determine whether there would be an adequate number of cases and controls overall for the comparative
study. The first concerns the mere number of eligible cases and controls that can be ascertained from the study population. From this, one would then need to take into account the percentage of subjects who choose to participate in the study (i.e., response rate), and the possible loss of subjects resulting from non-response. Finally, it is not only essential that there are adequate numbers of cases and controls meeting the sample size requirements, but that there is also useful data available for these subjects so that the objectives of the comparative study can be carried out. As will be discussed in a later section, useful data can represent a number of different conditions with respect to the chosen source(s) of OC information.

Examination of the quality of data available from the psychiatric charts and birth records also serves to determine whether the comparative study is feasible. It provides an indication of how valid the results of the comparative study would be with respect to using such data. One aspect of data quality that will be examined is the diagnostic information in the psychiatric charts concerning the time of onset of schizophrenia. This is important as clear diagnostic data would provide more assurance that subjects were actually included in the correct subject groups. Missing data with respect to potentially confounding variables and OC information in the charts, as well as the reliability of the OC data from the psychiatric charts and birth records are also important components in assessing data quality, and hence determining feasibility.

There is also a potential for bias with regard to the ascertainment and reporting of OC data that may render the comparative study infeasible. It is necessary to examine whether OC information is equally likely ascertained/recorded in the records of cases and controls. As well, the potential for recall bias from OC data in the charts will be assessed by comparing the time lapsed between the OC exposure and the recall, as well as the reporters of the OC data for cases and controls.
IV. METHODOLOGY

4.1 Research Design

The proposed strategy for the actual comparative study of OC histories of those with childhood-onset schizophrenia vs. adult-onset schizophrenia is a retrospective case-control design. Subjects with an onset of schizophrenia in childhood (cases) would be compared to subjects with an onset of schizophrenia in adulthood (controls) with respect to exposure to OCs. The OC information would be accessed from the retrospective review of psychiatric charts of selected facilities in the GTA, as well as hospital birth records. Since childhood-onset schizophrenia is very rare, the case-control design is well-suited for testing etiological hypotheses for this disease.

The strategy for determining the feasibility of conducting the comparative study of OC exposure in individuals with childhood-onset schizophrenia vs. adult-onset schizophrenia was therefore based on the above retrospective case-control design. Available data concerning the OC histories of subjects with childhood-onset schizophrenia (cases) and subjects with adult-onset schizophrenia (controls) was obtained from a retrospective review of psychiatric charts of selected sites in the GTA, as well as hospital birth records.

Normally, in a case control study, individuals with a given disease (cases) and individuals without the given disease (controls) are selected and compared with regard to the exposure of interest. The design for the present feasibility study is therefore unusual in the way that both cases and controls have schizophrenia but differ with respect to the age of onset of schizophrenia. Since the hypothesis of the comparative study is that individuals with childhood-onset schizophrenia have a higher rate and severity of OCs as compared to individuals with adult-onset schizophrenia,
it is necessary to compare the two groups with regard to their exposure to OCs. Given that persons with adult-onset schizophrenia do not have and never have had childhood-onset schizophrenia, it seems plausible to consider them as controls (i.e. not having the disease that cases have). Although there is evidence to suggest that childhood-onset schizophrenia may be continuous with adult-onset schizophrenia, it is still not known whether the two are actually the same disease with merely differing times of onset. It seemed reasonable therefore to consider the two groups as separate disorders, and use the proposed case-control design for this study.

4.2 Subject Criteria

The study population consisted of patients diagnosed with schizophrenia from selected sites in the GTA. The cases were defined as subjects who met DSM-IV criteria, or similar modern diagnostic criteria for schizophrenia at 15 years of age or under. The age cut-off used for cases was arbitrary but chosen to encompass the majority of the children included in previous studies which used differing age criteria, and to distinguish childhood-onset schizophrenia from that occurring in later adolescence. Both incident and prevalent cases were to be ascertained retrospectively for the period of 1988 to 1998, inclusive, from the chart records of Hospital for Sick Children, Whitby Mental Health Centre, Sunnybrook Health Science Centre, and Youthdale Treatment Centres. This meant that the patients had to be admitted to the facility during the specified time period with a diagnosis of schizophrenia, but did not necessarily have to have an onset of schizophrenia during that time period. Although it was necessary to ascertain cases from many years back due to the rarity of childhood-onset schizophrenia, the study was limited to ascertaining cases only as far back as 1988. This was because it would have been difficult to
locate and contact subjects based on information from charts accessed retrospectively over many years. Furthermore, the clinic from which cases were ascertained from Hospital for Sick Children was apparently not open prior to 1988 so it would have been difficult to obtain the charts of patients who were admitted at this site before this time.

The control group consisted of subjects who were given an incident diagnosis of schizophrenia (meeting DSM-IV criteria or similar modern diagnostic criteria) at 18 years of age or older. Both incident and prevalent controls were to be drawn retrospectively for the period of 1993 to 1996, inclusive, from the chart records of Queen Street Mental Health Centre, the Clarke Institute of Psychiatry, and Whitby Mental Health Centre. Similar to the cases, this meant that the patients had to be admitted to the facility during the specified time period with a diagnosis of schizophrenia, but did not have to have an onset of schizophrenia during that time period. The ascertainment of controls was restricted to the relatively recent time period of 1993 to 1996 since the farther back in time subjects were selected, the more difficult it would have been to locate and contact subjects, as well as to access their birth records. Also, unlike cases, it was felt that the three year time period would have consisted of an adequate number of admissions for patients with adult-onset schizophrenia from which to select a sample of controls for the study.

The inclusion of prevalent cases to increase the number of both cases and controls available for the study is justified since it is obvious that OC exposure would have preceded the onset of the disease. Subjects were to be excluded from the study if they were born outside of Canada or the United States, 60 years of age or older, or if they were adopted when older than 1 year of age. This was for the reason that OC information from retrospective reports as well as from birth records would be very difficult, if not impossible, to obtain for such individuals.
4.3 Sample Size Calculations

4.3.1 Proposed Comparative Study

In order to determine the required sample size for the present feasibility study, it was necessary to first calculate the required sample size for the comparative study of OC exposure in childhood-onset vs. adult-onset schizophrenia. Due to the exploratory nature of the comparative study, a range of values were used for certain parameters to calculate possible sample sizes. Since there was no data in the literature pertaining to the relative risk of childhood-onset schizophrenia compared to adult-onset schizophrenia due to exposure to OCs, a range of relative risks from 1.5 to 3.0 were considered as important to detect. Information on the prevalence of exposure to OCs for controls (i.e. adult-onset schizophrenics) was present in the literature, but varied across studies. Since the comparative study considers being "exposed" to OCs as having experienced one or more OC with a severity level of greater than or equal to 3 according to the McNeil-Sjostrom OC Scale, only OCs with severity level ≥3 (using the McNeil-Sjostrom scale), and OCs considered to be "definite" (using the Lewis et al. scale) were used in determining the prevalence of exposure. Therefore, based only on studies which provided data on the proportion exposed to OCs, with samples comprised exclusively of adults with schizophrenia, the prevalence of exposure was found to range from 0.17 to 0.40, with a mean of 0.30.

Table IV-1 shows the required sample sizes for the comparative study using a level of significance of \( \alpha = 0.05 \) (two-sided) and a power of 80\% (\( \beta = 0.20 \)) for the varying levels of relative risk (\( RR \)) and prevalence of exposure for controls (\( PE \)). As well, the use of up to 4 controls per case was examined for its effect in lowering the required sample size for cases. This is particularly relevant as the number of available cases in the study population is presumed to be
<table>
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<tr>
<th>Relative Risk (RR)</th>
<th>Prevalence of Exposure (PE)</th>
<th>Sample Size (n)</th>
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<td></td>
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<td>1:1 Cases Controls</td>
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very small. The sample sizes were calculated using the formula in Kelsey et al. (1986, p. 277). It is shown that the required sample sizes for both cases and controls tend to decrease as the relative risk and prevalence of exposure values increase. Also, the number of cases needed to maintain a power of 80% decreases as the ratio of controls to cases increases. As shown, the range of required sample sizes in terms of the number of cases is from 32 cases and 128 controls \((RR=3.0, PE=0.30, \text{and } r=1:4)\) to 664 cases and 664 controls \((RR=1.5, PE=0.15, \text{and } r=1:1)\).

4.3.2 Present Feasibility Study

Since all available cases of childhood-onset schizophrenia were to be ascertained due to the rarity of the disorder, the calculation of sample size for the present study was necessary only for the adult control group. Since the main determinant of feasibility in the present study is whether there are sufficient numbers of cases and controls with useful data to perform the comparative study, the required number of controls to be sampled for the present study was based on the minimum proportion of controls out of all possible controls in the study population who would be required to have useful data. This proportion was determined using the sample size requirements for controls calculated above for the comparative study. The total study population of adult-onset schizophrenic patients was not known at the start of the study and could only be approximated as the study progressed and more information was available to estimate the patient load at each of the sites. Based on initial sampling and information from the clinical records departments, the patient loads were estimated to be \(~100\) at Queen St., \(~200\) at Clarke, and \(~200\) at Whitby. Thus, the estimated total number of adult-onset schizophrenic patients that could be ascertained from the three sites was \(~500\).
As shown in Table IV-1, the minimum number of controls needed to carry out the comparative study based on the lowest required sample size for cases is 128 \((RR = 3.0, PE = 0.30, \ and \ r = 1:4)\). With the assumption that the estimated total study population for controls is \(\approx 500\), the number of available controls would not be sufficient for parameters which yield required sample sizes of more than 500 controls. Thus, from Table IV-1, the highest possible number of controls that could be required for the comparative study would be 471 \((RR = 1.5, PE = 0.25, \ r = 1:1)\). From the minimum required number of controls, it was estimated that out of all possible controls in the study population, a minimum proportion of 26% \((128/500)\) must have useful data in order to carry out the comparative study. Hence, out of the sampled controls in the present study, a minimum proportion of 26% must have useful data in order for the comparative study to be feasible with respect to the sample size of controls.

To calculate the number of controls that must be sampled in order to obtain a reasonable estimate of the proportion of controls with useful data from the study sample, a 95% confidence interval for a proportion was used (Ott, 1984, p. 186). Since the minimum required proportion \((p_o)\) would vary widely depending on the various parameters in Table IV-1, and because it is not known what the proportion will be in the sample \((p)\), a range of values for \(p_o\) was examined. As shown in Table IV-2, different confidence interval widths \((L)\) of \(\pm 0.05, \pm 0.10, \ and \pm 0.15\) for different minimum required proportions of controls having useful data \((p_o)\) of 10\%, 50\%, and 95\% were used to calculate possible sample sizes \((n)\) for the controls in the present study. It can be seen that for a given \(p_o\), the required sample size decreases as \(L\) increases. Also, the required number of controls for a given \(L\) is highest for \(p_o = 50\%\) and lowest for \(p_o = 95\%\). Thus, the estimated sample size requirement for controls in the present study ranges from \(\approx 8 \ (p_o = 95\%\),
Based on these calculated sample sizes, it is clear that a sample size of about 100 controls would provide a reasonably precise confidence interval for a range of proportions that may be found in the study sample. As seen in Table IV-2, sampling 100 controls would result in confidence interval widths of between 0.05-0.10 for the proportion of controls with useful data (p) if \( p_0 \) is between 10% to 50%. Similarly, if \( p \) is between 50% to 95%, sampling 100 controls would for the most part yield confidence interval widths of 0.05-0.10 for \( p \). As a \( p_0 \) of 95% is approached, the confidence interval width for \( p \) would even be less than 0.05. For these reasons, the initial aim was to sample ~100 controls.

<table>
<thead>
<tr>
<th>Minimum Required Proportion of Controls with Useful Data ( (p_0) )</th>
<th>Confidence Interval Width ( (L) )</th>
<th>Sample Size ( (n) )</th>
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</table>

**4.4 Subject Ascertainment**

Since the intention was to ascertain all available cases of childhood-onset schizophrenia due to the rarity of the disorder, the cases obtained would represent all of those seen at the child patient
sites. In selecting controls, the objective was to obtain a sample of subjects representative of each of the three adult patient sites. This was done through stratified sampling, in which each of the three sites represented a strata from which a simple random sample of patients was taken. The three within-site samples were then combined for an overall control sample. It was proposed that a simple random sample be taken proportionately from each strata according to the patient load or study population at each site; however, this proved to be difficult since the total number of patients in the study population from these three sites was not known prior to the start of sample selection. Thus, an attempt was made to sample proportionately from the three sites based on the estimates of patient load at each site (i.e. 100 at Queen St., 200 at Clarke, and 200 at Whitby). With a total study population of ~500 and an aim to sample ~100 controls, it was calculated that a random sample of ~20 controls from Queen St., ~40 controls from Clarke, and ~40 controls from Whitby should be taken. These figures only served as initial guides to the sampling, with necessary refinements made to the samples as data collection progressed and better estimates of patient load could be made.

Since this study involved the contacting of subjects in order to access birth record information, it was required that the study proposal be submitted for ethical review at the University of Toronto. An application was made to the Department of Psychiatry Review Committee in September 1997, and ethical approval was granted in December 1997. In order to begin the process of subject ascertainment from the chosen sites, it was necessary to obtain appropriate consent from each of the institutions. Upon obtaining approval from each site, procedures to be followed by the principal investigator for the selection of subjects were outlined. These methodological approaches varied among the different sites and are described below.
Queen St. Mental Health Centre (Queen St.)

The Queen St. Mental Health Centre is the largest psychiatric facility in Toronto, providing inpatient services and several outpatient clinics. The areas served include: Etobicoke, Toronto, York, North York (west of Yonge St.), Brampton, Mississauga, and Caledon. In early 1998, this hospital teamed with the Centre for Addiction and Mental Health, becoming a teaching hospital fully affiliated with the University of Toronto.

The study protocol was submitted for review to the Queen St. Mental Health Centre Research Committee in January 1998. Scientific and ethical approval for the study was granted in February 1998. The hospital consent allowed for the review of patient psychiatric charts without individual patient authorization, as well as the contacting of subjects by the principal investigator after having identified those meeting the study criteria.

To obtain a sample from this hospital, a patient list was generated from a computerized database by authorized personnel in the Clinical Records Department. The list was in ascending order by casebook number, and consisted of inpatient admissions between January 1, 1993 to December 31, 1996 with a primary and/or secondary ICD-9 diagnosis code of any 295.x. Although all disorders with the code 295.x represent the 'schizophrenic psychoses' in the ICD-9 coding system, schizophreniform disorder (295.4) and schizoaffective disorder (295.7) are not considered to represent schizophrenia. Individuals who had received either of these codes, however, were not excluded until their charts were reviewed to verify the coded diagnosis. Thus, with the above criteria, the sampling frame at this hospital consisted of 233 patients.

Each patient was assigned a number from 0 to 232 in ascending order by casebook number. A random number table was used to obtain a random sample of 115 adult patients. The selected
charts were retrieved by personnel in the clinical records department. Of these, a total of 89 patients were excluded as a review of their charts indicated that they were born outside of Canada or the U.S., 60 years of age and older, adopted at greater than 1 year of age, deceased, and/or did not meet the diagnosis for adult schizophrenia (e.g. given a diagnosis of schizoaffective disorder, diagnosis was unclear, etc.). Thus, the final sample consisted of 26 subjects meeting the inclusion criteria for the study.

The Hospital for Sick Children (HSC)

The Psychosis Clinic at the Hospital for Sick Children became defunct in the later part of 1998, but all data collection from this site was completed prior to this. The clinic provided psychiatric assessments as well as short-term inpatient and outpatient services for those under the age of 18. This site served children living in the Toronto area, as well as those from other parts of Ontario.

The study proposal was submitted to the Director of the Psychosis Clinic for review in January 1998. Permission only to review the charts in the Psychosis Clinic was obtained in February 1998. The contacting of subjects upon their identification from the charts required an application for approval to the HSC Research Ethics Board. The protocol was submitted in May 1998 and given final scientific and ethical approval in September 1998.

Information from the records of patients in the Adolescent Psychosis Unit was not systematically stored in a database, so it was not possible to have a list generated of patients with a diagnosis of schizophrenia. The director and nurse clinician in this unit came up with a list of patients 15 years of age and under who were seen at the clinic between 1988 and 1998, and who they felt could be cases of schizophrenia based on their assessments. As well, the principal investigator was allowed
to search through all closed files for potential cases. A total of 23 patient charts were reviewed. 12 of these patients were excluded as they did not meet the diagnosis for schizophrenia, had an onset of schizophrenia greater than 15 years of age, or were born outside Canada or the U.S. The final sample from this hospital consisted of 11 patients.

**Youthdale Treatment Centres (Youthdale)**

The Acute Support Unit of Youthdale Treatment Centres is a 10-bed emergency inpatient facility for the short-term treatment of youths under the age of 16 who are experiencing psychiatric crises. It is the only facility of its kind in all of Ontario.

A request was made in April 1998 to the Director of Psychiatric Crisis Services to access patient chart records from Youthdale. Since no formal ethical review process exists at this facility, the provision of a letter of ethical approval for the study received from another institution was sufficient. Permission to access chart records as well as to contact subjects identified from these records was obtained in May 1998.

Since the database at this facility did not include information regarding patient diagnoses, it was not possible to have a patient list drawn up according to diagnosis. Thus, in order to locate cases of schizophrenia, a manual search through all charts of patients admitted to this facility between 1988 and 1998 would be required. However, because schizophrenia in childhood is extremely rare, the low yield that would have resulted from such an extensive search did not justify the time and effort involved.

An alternative to the above procedure, although less systematic, was suggested. Psychiatrists at this facility were asked to come up with a list of patients they recalled seeing within the last two
or three years at this facility (1995 to 1998) who were 15 years of age and under with a possible diagnosis of schizophrenia. The total number of patients resulting from this list was 7. The charts of these patients were reviewed and 3 cases were excluded as they did not meet a diagnosis for schizophrenia. Thus, a total of 4 cases were located from this facility.

**Sunnybrook Health Science Centre (Sunnybrook)**

The Division of Youth Psychiatry at Sunnybrook Health Science Centre provides psychiatric inpatient services and outpatient programs to those between the ages of 14 and 20. This site is a teaching hospital affiliated with the University of Toronto. While services are primarily provided to those in the Toronto area, there are also regional services for anyone in Ontario.

The protocol was submitted for ethical review in January 1998 and approval was granted by the Vice President of Medical Affairs in June 1998. This approval permitted patient charts to be reviewed and subjects identified from the charts to be contacted.

A patient list was compiled from a computerized database by personnel in Health Data Resources. The list consisted of inpatients 15 years of age and under who were admitted between January 1, 1990 and March 31, 1998 and given a discharge diagnosis code of any 295.x (schizophrenic psychoses) or 299.9 (childhood type schizophrenia) as denoted by the ICD-9-CM coding system. A manual search was done for charts of patients admitted between January 1, 1988 and December 31, 1989 as these had not been entered into the database. A total of 22 patients resulted from the list and manual search (18 with code of 295.x & 4 with code of 299.9).

The charts of all 22 patients were retrieved by health records staff and reviewed by the principal investigator. A total of 12 patients were excluded from the sample as they did not meet
the criteria for schizophrenia, were born outside Canada or the U.S., and/or were adopted at greater than 1 year of age. The final sample from this hospital consisted of 10 cases of childhood-onset schizophrenia.

**Clarke Institute of Psychiatry (Clarke)**

The Clarke Institute of Psychiatry, which teamed with the Centre for Addiction and Mental Health in early 1998, is a psychiatric research institute and teaching hospital that is fully affiliated with the University of Toronto. There are established inpatient and outpatient programs for adults with schizophrenia. The Clarke-Metfors division is a medium secure inpatient and outpatient unit for those whose illness involves them in a legal situation. There are also outpatient clinics serving children. The Clarke mainly serves people in Toronto as well as other parts of Ontario.

The study proposal was submitted for ethical review in January 1998 and was granted approval by the Clarke Institute of Psychiatry Human Subjects Review Committee in April 1998. This approval allowed for the accessing of patient chart records as well as the contacting of subjects subsequent to their identification through the charts.

A computerized patient list was drawn up by personnel in the Medical Records Department. This list consisted of inpatients 18 years of age and over, admitted between January 1, 1993 and December 31, 1996 with a primary discharge diagnosis code of any 295.x, as designated by the ICD-9-CM system. The age on admission of patients were included on this list, so 51 patients were excluded as they were 60 years of age and older. The final sampling frame at this hospital consisted of 1012 patients.

The remaining patients were assigned a number from 0 to 1011 in ascending order by medical
records number. A random number table was used to select a random sample of 121 adult controls. Patient charts were pulled by personnel in the medical records department and a chart review was carried out. 25% (30/121) of patient charts were located at the METFORS department and were obtained and reviewed there. A total of 83 patients were excluded from the sample as a review of their charts showed that they were born outside of Canada or the U.S., adopted at greater than 1 year of age, deceased, or did not meet the diagnosis for adult-onset schizophrenia. Thus, the final sample from Clarke consisted of 38 adult controls who met the inclusion criteria for the study. 9 of these controls were ascertained from METFORS.

Patients under 18 years of age assessed at the Clarke can only be admitted as outpatients. Since ICD-9 codes are not entered into the medical records database for outpatients, a search for patients 15 years of age and under who meet the ICD-9 codes for schizophrenia would not yield any results. Thus, it was originally intended that this facility not be used to ascertain patients with childhood-onset schizophrenia. During the course of data collection, however, one case of childhood-onset schizophrenia seen at the Clarke was found through another means. This case happened to be the child of a subject from the adult-onset group who had heard about the study and volunteered to participate. Although this is not a systematic way of obtaining cases, it was felt that it was necessary to include this case for the purposes of this study.

**Whitby Mental Health Centre (Whitby)**

The Adolescents and Young Adults Program at Whitby Mental Health Centre provides inpatient and outpatient psychiatric programs as well as long-term rehabilitative services. The catchment area served is the Borough of East York, the cities of Scarborough and North York (east
of Yonge St.), the Regional Municipalities of York and Durham, and Victoria County.

The research proposal was submitted for review by the Director of Professional Affairs in January 1998. Approval to use Whitby as a study site was granted in March 1998, provided some modifications were made to the original protocol. First, the initial access to patient records would be limited to the identification of appropriate cases and controls as defined in the protocol, and any further chart review would require patient consent. Secondly, prior to contacting patients to request consent to participate in the study, the appropriate clinical team would be notified to ensure that there were no contraindications to such a contact.

Two lists from a computerized database were drawn up of patients who had been discharged from Whitby with a primary diagnosis code equal to any 295.x. The coding system for clinical records used at this hospital has been DSM-IV since 1996, and DSM-III prior to that. All disorders listed under the code 295 represent schizophrenia except schizophreniform disorder (295.4) and schizoaffective disorder (295.7). The first list consisted of 58 inpatients, admitted between January 1, 1988 and March 31, 1998, who were under 18 years of age on admission and born within North America. From this group, a total of 29 patients 15 years of age and under were identified and all were included in the case sample. The second list comprised 362 inpatients, admitted between January 1, 1993 and December 31, 1996, who were 18 years of age and over on admission and born within North America. Of these 362, 30 patients were excluded as they were 60 years of age or over as of January 1, 1998. The remaining 332 patients were assigned a number from 0 to 331 in ascending order by casebook number. A random number table was used to select a random sample of 48 adult controls.

The selected casebook numbers of the case and control samples were sent to the director of
clinical records so that information on patients' addresses and clinicians could be retrieved from their charts. For patients who were being followed by a clinician, a letter was mailed out to their clinicians requesting permission to contact patients about the study (see Appendix B). Only until after consent was given by the patient's clinician was an introductory letter (Appendix C) and consent form (Appendix D or E) mailed to the patient. For patients who no longer had active contact with the facility (i.e. were not being followed by a clinician), the introductory letter and consent form was mailed directly to them. All letters were written and sent out on behalf of the principal investigator by authorized personnel at Whitby Mental Health Centre.

Information from chart records could be examined only when a signed consent form was returned by the patient. Thus, for patients who did not respond to the mailed letter, a follow-up telephone call by the principal investigator could not be made as this would require the disclosure of personal information (i.e. telephone number) from their charts. For the same reasons, letters that were undeliverable and returned could not be resent to another address that may have been available in the charts.

A misunderstanding that occurred on the part of the clinical records staff concerning the use of the study consent form was acknowledged at the outset of reviewing patient charts. Although this consent form was intended to obtain the patient's permission to access both the psychiatric charts and birth records, it was originally approved by Whitby with the assumption that it would give permission to only access patient birth records from the general hospitals, but not to review patient psychiatric charts at Whitby. In order to perform the latter, this particular hospital required that a Form 14 be signed and returned by the patient. Thus, for patients who signed and returned their consent forms, a Form 14 had to be mailed to them. If the Form 14 was not returned, the
principal investigator could only attempt to access the patient's birth records, but could not examine the patient's psychiatric charts.

Upon examination of the chart records of patients who had given consent, patients were excluded from the samples if the diagnosis of schizophrenia was not made or was unclear, the onset of schizophrenia was clearly at greater than 15 years of age (for the case sample) or less than 18 years of age (for the control sample), they were born outside of Canada or the U.S., adopted at greater than 1 year of age, or were deceased. Since letters were mailed out before a chart review was done which would have confirmed the diagnosis, patients who did not meet the criteria for schizophrenia may have also been asked to participate in the study. Patients who consented to participate but on subsequent examination of their charts did not have a verified diagnosis of schizophrenia were excluded. Only 9 patients from Whitby consented to participate in the study and 3 were excluded (2 potential cases and 1 potential control) as they did not meet the criteria for schizophrenia. The final sample from Whitby consisted of 6 controls, and 0 cases.

In discussing the procedures involved in ascertaining subjects from the various sites, it is also important to take into account the potential for duplication of subjects across the different sites. For the present study, it was found that duplication occurred across two different sites for only one of the case subjects and one of the control subjects. In such instances, these subjects were counted only once as being ascertained from the site in which the most recent diagnosis of schizophrenia was given. It is also of note that one potential case subject for which duplication occurred across three of the sites was given a diagnosis of schizophrenia at the first two sites where he was assessed, but evidence was later obtained from the most recent third site to show that he did not meet the diagnosis of schizophrenia. Thus, although previously given a diagnosis of
schizophrenia at the other two sites, this patient was not included in the child case group. This reflects the importance of follow-up of children who are given a diagnosis of schizophrenia.

In summary, the total number of subjects ascertained from all sites was 96. This consisted of 26 cases and 70 controls. Table IV-3 provides an outline of the subject ascertainment procedures for the various sites, and Figures IV-1 to IV-7 show the sample selection procedures for all sites.

Table IV-3. Characteristics of Subject Ascertainment Procedures Across Various Sites

<table>
<thead>
<tr>
<th>Site</th>
<th>Ethical Review Guidelines</th>
<th>Method of Selecting Patient Sample</th>
<th>Coding System Used</th>
<th>Type of Patients Ascertained</th>
</tr>
</thead>
<tbody>
<tr>
<td>Queen St.</td>
<td>- Approval for both chart review and contacting of subjects</td>
<td>Random sample from computer-generated patient list</td>
<td>ICD-9</td>
<td>Inpatients</td>
</tr>
<tr>
<td>Clarke</td>
<td>- Approval for both chart review and contacting of subjects</td>
<td>Random sample from computer-generated patient list &amp; patient volunteer</td>
<td>ICD-9-CM</td>
<td>Inpatients &amp; Outpatients</td>
</tr>
<tr>
<td>Whitby</td>
<td>- Approval for chart review if patient consent obtained</td>
<td>Random sample from computer-generated patient list</td>
<td>DSM-III &amp; DSM-IV</td>
<td>Inpatients</td>
</tr>
<tr>
<td>HSC</td>
<td>- Not required for chart review</td>
<td>All from patient list generated by recall of clinicians and manual search</td>
<td>None</td>
<td>Inpatients &amp; Outpatients</td>
</tr>
<tr>
<td>Youthdale</td>
<td>- Not required</td>
<td>All from patient list generated by recall of clinicians</td>
<td>None</td>
<td>Inpatients</td>
</tr>
<tr>
<td>Sunnybrook</td>
<td>- Approval for both chart review and contacting of subjects</td>
<td>All from computer-generated patient list and manual search</td>
<td>ICD-9-CM</td>
<td>Inpatients</td>
</tr>
</tbody>
</table>
Figure IV-1. Subject Selection Procedures - Queen St. Mental Health Centre

233 (sampling frame)
- all 295.x (ICD-9)
- admitted 1993 to 1996
- ≥18 years of age

random sample of 115

89 (excluded)
- not a dx. of schizophrenia
- onset <18 years of age
- ≥60 years of age
- born outside Canada/US
- adopted at >1 year of age
- deceased

26 (sample)
- meets study inclusion criteria

Figure IV-2. Subject Selection Procedures - Clarke Institute of Psychiatry

1063 (sampling frame 1)
- all 295.x (ICD-9-CM)
- admitted 1993 to 1996
- ≥18 years of age

1012 (sampling frame 2)
- all 295.x (ICD-9-CM)
- admitted 1993 to 1996
- between 18 & 60 years of age

random sample of 121

51 (excluded)
- ≥60 years of age

83 (excluded)
- not a dx. of schizophrenia
- onset <18 years of age
- born outside Canada/US
- adopted at >1 year of age
- deceased

38 (sample)
- meets study inclusion criteria
Figure IV-3. Subject Selection Procedures for Controls
Whitby Mental Health Centre

362 (sampling frame 1)
- all 295.x (ICD-9)
- admitted 1993 to 1996
- ≥18 years of age
- born in North America

332 (sampling frame 2)
- all 295.x (ICD-9)
- admitted 1993 to 1996
- between 18 & 59 years of age
- born in North America
- random sample of 48
- request for consent

30 (excluded)
- ≥60 years of age

41 (consent not given)

1 (excluded)
- not a dx. of schizophrenia

6 (sample)
- meets study inclusion criteria
Figure IV-4. Subject Selection Procedures for Cases Whitby Mental Health Centre

58 (sampling frame 1)
- all 295.x (ICD-9)
- admitted 1988 to 1998
- <18 years of age
- born in North America

29 (excluded)
- >15 years of age

29 (sampling frame 2)
- all 295.x (ICD-9)
- admitted 1988 to 1998
- ≤15 years of age
- born in North America

- request for consent

27 (consent not given)

2 (excluded)
- not a dx. of schizophrenia

0 (sample)
- meets study inclusion criteria
Figure IV-5. Subject Selection Procedures - Hospital for Sick Children

16 (sampling frame)
- list of possible schizophrenia
- admitted 1988 to 1998
- ≤15 years of age
- born in Canada/US

5 (excluded)
- not a dx. of schizophrenia

11 (sample)
- meets study inclusion criteria

Figure IV-6. Subject Selection Procedures - Youthdale Treatment Centres

7 (sampling frame)
- list of possible schizophrenia
- admitted 1995 to 1998
- ≤15 years of age

3 (excluded)
- not a dx. of schizophrenia

4 (sample)
- meets study inclusion criteria
Figure IV-7. Subject Selection Procedures - Sunnybrook Health Science Centre

22 (sampling frame)
- all 295.x & 299.9 (ICD-9-CM)
- admitted 1988 to 1998
- ≤15 years of age

12 (excluded)
- not a dx. of schizophrenia
- born outside Canada/US
- adopted at >1 year of age

10 (sample)
- meets study inclusion criteria
4.5 Data Collection

The collection of required data from the review of psychiatric charts at all sites commenced in February 1998 and was completed in April 1999.

4.5.1 Data Collection Form

The research instrument used in this study was a form developed to abstract relevant data from the psychiatric charts and birth records for cases and controls (see Appendix I). Information was recorded onto a separate form for each subject. An identification number was assigned to each subject in order to ensure confidentiality of the abstracted patient information, and was recorded onto a separate form along with the subject's name.

Subject Identifying Information

The subject identifying information included data abstracted from the psychiatric chart such as sex, date of birth, and health card number. This information was used to check for possible duplication of selected patients among the various sites. Information from the chart regarding the most current address and telephone number of the subject and his/her next-of-kin was abstracted for the purpose of contacting the subject.

Subject Demographic Information

The section of the form regarding subject demographic information included the subject's place of birth, ethnic background, variables pertaining to socioeconomic status (see below), as well as maternal age and maternal parity. This information was extracted from the psychiatric charts in order to characterize the subject sample and to take into account potential confounding variables.
for the relationship between OCs and schizophrenia. Data on whether the subject was adopted were also included as this was relevant to the inclusion criteria of the study, as well as to the accessing of subject birth records.

A number of indicators for socioeconomic status (SES) were abstracted in order to measure the SES of the subject. Data on the subject’s current SES, which were recorded only for the adult controls, included the subject’s highest level of education, occupation, and source of income. This could only be relevantly applied to the measurement of SES in the adult controls since subjects in the child group were assigned the SES characteristics of their parents. Since these indicators were intended to reflect the SES of the subject before the onset of schizophrenia, the subject’s occupational and income data were considered that which occurred before the subject’s first psychiatric admission for schizophrenia. If these data were unclear or not available in the chart, then the subject’s occupational/income status at the time of the earliest admission for schizophrenia reported in the chart was recorded. The SES data collected also included the parents’ highest levels of education and occupations. These indicators were taken to measure the subject’s SES of origin. For the child cases, this was also considered to be their current SES.

Within this study, SES of origin was considered more suitable than current SES as a proxy measure for subject SES. In terms of controlling for potential confounding in the comparative study, the use of current SES for both subject groups could lead to inconsistency in matching due to the fact that many adult schizophrenics, who may have originated from higher social class families, tend to migrate into lower social classes as a consequence of their illness. Thus, in using SES of origin for both the adult and child groups, it would minimize the possibility that different concepts of subject SES are being measured among them. Another reason for using SES of origin
is that the content of the parental SES data would likely be less ambiguous than that of the
subject's own SES information. The occupational history of schizophrenic patients would be
difficult to evaluate as it may be short-lived, sporadic, and for many, may involve periods of
unemployment. Added to this would be the speculation as to whether such occupational
circumstances may be results of, rather than antecedents to the schizophrenic process.

Finally, SES of origin is a preferable proxy for subject SES because it is more temporally
related to the presumed exposures (i.e. OCs) and causal pathways of this study. Since current
hypotheses suggest that brain abnormalities linked to schizophrenia are neurodevelopmental in
origin, parental SES, particularly at the time of birth, would appear to have more influence than
the subject's current SES on the causal pathway to schizophrenia. Thus, while data on SES of
origin were considered important with respect to potential confounding, data on the subject's own
education and occupation/source of income were relevant for descriptive purposes only.

The socioeconomic index used for the above information was based on 1981 Census data for
the total Canadian labour force (Blishen et al., 1987). The index provided SES scores for 514
occupation categories based on a composite measure of the prevailing income and education levels
in each occupation. Although only data on occupational titles were required to obtain SES scores
from this composite index, information regarding the level of education for both parents was
extracted so that the separate, possibly differential effect of education level (without occupational
income) could still be examined.
**Diagnostic Information**

Information concerning the patient's history of psychiatric admissions and diagnoses was abstracted from the psychiatric charts in order to confirm that a diagnosis of schizophrenia (as outlined in section 4.5.3 below), was met by the patient. The clinical symptoms experienced by the patient, as described in the charts, were also recorded for the purposes of further confirming that the patient did meet the criteria for schizophrenia.

**Obstetrical History**

Details on the OC information available from the subject's psychiatric charts and/or hospital birth records were extracted verbatim. The way and the extent in which the OC information was elicited by these two sources was examined. The availability of general obstetrical information such as duration of labour, gestational age, and birth weight was also assessed. Available OC data were appropriately recorded under pregnancy, labor and/or delivery, or neonatal complications according to the McNeil-Sjostrom OC Scale. This scale provides an alphabetical index of several hundred specific OCs/conditions with the corresponding page location(s) for these specific OCs in the 'Scoring System' section of the scale. In the 'Scoring System' section, each OC/condition belonging to a gestational period is categorized and weighted according to one of six severity levels. The OCs/conditions abstracted from the psychiatric charts and/or hospital birth records were each given a severity score according to the McNeil-Sjostrom OC Scale.

**4.5.2 Missing Information**

The patient's chart may not have contained all the information required on the data collection form. The following is a list of definitions to describe the nature of the data that could not be
obtained from the chart:

a) *No Response.* This applied when there was evidence in the chart showing that the information had been requested but was not given (e.g. a form or question which had asked for these data had not been filled out or answered). On the data collection form, this was denoted as 'NR'.

b) *Unclear.* This applied when there was evidence in the chart that the information had been requested, but the responder did not know the answer (e.g. on a form or for an interview the answer provided was "I don't know"). On the data collection form, this was indicated as 'DK'.

c) *Not Available.* This applied when the information was not in the charts and there was no evidence that it had been requested. On the data collection form, this was denoted as 'NA'.

It should be noted that although information regarding a patient's place of birth and whether he/she was adopted was part of the inclusion criteria for the study, if this information was not available from the charts, the patient was still included in the study. Only if it was explicitly stated or suggested that the patient was born outside of Canada or the U.S., or that the patient was adopted at greater than 1 year of age would he/she be excluded from the study.

All information pertaining to the obstetrical history of the patient was recorded. The fact that it was reported in the chart that the obstetrical history of the patient was unremarkable or that the reporter of the information did not know anything about the obstetrical history when asked was also relevant.
4.5.3 Confirmation of Diagnosis

As described in section 4.4, the patient lists compiled by the various hospitals, after having minor exclusions made from some of them, were considered to be sampling frames for each hospital. For hospitals which drew up these lists using a diagnostic coding system, the code used to identify patients with a diagnosis of schizophrenia (i.e. 295.x) would have also included other psychotic disorders, such as schizophreniform disorder and schizoaffective disorder. Similarly, for the two hospitals which did not use diagnostic coding systems, but compiled lists of potential cases of childhood-onset schizophrenia based on clinicians' recollections, there was the likelihood that these lists in fact included patients suffering from other childhood psychoses.

Even with the awareness that there were patients included on these lists who had not necessarily been diagnosed with schizophrenia, it was from these lists which subjects were sampled and their charts reviewed. For hospitals that compiled a computerized patient list, patients who may have been diagnosed with other psychotic disorders were not automatically excluded from the chart review in order to take into account the possibility of errors in diagnostic coding. For hospitals that did not have a systematic diagnostic database, a review of the diagnostic chart information was done for all patients on the list as there was the likelihood of error in the recall of the clinicians who compiled the lists. Thus, it was only from the diagnostic information in the patient's charts that a patient's diagnosis of schizophrenia could be confirmed and that exclusion of patients not meeting a confirmed diagnosis of schizophrenia be made.
Diagnosis of Adult-onset Schizophrenia

Subjects in the adult group may have been given a diagnosis of schizophrenia at some point during the history of their psychiatric admissions, but if they were not given a diagnosis of schizophrenia for their most recent hospital admission, they were excluded from the sample. For those who did have a final diagnosis of schizophrenia from the most recent hospital admission, the mere presence of a diagnosis of schizophrenia in the chart records was not sufficient to verify that a patient did meet the criteria for schizophrenia. To further confirm the diagnosis of schizophrenia, the description of symptoms in the patient's chart must have provided evidence that the patient had manifested the necessary symptoms for schizophrenia as outlined in DSM-IV.

Although the subjects in this study had to be admitted to the chosen hospitals within a specified time frame, they did not have to be incident diagnosed with schizophrenia at these hospitals during this time period. In ascertaining adult controls, it was necessary to establish the patient's age of onset or incident diagnosis of schizophrenia so as to reduce the possibility of including the patient in the adult-onset sample when he/she actually had an onset of schizophrenia under the age of 18. Since the actual time of onset of schizophrenia is quite difficult to determine, the time of the patient's first psychiatric admission with a diagnosis of schizophrenia was used as an approximation, from which the age of onset of schizophrenia was estimated.

The information used to determine the time of first admission with a diagnosis of schizophrenia could be described by different categories: a) 'Explicitly stated (incidence diagnosis)', b) 'Explicitly stated (not incidence diagnosis)', c) 'Not explicitly stated', d) 'Estimated', and e) 'Not Available'. If it was explicitly stated in the chart that the current admission had been the patient's first psychiatric admission and a diagnosis of schizophrenia had been given (a), then the patient's
age on admission was taken as the age of onset of schizophrenia. If the information in the chart indicated that the patient had had previous psychiatric admissions and the first psychiatric admission was made explicit (b), the earliest admission in which a diagnosis of schizophrenia was given was used as the time of onset of schizophrenia. Similarly, if it was clearly stated that the first psychiatric admission had resulted in a diagnosis of schizophrenia (b), this was considered the time of onset of schizophrenia.

There were instances in which the determination of the patient's time of first admission with a diagnosis of schizophrenia was met with ambiguity. The information in the chart may have described the patient's previous psychiatric admissions, but there was no clear date of the patient's first psychiatric admission and/or it was not apparent whether the patient had been previously diagnosed with schizophrenia (c). In such cases, if the earliest psychiatric admission that was recorded in the chart coincided with the patient being less than 18 years of age, or if the chart made any indication that the patient's illness dated back to when he/she was a child, the subject was automatically excluded from the adult sample. For the remaining, only an approximation to the first admission with a diagnosis of schizophrenia could be made. This was taken as the earliest admission available in which a diagnosis of schizophrenia was given.

There were also some cases in which the time of first admission and thus the age of onset were even more difficult to estimate. Such were patients who may have endured a lengthy history of treatment for psychiatric illness, but information pertaining to their psychiatric histories was rather scarce. If there was information in the chart providing any indication of the length of time the patient had been suffering from schizophrenia (i.e. "dates back 20 years") (d), then this was used to estimate the patient's time of onset of schizophrenia. If there was no such indication of the
length of the patient's illness (e), then a time of onset of schizophrenia could not be estimated.

**Diagnosis of Childhood-onset Schizophrenia**

It is often the case that children who may meet the diagnostic criteria for schizophrenia are not given a definite diagnosis of schizophrenia due to a need for follow-up, in which case a variety of differential diagnoses are assigned to them. This caution taken in assigning a definite diagnosis, combined with the rarity of childhood-onset schizophrenia, would make it difficult to locate a sufficient number of actual cases. Thus, the requirements for confirming a diagnosis for subjects in the childhood-onset schizophrenia group were less restrictive than those pertaining to the adult-onset schizophrenia group.

Subjects included in the childhood-onset schizophrenia group were divided into two subgroups: those having a 'definite' diagnosis of schizophrenia and those having a 'possible' diagnosis of schizophrenia. Subjects were classified as having a 'definite' diagnosis of schizophrenia when the chart indicated a most recent primary diagnosis of schizophrenia made by a physician, and symptoms that were recorded in the chart supported the diagnosis of schizophrenia. For cases to be considered as having a 'possible' diagnosis of schizophrenia, the one of the following three conditions could apply:

1) a most recent primary diagnosis of schizophrenia was not made by a physician, but a most recent differential diagnosis of schizophrenia and/or previous primary or differential diagnoses of schizophrenia were given, and symptoms recorded in the chart provided evidence to support the criteria for schizophrenia;

2) a most recent primary diagnosis of schizophrenia was given by a physician, but the symptoms
recorded in the chart did not provide adequate support for a diagnosis of schizophrenia;

3) a most recent primary diagnosis of schizophrenia was not made by a physician and recorded symptoms did not support the diagnosis of schizophrenia, but there were two or more previous diagnoses of schizophrenia by at least two different physicians.

Patients were excluded from the case sample if none of the above conditions of diagnosis were met. In the event that there was a duplication of cases among different hospitals, and there was discrepancy in meeting the above diagnostic requirements (i.e. a confirmed diagnosis of schizophrenia was obtained from the diagnostic information provided by one hospital but not from that of another hospital), the subject was included in the sample with a 'possible' diagnosis of schizophrenia unless there was documented evidence to suggest that the diagnosis of schizophrenia was unwarranted. Thus, out of the total 26 cases ascertained, the number of 'definite' cases was determined to be 12, while the number of 'possible' cases was found to be 14.

Similar to the adult control group, it was necessary to try and determine the age of onset of schizophrenia for subjects in the child group to ensure that it meets the criteria of 15 years of age and under. Also, although it was required that the cases have a psychiatric admission with the diagnosis of schizophrenia (as defined above) during the chosen time criteria (i.e. 1988-1998), it was not necessary that the cases be given an incidence diagnosis of schizophrenia within this period. Thus, the same categories of information used to describe the time of first admission with a diagnosis of schizophrenia for the adult group was also used for the child group.
4.6 Subject Recruitment

A request was made to subjects who were identified from the chart review to access their birth records. This was done for subjects selected from all hospitals except Whitby. Subjects were mailed an explanatory letter which was placed on letterhead according to the institution from which the subject was identified (see Appendix C). Enclosed was a consent form outlining the study (see Appendix D & E). For the HSC, it was required that the consent and assent forms follow the hospital's template (see Appendices F to H).

The addresses found in the patient charts are not often reliable and up-to-date, so attempts were made to confirm or obtain more accurate mailing addresses before sending out letters. The addresses of the patient as well as the next-of-kin (if either were available) were first confirmed by checking if there was a match for it in the Canada 411 White Pages. If there was a match for either the patient's address or next-of-kin's address, the letter was mailed to that address. If there was no address available or no match, the patient's attending/follow-up physician, caseworker, and/or any other type of community worker involved in the patient's care was contacted to confirm or obtain the correct mailing address. Information on such sources was obtained from the patient's chart. In some cases, a number of intermediate contacts were made in locating the patient. If one of these sources was found to be currently following the patient, the letter was mailed either to the patient's current address, or care of the person involved with the patient's care. If the address was still not confirmed by these sources, the patient's next-of-kin was contacted. The letter was then sent to the patient's current address as disclosed by the next-of-kin, or care of the next-of-kin's confirmed address. If all of the above sources failed to confirm the patient's mailing address, the
letter would be sent to the unconfirmed address listed for the patient or his/her next-of-kin, or a letter would not be sent if there was no address available. Due to the nature of the illness, no contact was made directly with patients before sending out the letters.

4.7 Subject Follow-up

Follow-up of subjects began on December 1, 1998 and ended on March 15, 1999. Subjects who responded were considered to be those who returned a signed consent form, while subjects who did not respond were considered as those who did not return a signed consent form. This latter group of subjects included: a) those who refused participation or had someone else refuse on their behalf when contacted at follow-up; b) those who did not receive the study information as they were either not mailed a letter due to the lack of a contact address, or their letters were returned undeliverable due to an incorrect/incomplete address; and c) those who did not return a signed consent form for unknown reasons, as they were not reachable at follow-up.

If there was no response from the subject within 2 weeks of mailing the letter, a follow-up phone call was made to the person to whom the letter was sent (i.e. subject, next-of-kin, physician, etc.). This was carried out for subjects from all sites except Whitby. If it was communicated by the subject or another informant that the subject did not want to give permission to access his/her birth records, this was considered to be a refusal. If on the first phone call, the subject conveyed that he/she was interested in participating, but the consent form was still not returned 2 weeks later, the subject was called again. If the consent form was still not returned by the follow-up end date, this was considered a non-response under category c) above and denoted
as 'Not Returned'. In cases where subjects had lost or misplaced the letter, the letter was resent and a follow-up phone call was again made if there was no response within 2 weeks.

In cases where the letter was returned undeliverable, it was resent if another address was available. If the letter was returned once again, this was considered a non-response due to not having received the letter (category b) above) and denoted as 'Undeliverable'. In the event that there was no telephone number available for the address, the number was wrong or not in service, and there was no other contact available, a follow-up phone call could not be made. If there was nothing returned by the follow-up end date, this was considered to be a non-response denoted as 'Not Returned'. This also applied to all subjects from Whitby who did not return a signed consent form since follow-up could not be carried out for such subjects.

For subjects who returned a signed consent form, a request was made to the appropriate birth hospital to access their birth records (see Appendix J). The ascertainment of patient birth records began on January 5, 1999 and ended on June 20, 1999. If further information was required from the birth hospitals in order to locate the subject's birth records (e.g. mother's name and date of birth), the subject was contacted to request this information.

4.8 Definitions of Useful Data for Comparative Study

The term 'useful data' was considered to represent a number of different conditions in which certain information from psychiatric charts and/or birth records was essential to carry out the comparative study. The different conditions of having 'useful data' required that OC information was available from one of the following sources: a) both psychiatric charts and birth records; b)
either psychiatric charts or birth records, or both; c) psychiatric charts only; or d) birth records only. This OC information included any specific OC data (e.g. birthweight), as well as general OC data (e.g. statements that "labour/delivery was normal" or that "no OCs were experienced").

In addition to OC information, data from the psychiatric charts on a number of variables listed on the data collection form were considered to be essential in order to carry out the comparative study. The required variables were: i) sex; ii) date of birth; iii) either subject address or next-of-kin/correspondent's address; iv) either place of birth (this could be indicated by a city, province, or country) or birth hospital; v) ethnicity; vi) either occupation of mother or occupation of father; vii) date of onset; and viii) date of study diagnosis of schizophrenia. Thus, the numbers of subjects having all of these required variables plus OC information (for any of the different OC source categories) was examined. Also, to assess the effect of using slightly less stringent data requirements, the numbers of subjects having OC information and all but either one or two of the required variables was examined. The one or two missing variables could only be those of a demographic nature (i.e. place of birth, ethnicity, and occupation of mother or father).

4.9 Ethical Considerations

Since hospital records are considered private, the review of psychiatric charts for the purposes of identifying and abstracting relevant information for eligible study subjects required appropriate institutional consent. Ideally, all potential subjects should have also been given the choice of whether or not to participate in the study, and are entitled to any information which might have influenced their decision. However, it must be pointed out that obtaining the consent of all
potential subjects would have been difficult if not impossible, particularly for the child cases whose records were accessed retrospectively over the past ten years. Therefore, since consulting patient records did not involve contact with the potential subjects and did not present any significant risk or discomfort to them, it had been proposed that consent of the appropriate institutions was adequate. The accessing of subject birth records, however, required both the consent of the subjects and institutions involved. All sites approved of this with the exception of Whitby which maintained that for the purposes of confidentiality, patient consent was required prior to the disclosure of any information in the charts to the principal investigator.

In this study, there are two types of individuals who may be incapable of determining their own participation. These are children under the age of 16, and individuals suffering from a mental illness. In such cases, proxy consent of a parent or guardian, spouse, or other next-of-kin must be obtained. Since consent from subjects must not only be informed but also freely given, subjects who are incapable of exercising free choice, should not, in principle, be employed in a study. The proposed study, however, would be impossible to carry out without using information obtained from such individuals. As there was no significant risk or discomfort to the subjects, and any potential risk or discomfort would be outweighed by the benefit provided to schizophrenia research, the use of such subjects was justified.

It is important that consent of the subject be sought to the fullest degree possible. A subject who is not capable of consenting may be capable of refusing, and the subject's refusal to participate may supercede proxy consent. Thus, for the child with schizophrenia whose ability to act autonomously is hampered by both age and mental illness, the consent of the child, in addition to the parent or other proxy was sought. Every effort should have been made to ensure the child's
understanding of what procedures were involved in the study. Similarly, for the adult with schizophrenia, whose autonomy is affected by mental illness, the informed consent of the adult subject was sought with or without the additional consent of the parent/guardian, spouse, or other proxy.

Another ethical issue involves the letter and consent forms that were sent out to potential subjects requesting permission to access their charts and/or birth records. As shown in Appendices C to H, all references to the nature of the psychiatric disorder were omitted, including the title of the study, and the fact that the patient was asked to participate because he/she had been given a diagnosis of schizophrenia. This was done to take into account the sensitive nature of the illness, and the possibility that many patients and their families may not recall that the diagnosis of schizophrenia had been given, or that the diagnosis of schizophrenia shown in the chart had not been communicated to them. Thus, instead of making reference to the fact that the study involved individuals with schizophrenia, the letter and consent forms made reference to those with 'mental health or behavioural problems'. This omission of the fact that specifically individuals with schizophrenia were being studied might be considered as being deceptive to the study subjects. However, considering the potential for distressing patients and their families by referring to a diagnosis of schizophrenia, the use of the phrase 'mental health or behavioural problems', which does encompass schizophrenia, seems justified.

Finally, in order to ensure that confidentiality was maintained during conduct of the research, the data gathered was kept secure from theft, unauthorized reading, and copying. This entailed storing the collected data in a safe place, as well as minimum disclosure of the data to others involved with the study. The confidentiality of subjects was also ensured by omitting names and
any other identification from the data abstraction form, and identifying the data by subject identification numbers. The anonymity of the subjects was also preserved in the reporting of findings by combining results to make totals, and by avoiding personal identification of subjects.

4.10 Data Analysis

Due to the objectives and exploratory nature of the present study, statistical analysis of the data was carried out to a limited extent. $\chi^2$ tests were conducted to compare cases and controls on demographic characteristics for the initial analysis, as well as to compare response rates for cases and controls. A 95% C.I. was calculated for the proportion of controls found to have useful data. To compare the missing data rates among cases and controls, a two-tailed $t$-test was employed. A further comparison of missing data rates among the six sites was carried out using a one-way ANOVA.
V. RESULTS

5.1 Subject Demographic Characteristics

The initial data analysis compared the two subject groups on a number of demographic variables. Table V-1 shows the distribution among cases and controls of the variables sex, ethnicity, and SES. With respect to sex, the proportion of males to females appeared to be higher for controls compared to cases (3:1 vs. 1:1, respectively), but this difference did not reach significance. Further examination of sex by site showed that a higher proportion of males to females was found at Queen St., Clarke, Youthdale, and Sunnybrook (data not shown). Subjects from HSC, however, tended to be female compared to male (2:1), while those at Whitby had an equal sex distribution.

Figure V-1 shows the distributions of all five ethnicity categories among cases and controls with this information. The controls were largely concentrated in the 'White' category (95%), while the distribution of cases was more evenly spread among the ethnic groups, with the highest proportions of cases being white (41%) and black (36%). In particular, it can be seen that none of the controls were black. In determining whether there was any association between subject status and ethnicity, it was necessary to group the four non-white categories together into one 'Non-white' category due to the low numbers in each of the categories. Table V-1 shows that based on the available data, highly significant differences in ethnicity were found among cases and controls. This was likely due to the high percentage of white subjects in the control group. Further examination of ethnicity among the six sites revealed that Clarke had the highest proportion of white to non-white subjects (37:1), while the only two sites with proportionally more
non-white compared to white subjects were HSC (2:1) and Youthdale, which did not include any white subjects (data not shown).

Table V-1. Analysis of Subject Demographic Characteristics

<table>
<thead>
<tr>
<th>Demographic Variable</th>
<th>Cases (n=26)</th>
<th>Controls (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>14 (53.8%)</td>
<td>53 (75.7%)</td>
</tr>
<tr>
<td>Female</td>
<td>12 (46.2%)</td>
<td>17 (24.3%)</td>
</tr>
<tr>
<td></td>
<td>$\chi^2 = 3.33, 1 \text{ df}, P = 0.068$</td>
<td></td>
</tr>
<tr>
<td><strong>Ethnicity</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>9 (40.9%)</td>
<td>60 (95.2%)</td>
</tr>
<tr>
<td>Non-white*</td>
<td>13 (59.1%)</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Missing values</td>
<td>4</td>
<td>7</td>
</tr>
<tr>
<td></td>
<td>$\chi^2 = 28.04, 1 \text{ df}, P &lt; .0001$</td>
<td></td>
</tr>
<tr>
<td><strong>SES of mother</strong>**</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D.)</td>
<td>37.9 (11.7)</td>
<td>44.1 (15.2)</td>
</tr>
<tr>
<td>Missing values</td>
<td>11</td>
<td>57</td>
</tr>
<tr>
<td><strong>SES of father</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (S.D.)</td>
<td>45.9 (20.0)</td>
<td>48.1 (19.7)</td>
</tr>
<tr>
<td>Missing values</td>
<td>12</td>
<td>43</td>
</tr>
</tbody>
</table>

*Includes Black, Asian, Hispanic, and Other

**Mothers with occupation listed as 'Housewife' excluded

SES variables for both the subject's mother and father were also compared among cases and controls. Table V-1 shows that cases had lower mean SES scores for both maternal SES and paternal SES as compared to controls. These results, however, are based on less than half of all subjects for both SES variables (29% for maternal SES and 43% for paternal SES) due to the high numbers of missing values. Due to this lack of valid data, further analyses comparing SES variables among cases and controls were not carried out.
Figure V-1. Ethnicity Distribution Among Cases and Controls

Age distributions were also examined among cases and controls. Two age variables were created using the original date variables in the dataset: age of onset of schizophrenia, and present age. As shown in Table V-2, the mean age of onset of schizophrenia was 14.1 years for cases and 28.6 years for controls. The mean age of onset for male and female cases was 14.2 years and 14.0 years, respectively, while the mean age of onset for male and female controls was 27.2 years and 33.0 years, respectively (data not shown). The stem-and-leaf plots in Figure V-2 show the distributions for age of onset of schizophrenia among cases and controls. For cases, the age of onset of schizophrenia ranged from 10 to 15 years with 77% of cases having an onset between 13 and 15 years of age. The age of onset for controls ranged from 18 to 46 years, with the highest proportion of subjects (33%) having an onset of schizophrenia between 20 to 24 years of age.
Also shown in Table V-2, the present age variable denotes the age of the subject as of January 1, 1998, which was the approximate start date of the data collection procedures.

Table V-2. Mean Age Within Subject Group: Age of Onset and Present Age

<table>
<thead>
<tr>
<th>Age Variable</th>
<th>Cases (n=26)</th>
<th>Controls (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean (S.D.)</td>
<td>95% C.I.</td>
</tr>
<tr>
<td>Age of onset of schizophrenia (years)</td>
<td>14.1 (1.3)</td>
<td>(13.6-14.7)</td>
</tr>
<tr>
<td>Present age (years)</td>
<td>18.0 (3.2)</td>
<td>(16.7-19.3)</td>
</tr>
</tbody>
</table>

*Number of missing values = 3

Figure V-2. Stem-and-leaf Plot for Age of Onset of Schizophrenia by Subject Status

VARIABLE = Age of onset of schizophrenia (years)
STATUS = Case

Frequency Stem & Leaf
1.00 10 . 9
.00 11 .
5.00 12 . 57788
8.00 13 . 02556899
4.00 14 . 2789
8.00 15 . 14577889

Stem width: 1.00
Each leaf: 1 case(s)

VARIABLE = Age of onset of schizophrenia (years)
STATUS = Control

Frequency Stem & Leaf
8.00 1 . 88999999
22.00 2 . 000111111122333334444444
12.00 2 . 555666677889
7.00 3 . 0000011
9.00 3 . 555566669
6.00 4 . 012334
3.00 4 . 578

Stem width: 10.0
Each leaf: 1 case(s)
5.2 Sample Size Requirements for Comparative Study

5.2.1 Subjects Meeting Required Sample Size

In order to determine whether it is possible to ascertain an adequate number of subjects from the selected sites to carry out the comparative study, the total number of eligible subjects was calculated for cases and controls. Although an approximation for this was made in section 4.3.2 of Chapter IV, more precise study population estimates could be calculated by using the estimates of the patient load at each site which were obtained as data collection progressed.

*Availability of Subjects with Adult-onset Schizophrenia*

Since 23% (26) of the 115 subjects sampled at Queen St. met the inclusion criteria for the study, the approximate study population at this site was 53 (23% of 233). Similarly, since 31% (38) of the 121 subjects sampled at Clarke were eligible for the study, the study population was ~310 (31% of 1012). Unlike Queen St. and Clarke, the procedures followed at Whitby did not permit the study population to be estimated by the proportion of patients meeting the study eligibility criteria based on a review of a sample of patient charts. It could only be estimated by the number of patients on the clinical records list with a given diagnostic code for schizophrenia (any 295.x, except 295.4 and 295.7). Since the patient list for Whitby only included those born within North America, it was likely that a large proportion of patients on the list given a diagnostic code of schizophrenia would have met the study inclusion criteria (as opposed to at Queen St. and Clarke, where the patient lists included those born outside of Canada or the U.S.). The study population for Whitby was estimated to be 260 out of the 332 listed patients.

In summing together the estimated patient loads from the three sites, the total study population
of adult-onset schizophrenic patients from these sites was ~623, which is somewhat higher than the initially estimated 500. This total number of eligible controls was compared to the required sample sizes for the comparative study based on the given sets of parameters in Table IV-1. It can be seen that the sample size requirements for controls for a power of 80% would be met for all sets of parameters involving a relative risk of 2.0, 2.5, and 3.0. However, for a relative risk of 1.5, only when the $PE=0.20$ to 0.40 under a ratio of cases to controls of 1:1, and when the $PE=0.35$ to 0.40 under a ratio of cases to controls of 1:2, would the available number of controls in the study population meet the sample size requirements for the comparative study.

**Availability of Subjects with Childhood-onset Schizophrenia**

For the child cases, the approximated study populations at HSC, Youthdale, Sunnybrook, and Clarke were the same as the number of subjects ascertained at each of these sites since all available patients were included (11, 4, 10, and 1, respectively). Although there were no cases ascertained from Whitby, the study population of child cases from this site could be estimated from the patient list (as done for the controls above), and was found to be 23. Thus, the total study population of childhood-onset schizophrenic patients from all four sites was about 49. It must be kept in mind that this is a rough estimate and likely lower than the actual study population, since the ascertainment of subjects from these sites was not carried out systematically.

The calculated study population for cases was related to the sample size requirements in Table IV-1. As shown, the sample size requirements for cases for a power of 80% would not be met for all given sets of parameters except when $RR=3.0$, using all values of $PE$ under a ratio of cases to controls of 1:3 and 1:4, and when $PE=.20$ to .40 under a ratio of cases to controls of 1:2.
5.2.2 Response Rates

Table V-3 shows the response rates for cases and controls after having been sent a letter requesting their participation in the study and the accessing of their birth records. The overall response rate for the 150 subjects who were sent letters was 19% (95% C.I. = .13-.27). Examination by subject group shows that the response rate of the controls was higher than that for cases (20% vs. 16%), but this difference was not significant (two-tailed $P=0.77$). The rate of refusal was somewhat higher for controls compared to cases (18% vs. 14%), as was the proportion of subjects whose letters were returned undeliverable due to an incorrect or incomplete address (22% vs. 16%). The highest percentage of subjects in both groups did not return the consent form for unknown reasons, and this was higher in cases than controls (53% vs. 39%). Subjects who did not return the consent form and were followed up with a phone call (i.e. excluding the 40 subjects from Whitby who did not return the consent form and could not be followed up) were either unreachable due to not having a phone number, having an incorrect number or one that was no longer in service (80% or 20/25), or because repeated attempts to reach them by phone were unsuccessful (20% or 5/25).

<table>
<thead>
<tr>
<th>Type of Response</th>
<th>Cases ($n=49$)</th>
<th>Controls ($n=101$)</th>
<th>Total ($n=150$)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consent Given</td>
<td>16.3% (8)</td>
<td>19.8% (20)</td>
<td>18.7% (28)</td>
</tr>
<tr>
<td>Refused</td>
<td>14.3% (7)</td>
<td>17.8% (18)</td>
<td>16.7% (25)</td>
</tr>
<tr>
<td>Undeliverable</td>
<td>16.3% (8)</td>
<td>21.8% (22)</td>
<td>20.0% (30)</td>
</tr>
<tr>
<td>Not Returned</td>
<td>53.1% (26)</td>
<td>39.0% (39)</td>
<td>43.6% (65)</td>
</tr>
<tr>
<td>Not Mailed</td>
<td>0</td>
<td>2.0% (2)</td>
<td>1.3% (2)</td>
</tr>
</tbody>
</table>
It can be observed from Table V-3 that the total number of subjects in each group for calculating response rates (i.e. cases: \( n=49 \), controls: \( n=101 \)) was higher than the total number of cases and controls ascertained for the study sample (i.e. \( n=26 \) and \( n=70 \), respectively). This is due to the method of subject ascertainment at Whitby, in which consent had to be obtained from potential subjects prior to accessing their charts. While only patients who provided consent could be included as subjects from Whitby in this study, all patients from other sites who were sent letters were automatically included as subjects since their charts had been reviewed. In determining response rates, however, the total number of patients from Whitby to whom letters were mailed were included in the subject totals. Although a total of 77 patients from Whitby all having a code of 295.x were mailed letters, it was necessary to examine only the patients with a diagnosis of schizophrenia. Since the charts could not be reviewed to confirm the diagnosis prior to the mailing of letters, the number of patients with schizophrenia who were sent letters was estimated by looking at the diagnosis codes (any 295.x except 295.4 and 295.7) on the patient list. Thus, the total number of potential subjects from Whitby to whom letters were sent was 60. This consisted of 23 childhood-onset schizophrenic and 37 adult-onset schizophrenic patients.

The response rates for the individual sites are shown in Figure V-3. Sunnybrook had the highest response rate at 40\%. Notably, the response rate for the cases from Whitby was 0\%. Also, consent was not obtained from any of the subjects from Youthdale due to non-returns or letters being undeliverable. It is of relevance to compare the response rates between Whitby and all other sites combined, since the method of subject ascertainment differed for these two groups. While the response rate from Whitby was 10\% (0\% for cases, 16\% for controls), the overall response rate from all other sites was 24\% (31\% for cases, 22\% for controls).
In assessing the effectiveness of the follow-up procedures used to increase the response rate, it was found that out of all subjects for which a letter had to be resent, 29% (7/24) subsequently consented to participate in the study. This was more effective within the cases (60% or 6/10) than within the controls (7% or 1/14). In terms of all subjects who were followed up with a phone call, 20% (7/35) subsequently gave their consent. Again, this procedure appeared to be more useful in increasing the response rate for cases (40% or 6/15) than for controls (5% or 1/20).
5.2.3 Subjects Meeting Minimum Data Requirements

For the comparative study to be feasible with respect to sample size, it is not only important that a sufficient number of cases and controls are available in the study population who then provide consent to participate in the study, but that the minimum required demographic, diagnostic, and obstetric data (i.e. 'useful data' as described in section 4.8 of Chapter IV) for the comparative study can be obtained from the charts and/or birth records of cases and controls.

Ascertainment of Subjects with Useful Data

Table V-4 shows the results of subjects meeting different types of data requirements for the comparative study. All subjects in this study who had any type of OC data had at most two missing required variables from the psychiatric charts; thus, all subjects in this study who had OC data were considered to have some form of useful data and were included in Table V-4.

It is shown in Table V-4 that the overall highest proportions of subjects having useful data ($p$) for both cases and controls occurred for the condition in which OC information was taken from psychiatric charts and/or birth records (cases: 50%-88%; controls: 26%-49%). The lowest overall proportions of cases having useful data occurred when supplemented OC data (i.e. from both charts and birth records) was used as the criteria (12%-19%). For controls, the lowest values of $p$ also resulted when the data requirements involved supplemented OC information (1.4%-2.8%).

In comparison to the proportions of subjects having useful data in which OC information was taken from any source(s), the proportions of those having useful data from psychiatric charts alone are only slightly lower for cases, and almost equal for controls. It can be seen from Table V-4 that for every type of data requirement, the value of $p$ for controls is consistently lower than that for
cases. Also, for all source categories of OC information, there is little or no difference in the proportions of cases or controls with useful data when there is one vs. two missing demographic variables. While not shown in the table, Sunnybrook was the only site with 100% of subjects meeting any of the given data requirements. 80% (4/5) of the cases having OC data from both charts and birth records were from Sunnybrook.

**Childhood-onset Schizophrenic Subjects Meeting Minimum Data Requirements**

In terms of meeting sample size and data requirements for the comparative study, it can be seen from Table V-4 that at most, 23/26 (88%) of the cases would have useful data. This total of 23 cases, however, would not be adequate to meet the lowest calculated number of 32 cases that are required to have useful data for the comparative study (using \( RR=3.0, PE=0.30 \), and \( r=1:4 \) from Table IV-1). Therefore, at least 36 cases would need to be available to have at least 32 cases meeting the minimum data requirements.

**Adult-onset Schizophrenic Subjects Meeting Minimum Data Requirements**

To assess whether there are an adequate number of controls meeting the data requirements for the comparative study, it was necessary to calculate the required proportion of controls with useful data \( (p_o) \). Since only a rough approximation to the study population was initially used to estimate \( p_o \) (see section 4.3.2 in Chapter IV), it was necessary to re-calculate the range of \( p_o \) using the more precise study population estimate for controls. With the assumption that the study population for controls is 623 (see section 5.2.1), it can be seen from Table IV-1 that the minimum required number of controls for the comparative study based on the lowest required sample size for cases would be 128 \( (RR=3.0, PE=0.30, \text{ and } r=1:4) \). Thus, out of all controls in the study population,
### Table V-4. Subjects with Useful Data for Comparative Study

<table>
<thead>
<tr>
<th>Type of Useful Data</th>
<th>Proportion of Subjects with Useful Data ($p$)</th>
<th>Cases ($n=26$)</th>
<th>95% C.I.</th>
<th>Controls ($n=70$)</th>
<th>95% C.I.</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC Data from <em>Both Psychiatric Charts and Birth Records</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.12 (3)</td>
<td></td>
<td>(0.03-0.31)</td>
<td>0.014 (1)</td>
<td>(0.00-0.07)</td>
</tr>
<tr>
<td>≤1 missing demographic variable</td>
<td>0.15 (4)</td>
<td></td>
<td>(0.04-0.35)</td>
<td>0.028 (2)</td>
<td>(0.00-0.09)</td>
</tr>
<tr>
<td>≤2 missing demographic variables</td>
<td>0.19 (5)</td>
<td></td>
<td>(0.07-0.40)</td>
<td>0.028 (2)</td>
<td>(0.00-0.09)</td>
</tr>
<tr>
<td>OC Data from <em>Birth Records Only</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.15 (4)</td>
<td></td>
<td>(0.04-0.35)</td>
<td>0.014 (1)</td>
<td>(0.00-0.07)</td>
</tr>
<tr>
<td>≤1 missing demographic variable</td>
<td>0.27 (7)</td>
<td></td>
<td>(0.12-0.47)</td>
<td>0.071 (5)</td>
<td>(0.03-0.16)</td>
</tr>
<tr>
<td>≤2 missing demographic variables</td>
<td>0.31 (8)</td>
<td></td>
<td>(0.14-0.52)</td>
<td>0.071 (5)</td>
<td>(0.03-0.16)</td>
</tr>
<tr>
<td>OC Data from <em>Psychiatric Charts Only</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.46 (12)</td>
<td></td>
<td>(0.26-0.67)</td>
<td>0.26 (18)</td>
<td>(0.16-0.38)</td>
</tr>
<tr>
<td>≤1 missing demographic variable</td>
<td>0.65 (17)</td>
<td></td>
<td>(0.46-0.87)</td>
<td>0.44 (31)</td>
<td>(0.32-0.57)</td>
</tr>
<tr>
<td>≤2 missing demographic variables</td>
<td>0.77 (20)</td>
<td></td>
<td>(0.56-0.91)</td>
<td>0.44 (31)</td>
<td>(0.32-0.57)</td>
</tr>
<tr>
<td>OC Data from <em>Psychiatric Charts and/or Birth Records</em></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.50 (13)</td>
<td></td>
<td>(0.30-0.70)</td>
<td>0.26 (18)</td>
<td>(0.16-0.38)</td>
</tr>
<tr>
<td>≤1 missing demographic variable</td>
<td>0.77 (20)</td>
<td></td>
<td>(0.56-0.91)</td>
<td>0.49 (34)</td>
<td>(0.37-0.62)</td>
</tr>
<tr>
<td>≤2 missing demographic variables</td>
<td>0.88 (23)</td>
<td></td>
<td>(0.70-0.96)</td>
<td>0.49 (34)</td>
<td>(0.37-0.62)</td>
</tr>
</tbody>
</table>
a minimum proportion of 20% (128/623) must have useful data in order to carry out the comparative study. Hence, the minimum proportion of sampled controls in this study required to have useful data was 20%.

From Table V-4, it can be seen that the data requirements for controls would not be met for all conditions in which OC information must be obtained from both psychiatric charts and birth records, or in which OC information must be obtained from birth records only, as the values of \( p \) are less than 20%. The condition that subjects have OC data from psychiatric charts and/or birth records was met by up to 49% of controls, which would satisfy the required \( p_o \). From this, it follows that at most, 305 controls out of the study population of 623 would meet the above data requirements. Thus, the various study parameters in Table IV-1 that correspond to required sample sizes of up to 305 controls could be used for the comparative study. For example, all case to control ratios and all values of \( PE \) (.15 to .40) for a \( RR \) of 2.5 or 3.0 could be used for the comparative study when the condition that subjects have OC data from psychiatric charts and/or birth records and up to two missing required variables applies. For the other conditions of OC data from psychiatric charts and/or birth records, as well as OC data from psychiatric charts only, in which the proportion of controls having useful data satisfied the required \( p_o \), the same process of deducing the feasible sets of study parameters was used. Table V-5 outlines these results for the different combinations of study parameters that can be used in order for the comparative study to be feasible with respect to the sample size and data requirements of controls.

Subjects having any type of useful data (i.e. coming from psychiatric charts and/or birth records) were compared with those who did not have useful data. There were no differences found with respect to the sex distribution among the cases (\( \chi^2 = 1.19 \), two-tailed \( P = 0.276 \)), or the controls
Table V-5. Feasible Combinations of Study Parameters for the Comparative Study With Respect to Meeting Sample Size Requirements for Controls

<table>
<thead>
<tr>
<th>Type of Useful Data</th>
<th>Proportion of Controls with Useful Data (p)</th>
<th>95% C.I.</th>
<th>Feasible Sample Size</th>
<th>Feasible Combination(s) of Study Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC Data from Psychiatric Charts and/or Birth Records</td>
<td></td>
<td></td>
<td></td>
<td>For RR = 3.0: all values of PE (.15 to .40) for all r (1:1 to 1:4)</td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.26 (18)</td>
<td>(0.16-0.38)</td>
<td>56 - 162</td>
<td>For RR = 2.5: up to r = 1:3 with lowest PE = .20</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For RR = 2.0: up to r = 1:1 with lowest PE = .25</td>
</tr>
<tr>
<td></td>
<td>s1 or s2 missing demographic variable(s)</td>
<td>0.49 (34)</td>
<td>(0.37-0.62)</td>
<td>For RR = 3.0 &amp; 2.5: all values of PE (.15 to .40) for all r (1:1 to 1:4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For RR = 2.0: up to r = 1:3 with lowest PE = .25</td>
</tr>
<tr>
<td>OC Data from Psychiatric Charts Only</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No missing required variables</td>
<td>0.26 (18)</td>
<td>(0.16-0.38)</td>
<td>56 - 162</td>
<td>For RR = 3.0: all values of PE (.15 to .40) for all r (1:1 to 1:4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For RR = 2.5: up to r = 1:3 with lowest PE = .20</td>
</tr>
<tr>
<td></td>
<td>s1 or s2 missing demographic variable</td>
<td>0.44 (31)</td>
<td>(0.32-0.57)</td>
<td>For RR = 3.0 &amp; 2.5: all values of PE (.15 to .40) for all r (1:1 to 1:4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>For RR = 2.0: up to r = 1:2 with lowest PE = .20</td>
</tr>
</tbody>
</table>
\( \chi^2 = 0.96, \text{two-tailed } P = 0.327 \). In terms of present age, while there were no significant differences among the cases (18.4 years vs. 18.0 years, \( t = 0.2 \), two-tailed \( P > 0.5 \)), the controls who had useful data were significantly younger than those who did not have useful data (34.3 years vs. 39.3 years, \( t = 2.46 \), two-tailed \( P < 0.02 \)).

5.3 Data Quality

5.3.1 First Admission Diagnosis of Schizophrenia

Information pertaining to the subject's first admission diagnosis of schizophrenia was assessed as an aspect of diagnostic data quality. To provide an indication of the accuracy of the diagnostic data used to determine the time of first admission with a diagnosis of schizophrenia, the type of diagnostic information available in the charts was assessed for cases and controls. The different categories of information used to determine the time of first admission with a diagnosis of schizophrenia were discussed in section 4.6 of Chapter IV. These different categories corresponded to different levels of accuracy (i.e. explicitly stated information would be most accurate).

As shown in Table V-6, a large proportion of cases compared to controls fell into the 'Explicitly stated (incidence diagnosis)' category (35% vs. 3%, respectively). On the other hand, 23% of controls compared to 4% of cases had information which fell under the 'Explicitly stated (not incidence diagnosis)' category. For a large proportion of both cases and controls (62% and 66%, respectively), explicit detail as to when the incident diagnosis of schizophrenia occurred was not given. Thus, it was necessary to use the earliest admission date in which a diagnosis of
schizophrenia was given to estimate the time of incident diagnosis of schizophrenia. While not pertaining to cases, the two categories providing the least accurate measures of first admission diagnosis applied to a small proportion of controls (4%).

Table V-6. Type of Information for Time of First Admission Diagnosis of Schizophrenia

<table>
<thead>
<tr>
<th>Type of Information</th>
<th>Cases (n=26)</th>
<th>Controls (n=70)</th>
<th>Total (n=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Explicitly stated</td>
<td>9 (34.6%)</td>
<td>2 (2.9%)</td>
<td>11 (11.4%)</td>
</tr>
<tr>
<td>(incidence diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Explicitly stated</td>
<td>1 (3.8%)</td>
<td>16 (22.9%)</td>
<td>17 (17.7%)</td>
</tr>
<tr>
<td>(not incidence diagnosis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not explicitly stated</td>
<td>16 (61.5%)</td>
<td>46 (65.7%)</td>
<td>62 (64.6%)</td>
</tr>
<tr>
<td>Estimated</td>
<td>0</td>
<td>3 (4.3%)</td>
<td>3 (3.1%)</td>
</tr>
<tr>
<td>Not available</td>
<td>0</td>
<td>3 (4.3%)</td>
<td>3 (3.1%)</td>
</tr>
</tbody>
</table>

5.3.2 Missing Data

To determine the nature and extent of missing data in the psychiatric charts, a number of analyses were carried out. As shown in Table V-7, the overall missing data rate for the 30 variables on the data collection form was 37%. This was determined by taking the average of the missing data rates calculated for each subject. In comparing the missing data rates between subject groups, cases had a significantly lower mean proportion of missing data (29%) than controls (40%) (t-test, two-tailed $P = 0.001$).
The overall missing data rates within each of the six study sites were also examined (data not shown). Sunnybrook had the lowest missing data rate at 22%, while Queen St. had the highest at 47%. A one-way ANOVA demonstrated an overall significant difference in the missing data rates of the six sites \((F=8.310, P < 0.0001)\). Using the Bonferroni Multiple Comparisons Procedure to assess for possible differences between pairs of sites, it was found that the missing data rate for Queen St. was significantly higher than that of all other sites except for Youthdale.

As shown in Table V-8, the percentage of missing information from the psychiatric charts was calculated for each variable. There was no missing data for the variables sex, date of birth, subject address, and date of study diagnosis of schizophrenia (13% or 4/30). Variables with the highest proportions of missing information were: duration of labor (99%), gestational age (98%), highest level of education of father (94%), birth hospital (93%), and highest level of education of mother (92%). The type of missing information from all of these was 'Not available' (i.e. there was no evidence in the chart that the information was requested).

Missing data attributed to the two subject groups was also examined. Table V-8 shows that of all variables with missing information, 38% (10/26) had missing data which was entirely
accounted for by subjects in the control group. These included subject telephone number and all next-of-kin/correspondent items. The type of missing data for the majority of these variables was 'No response' (i.e. the information was not provided, but there was evidence in the chart that it was requested). There were no variables with missing data attributed only to the cases.

In 75% (12/16) of the variables in which missing information was attributed to both cases and controls, the proportion of subjects with missing data was higher within the controls than the cases. These included all the variables related to pregnancy and birth history. For 3 of the 4 variables in which the proportion of subjects with missing information was higher within the case group rather than the control group, the proportions of subjects with missing data was quite similar for cases and controls (92% vs. 91% for highest level of education attained by mother; 96% vs. 94% for highest level of education attained by father; 15% vs. 10% for ethnicity). For the other variable, place of birth, the proportion of missing data was much higher for cases compared to controls (31% vs. 4%).

Of particular relevance is the missing information with regard to pregnancy and birth data. As shown in Table V-8, there was no evidence in the charts that the missing data from these variables was requested (i.e. type 'NA'). The range of proportions of missing data for the four specific obstetric variables was generally high for both cases (69% to 92%) and controls (89% to 100%), and as discussed above, were among the highest. As seen in Table V-9, the variable OC information, which consists of any data on the presence or absence of any OC or obstetrical event, had the highest within-site proportion of missing data from Queen St. (77%), with no missing data from Sunnybrook. Of further relevance is the fact that in both the duration of labour and gestational age variables, 100% of the data are missing from all sites except Sunnybrook. For the
Table V-8. Missing Data Rates According to Each of the 30 Variables Requested from Psychiatric Charts

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total Missing Data (%) (n=96)*</th>
<th>Type of Missing Data** (%) (n=96)</th>
<th>Missing Data for Subject Group (%)</th>
<th>Cases (n=26)</th>
<th>Controls (n=70)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>0</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Date of birth</td>
<td>0</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Health card #</td>
<td>14.6</td>
<td>14.6 - NR</td>
<td>0</td>
<td>20.0</td>
<td></td>
</tr>
<tr>
<td>Subject address</td>
<td>0</td>
<td>--</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subject telephone #</td>
<td>19.8</td>
<td>19.8 - NR</td>
<td>0</td>
<td>27.1</td>
<td></td>
</tr>
<tr>
<td>Next-of-kin/ correspondent</td>
<td>9.4</td>
<td>9.4 - NR</td>
<td>0</td>
<td>12.8</td>
<td></td>
</tr>
<tr>
<td>Next-of-kin relationship</td>
<td>1</td>
<td>1.0 - NR</td>
<td>0</td>
<td>1.4</td>
<td></td>
</tr>
<tr>
<td>Next-of-kin address</td>
<td>11.5</td>
<td>11.5 - NR</td>
<td>0</td>
<td>15.7</td>
<td></td>
</tr>
<tr>
<td>Next-of-kin telephone #</td>
<td>5.2</td>
<td>5.2 - NR</td>
<td>0</td>
<td>7.1</td>
<td></td>
</tr>
<tr>
<td>Place of birth</td>
<td>11.5</td>
<td>8.3 - NA 3.1 - DK</td>
<td>30.8</td>
<td>4.3</td>
<td></td>
</tr>
<tr>
<td>Birth hospital</td>
<td>92.7</td>
<td>92.7 - NA</td>
<td>84.6</td>
<td>95.7</td>
<td></td>
</tr>
<tr>
<td>Maternal age</td>
<td>61.5</td>
<td>58.3 - NA 3.1 - NR</td>
<td>30.8</td>
<td>72.8</td>
<td></td>
</tr>
<tr>
<td>Ethnicity</td>
<td>11.5</td>
<td>11.5 - NA</td>
<td>15.4</td>
<td>10.0</td>
<td></td>
</tr>
<tr>
<td>Number of siblings</td>
<td>20.8</td>
<td>16.7 - NA 3.1 - DK 1.0 - NR</td>
<td>7.7</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Birth order</td>
<td>31.3</td>
<td>30.2 - NA 1.0 - NR</td>
<td>11.5</td>
<td>38.6</td>
<td></td>
</tr>
<tr>
<td>Adoption status</td>
<td>18.8</td>
<td>18.8 - NA</td>
<td>3.8</td>
<td>24.3</td>
<td></td>
</tr>
</tbody>
</table>
Table V-8 cont'd...

<table>
<thead>
<tr>
<th></th>
<th>Controls</th>
<th>Case</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age of adoption</td>
<td>21.9</td>
<td>19.8</td>
<td>0</td>
</tr>
<tr>
<td>Employment status</td>
<td>1.4</td>
<td>1.4</td>
<td>1.4</td>
</tr>
<tr>
<td>Highest level of education</td>
<td>11.4</td>
<td>14.2</td>
<td>11.4</td>
</tr>
<tr>
<td>(subject)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest level of education</td>
<td>91.7</td>
<td>91.4</td>
<td>92.3</td>
</tr>
<tr>
<td>(mother)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Highest level of education</td>
<td>93.8</td>
<td>93.8</td>
<td>96.2</td>
</tr>
<tr>
<td>(father)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Occupation (mother)</td>
<td>58.3</td>
<td>58.3</td>
<td>26.9</td>
</tr>
<tr>
<td>Occupation (father)</td>
<td>55.2</td>
<td>55.2</td>
<td>38.5</td>
</tr>
<tr>
<td>Date of onset of schizophrenia</td>
<td>3.1</td>
<td>3.1</td>
<td>0</td>
</tr>
<tr>
<td>Date of study diagnosis of</td>
<td>0</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>schizophrenia</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OC information</td>
<td>47.9</td>
<td>47.9</td>
<td>23.1</td>
</tr>
<tr>
<td>Duration of labor</td>
<td>99</td>
<td>99.0</td>
<td>96.2</td>
</tr>
<tr>
<td>Gestational age</td>
<td>97.9</td>
<td>97.9</td>
<td>92.3</td>
</tr>
<tr>
<td>Term of birth</td>
<td>82.3</td>
<td>82.3</td>
<td>65.4</td>
</tr>
<tr>
<td>Birthweight</td>
<td>84.4</td>
<td>84.4</td>
<td>69.2</td>
</tr>
</tbody>
</table>

* Note: Since data for employment status and highest level of education (subject) is collected only for controls, n=70 for these variables.

**Types of missing data: 'NA' = Not Available; 'DK' = Don't Know; 'NR' = No Response
variables term of birth and birthweight, data are not completely missing from all other sites, but Sunnybrook still had the lowest within-site proportions of missing information (40% and 30%, respectively). It is of further interest to note that Sunnybrook had no missing data for other variables related to developmental history (i.e. number of siblings, birth order, and adoption status).

Table V-9. Missing Data from Psychiatric Charts for OC-Related Variables by Study Site

<table>
<thead>
<tr>
<th>Variable</th>
<th>Queen St. (n=26)</th>
<th>Clarke (n=39)</th>
<th>Whitby (n=6)</th>
<th>HSC (n=11)</th>
<th>Youthdale (n=4)</th>
<th>Sunnybrook (n=10)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OC information</td>
<td>76.9</td>
<td>46.2</td>
<td>50.0</td>
<td>36.4</td>
<td>25.0</td>
<td>0</td>
</tr>
<tr>
<td>Duration of labor</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>90.0</td>
</tr>
<tr>
<td>Gestational age</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>80.0</td>
</tr>
<tr>
<td>Term of birth</td>
<td>96.2</td>
<td>87.2</td>
<td>66.7</td>
<td>72.7</td>
<td>100</td>
<td>40.0</td>
</tr>
<tr>
<td>Birthweight</td>
<td>92.3</td>
<td>94.9</td>
<td>50.0</td>
<td>90.9</td>
<td>100</td>
<td>30.0</td>
</tr>
</tbody>
</table>

5.3.3 Quality of OC Data

Prior to assessing the quality of OC data obtained from psychiatric charts or birth records, it is useful to examine the sources of available OC data among cases and controls. As shown in Table V-10, OC data could not be obtained from psychiatric charts or birth records for 41% of the subjects, but was available from either psychiatric charts, birth records, or both for over half of all subjects (59%). The rate of available OC data for cases was almost twice as much as that for the controls (88% vs. 49%). Of the subjects with OC data, a high proportion had this information available in their psychiatric charts (89% or 51/57), compared to only 23% (13/57) whose OC data
were obtained from birth records. While birth records could be accessed for 31% (8/26) of cases, this occurred for only 7% (5/70) of controls. While cases and controls were somewhat similar with regard to having OC data available from either psychiatric charts only or birth records only, a higher proportion of cases compared to controls had both psychiatric charts and birth records as sources of OC data (19% vs. 3%).

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<tr>
<th>Table V-10. Sources of OC Data Among Cases and Controls</th>
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<tr>
<td></td>
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<tr>
<td><strong>Cases (n=26)</strong></td>
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<tr>
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<tr>
<td>Subjects with No OC Data Available</td>
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<tr>
<td>Subjects with OC Data from Psychiatric Charts Only</td>
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<tr>
<td>Subjects with OC Data from Birth Records Only</td>
</tr>
<tr>
<td>Subjects with OC Data from Both Psychiatric Charts &amp; Birth Records</td>
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<tr>
<td>Total Subjects with OC Data Available</td>
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**Reliability of OC Data from Psychiatric Charts and Birth Records**

As seen in Table V-10, the total number of cases and controls having OC data from both psychiatric charts and birth records was only 7; thus, analyses that examine the reliability of these two sources of OC information are limited. Nevertheless, a descriptive examination of the extent of agreement between OC data in the psychiatric charts vs. birth records of these 7 subjects was carried out. Table V-11 shows the extent of agreement between the charts and birth records for
OC data pertaining to different reproductive periods, and general obstetric data.

OC information for the reproductive phases constitutes any data which indicate the presence or absence of OCs during the pregnancy, labour/delivery, and/or neonatal periods. These data can consist of a general statement about the presence or absence of OCs (e.g. "pregnancy was normal"), or it can involve the reporting of a specific OC experienced (e.g. breech delivery). Agreement between psychiatric charts vs. birth records for this information was considered to occur when it was indicated in both sources that OCs were absent for a particular phase, or when both sources reported the presence of a specific OC during a particular period. OC information from charts and birth records was considered to be discrepant when one source reported the absence of any OCs during a particular phase, while the other source reported the presence of a

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<tr>
<th>Table V-11. Comparison of OC and Related Data from Psychiatric Charts vs. Birth Records</th>
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<tr>
<td>OC Information for Different Reproductive Phases*</td>
</tr>
<tr>
<td>Cases (n=5)</td>
</tr>
<tr>
<td>PCs</td>
</tr>
<tr>
<td>Agreement</td>
</tr>
<tr>
<td>Discrepancy</td>
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<tr>
<td>Data only in psychiatric charts</td>
</tr>
<tr>
<td>Data only in birth records</td>
</tr>
<tr>
<td>No data available</td>
</tr>
</tbody>
</table>

*PCs = Pregnancy Complications  **GA = Gestational Age
LDCs = Labour/Delivery Complications  DL = Duration of Labour
NCs = Neonatal Complications  BW = Birthweight
specific OC for that phase. Also considered as discrepant is when a specific OC was reported to occur during a reproductive phase in one source, but a different specific OC was described for the same phase in the other source. It can be seen from Table V-11 that only 40% (6/15) of potential comparisons for cases, and only 33% (2/6) of potential comparisons for controls could be made between charts and birth records as data on particular items were not available from both sources. For the 5 cases, 3 out of the 6 (50%) data comparisons made showed agreement, while 3 other comparisons of labour/delivery data were discrepant. For the 2 controls, there was one instance of agreement and one of disagreement (50%) out of the 2 data comparisons made.

In Table V-11, general obstetric information pertaining to data on the subject's gestational age, duration of labour, and birthweight was also compared among psychiatric charts and birth records. Agreement was considered to occur when both sources reported the same information (birthweight could vary as much as ±5 oz). It is shown that for 4 out of the 5 cases (80%), there was agreement between the birthweight data reported in the psychiatric charts and birth records. On the other hand, 80% (4/5) of the cases did not have data regarding duration of labour from either of the two sources.

5.4 Potential for Measurement Bias

5.4.1 Method of Eliciting OC Data

The method of eliciting OC data from the psychiatric charts was compared for cases and controls. It is shown in Table V-8 that for all cases and controls who did not have any OC information in their psychiatric charts, there was no evidence in the chart to indicate that OC data
were elicited in the form of an interview or through questions asked on a form. Out of the controls who did have OC data in their psychiatric charts, there was evidence to indicate that in 77% (24/31), the OC data were elicited through an interview. For most of the remaining controls with OC data from their charts (6/31), the OC data were included in a report (e.g. an admission or discharge summary) but it was not clear how the data were elicited. For only one control, a form containing one general question which asked to describe any OCs experienced was used.

For cases with OC data in their psychiatric charts, 75% (15/20) had OC data elicited through an interview. Two of these cases also had a form in their charts that requested OC data. One form asked two general questions about any OCs experienced during pregnancy and delivery, and three specific OC-related questions, while the other form asked a general question about any OCs experienced during pregnancy or delivery. Another 10% (2/20) of cases had their OC data come from other sources, such as a physician's letter. For the remaining cases, the OC data were described in an admission summary or social work report, but it was unclear how they were derived.

The elicitation of OC information in the birth records of cases vs. controls was also assessed. For all subjects with birth records, there was some type of OC-related data requested. As shown in Table V-12, general open-ended requests only for OC-related information (e.g. a request for "Complications:" ) were present for 50% of cases and 20% of controls. Similar open-ended requests for OC-related information but for particular gestational phases (e.g. a request for "Pregnancy Complications:" and/or "Labour/Delivery Complications:" ) were found in the birth records of 38% of cases and 60% of controls.

The elicitation of particular items was also assessed by calculating the mean number of items
elicited for cases and controls. These were categorized into general OC-related items, which are common quantitative measures that could indicate either the presence or absence of OCs (e.g. birthweight, duration of labour), and specific OC-related items, which elicit the presence or absence of particular OCs (e.g. whether jaundice was experienced). Only specific items which had a severity level of ≥3 in the McNeil-Sjostrom scale were counted. Table V-12 shows that the mean number of items elicited from both categories was higher for cases compared to controls. All cases and controls had requests for general OC-related items, but 2/8 cases and 1/5 controls did not have specific OC-related items elicited from their birth records.

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=8)</th>
<th>Controls (n=5)</th>
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<tbody>
<tr>
<td>Subjects Having General OC Information Elicited</td>
<td>50% (4)</td>
<td>20% (1)</td>
</tr>
<tr>
<td>Subjects Having OC Information for Particular Gestational Phase(s) Elicited</td>
<td>38% (3)</td>
<td>60% (3)</td>
</tr>
<tr>
<td>Mean Number of General OC-Related Items Elicited</td>
<td>4.9</td>
<td>2.8</td>
</tr>
<tr>
<td>Mean Number of Specific OC-Related Items Elicited</td>
<td>6.5</td>
<td>4.8</td>
</tr>
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### 5.4.2 Recall of OC Information

The mean length of time between the OC event and the time at which the event was reported was compared for cases and controls. The length of time was determined by subtracting the subject's year of birth from the year that the OC data was reported. If there was more than one date in which OC data was reported, the earliest time at which the most OC information had been
obtained was used. For the 20 cases who had OC data reported in their charts, the mean length of time that had passed since the OC event and the time of recall was 14.2 years. For the 30 controls (1 missing), the mean length of time passed was 26.9 years, which was almost twice as long as that for cases.

The reporter of the OC information in the psychiatric charts was also examined for cases and controls. For 35% (7/20) of cases and 23% (7/31) of controls, it was not clear how the OC data were reported. It was, however, indicated in the chart that the subject's mother reported the OC information for 65% (13/20) of cases vs. 39% (12/31) of controls. As expected, none of the OC information for the cases was reported by the patients themselves, while it was indicated in the chart that 26% of the controls were the reporters of their own OC data.
VI. DISCUSSION

The present study was the first to examine the feasibility of obtaining obstetrical data from the psychiatric charts and birth records of individuals with childhood-onset and adult-onset schizophrenia in the Greater Toronto Area. In addition to addressing the research questions that served to determine the feasibility of the proposed comparative study, the present study provided insight into the administrative and ethical practices of the facilities involved, and in particular, the impact that such practices had on the conduct of the research.

The feasibility of the comparative study was analyzed separately in terms of three main issues: sample size requirements, data quality, and potential for measurement bias. The main finding was that the comparative study would not be feasible with respect to meeting the overall sample size requirements. In general, this was due to the resulting inadequate number of childhood-onset schizophrenia subjects having useful data. Based on the given sets of parameters in Table IV-1, the minimum required number of cases having useful data was 32. While it was approximated that 49 eligible cases are present in the study population, only 23 of these cases would be available with useful data for the comparative study.

In examining the factors that contributed to the inadequate number of cases with useful data available for the study, the number of eligible cases in the study population was quite low to begin with, and in fact was inadequate to meet most of the sample size requirements for the given sets of study parameters in Table IV-1. However, the main reason for cases not meeting the overall sample size requirements was due to the low response rate of cases (16%) in providing consent to access their birth records. Much of this low response rate was attributed to subjects who did
not return the consent form for unknown reasons, including all eligible cases from Whitby. As discussed in more detail below, since subjects from all sites except Whitby were not necessarily excluded from the study sample for non-response, the loss of eligible cases in the population through non-response was mainly due to all child patients at Whitby who did not respond to the study. In fact, almost half (23) of the initially eligible cases in the study population were directly lost through the non-response of eligible cases at Whitby.

With respect to meeting minimum data requirements, this was not a major factor in terms of cases not meeting the overall sample size requirements. In fact, it was shown that up to 88% of the ascertained cases had useful data with the use of psychiatric charts and/or birth records. As previously outlined in Chapter IV, there were different conditions in which subjects were considered to have met the minimum data requirements. The most important requirement was to have OC exposure data which could come from either both charts and birth records, birth records only, charts only, or charts and/or birth records, depending on the criteria for the source(s) of OC information to be used for the study. In addition to data on OC exposure, there were minimum required diagnostic and demographic variables. It was found that when the criteria for the source(s) of OC information used were both charts and birth records, or birth records only, approximately 70% or more of available cases would be lost due to not meeting these data requirements. Thus, the use of such OC data sources that are possibly more complete would be a major factor contributing to the loss of eligible cases for the comparative study.

With respect to the control subjects, the sample size and minimum data requirements were met for the comparative study. This was mainly due to the much higher number of eligible controls estimated to be present in the study population as compared to that for cases. In fact, the number
of eligible controls in the population was adequate to meet the sample size requirements for most of the given sets of parameters in Table IV-1. Although the response rate for controls (20%) was similarly low as that for cases, a much smaller proportion of eligible controls were excluded from the sample due to non-respondents from Whitby. With respect to having useful data, it was found that for every type of data requirement, the proportion of controls having useful data was consistently lower than that for cases. When the data requirement involved psychiatric charts and/or birth records, or psychiatric charts alone, the proportions of controls having useful data (i.e. up to 49%) met the minimum required proportion (i.e. 20%) for the comparative study. Thus, the results indicate that given specific combinations of study parameters (see Table V-5), and the use of either of these two types of OC sources, there would be an adequate number of controls having useful data to meet the sample size requirements for controls in the comparative study. Furthermore, the estimate of up to 49% of controls having useful data suggests that the results of the comparative study would be fairly generalizable. It should be considered, however, that while the use of charts and/or birth records as the source(s) of OC data would be feasible in terms of sample size, the source(s) and perhaps quality of the OC data would not be comparable among subjects (i.e. some controls would have OC data only from charts, while some would have OC data from both charts and birth records). Finally, the use of supplemented OC information or OC data from birth records alone would result in a loss of control subjects that would render the study infeasible with respect to sample size requirements.

It should be kept in mind that the above findings with respect to cases and controls meeting sample size requirements are based on a number of assumptions. First, due to the exploratory nature of the present study, the required sample sizes calculated for cases and controls in Table
IV-1 were based on a range of values for the prevalence of exposure for controls as well as for the relative risk regarded as important to detect. The findings were also largely based on the estimated study populations for cases and controls. The study population for cases was estimated based on the assumption that all eligible cases of childhood-onset schizophrenia in the population had been identified. Since it is very likely that there were cases missed due to the unsystematic ascertainment of cases from study sites, the estimated study population for cases was probably lower than the actual study population.

As shown for both cases and controls, the component of sample size that is a potential problem for achieving adequate numbers of subjects with useable data is the response rate. In comparison to the generally acceptable response rate of ≥80% (Sackett, 1979), the overall response rate obtained for the present study (19%) was extremely low. An important factor in the low response rates for cases and controls was the absence of follow-up for subjects from Whitby due to the requirement that patient consent be obtained prior to reviewing psychiatric charts. Non-responders from Whitby would thus be excluded from the study sample since information from their psychiatric charts which would allow them to be included in the study could not be obtained. As such, birth records could not be used as a source of OC data for a high proportion of subjects, as evidenced. For subjects from the other sites, there were also non-responders that contributed to the low response rates. However, non-response for these subjects did not necessarily indicate that they could not be included in the study. This was because psychiatric charts were examined prior to seeking patient consent to access birth records so that all eligible subjects were automatically included in the study when their charts were reviewed, regardless of whether or not they consented to have their birth records accessed. In this way, non-response did not reduce the number of
eligible subjects available, but essentially decreased the number of subjects whose birth records could be obtained.

When ascertaining the number of subjects having useful data, however, there were subjects from all sites except Whitby who may have been excluded from the study sample indirectly due to non-response. While some non-responders from all sites except Whitby may have had OC information in their psychiatric charts, and thus could be included among subjects having useful data, other non-responders may not have had OC data in their psychiatric charts, and would thus be excluded from the number of subjects having useful data. This was the situation for the three eligible cases in the study sample that did not have useful data. In this way, non-response would indirectly contribute to a loss of subjects having useful data. At the same time, those who responded may not necessarily have had OC exposure information available due to difficulties in locating their birth records, and the fact that they did not have OC data in their psychiatric charts. As such, subject response did not necessarily indicate that the subject would be included in the number of subjects having useful data.

Thus, the loss of eligible subjects having useful data involved several factors: non-response of subjects from Whitby, non-response of subjects who did not have OC data in their psychiatric charts, and responders who did not have OC data in their psychiatric charts, and whose birth records could not be located. In view of this, a potential source of bias related to the selection of subjects concerns the fact that subjects with any type of useful data, who could be used for the comparative study, would be different from those without useful data, who would be excluded from the study. It was found that these two groups did not differ with respect to their sex distributions among cases and controls. In terms of present age, while cases with useful data were
not significantly different than those without useful data, controls with useful data were significantly younger than those without useful data. This could be due to the fact that OC exposure information was more easily obtainable, in terms of being provided in the charts or being able to access birth records, for controls who were younger at present.

Although the procedure of ascertaining subjects at Whitby was inconsistent with that of the other sites, it allowed for the examination of how response rates might vary in relation to differences in the method of subject ascertainment. Methods to increase the rate of response such as resending letters to patients and/or following up with a phone call were employed for all sites except Whitby. The finding that the overall response rate from all other sites combined was more than twice as high as that for Whitby alone likely reflects the differences in intensity of subject follow-up between the two groups. This was given support by the finding that the procedures of resending letters and following up with a phone call led to subsequent increases in the number of subjects consenting to participate in the study. Notably, the follow-up procedures appeared to be more effective in increasing response rates for cases than for controls. This is likely due to the fact that cases were more easily contactable as they still may have been living with their parents, whereas the rather unstable housing situation for many controls may not have allowed for an address or telephone number where they could have been reached. With respect to the above findings, it is likely that the use of such follow-up procedures at Whitby would increase the number of cases ascertained from this site, possibly making the comparative study feasible with respect to having an adequate number of cases available with useful data.

It is interesting to recognize that Sunnybrook had a fairly high response rate (40%) in relation to the response rates of the other study sites. Related to this is the fact that 100% of the cases from
Sunnybrook had some type of useful data, and that a large proportion of cases who had OC information from birth records was attributed to subjects from Sunnybrook. While some of this may be related to the fact that subjects from Sunnybrook were cases and, by definition, younger and thus more easier to contact and have their birth records accessed, it did not totally explain the higher response rate compared to HSC and Youthdale. Thus, the fact that the cases from Sunnybrook may have had more complete and accurate contact information (i.e. subject telephone number and address) in their psychiatric charts, as well as the possibility that the parents of such cases may have differed with respect to factors related to participation in research (e.g. higher education), may provide more of an explanation for this higher response rate which contributed to all cases from Sunnybrook having useful data.

A final consideration with respect to response rate is that the acceptability of the overall response rate achieved should take into consideration the nature of the target group. For individuals with schizophrenia, issues such as the difficulty in locating such persons, many of whom do not have a fixed address, the inability of these individuals to provide informed consent due to mental incapacity, and the sensitive nature of the illness would all work to reduce the response rate. As such, the overall low response rate found for the subjects in this study was not surprising, although it was expected that the response rate for cases would be higher than that for controls since a large proportion of cases may have still been under parental care. At the same time, however, since cases were ascertained farther back in time compared to controls (i.e. 1988-1998 vs. 1993-1996, respectively), the higher likelihood of outdated contact information for cases may have accounted for their lower response rate. For reasons outlined above, although the overall response rate achieved would, in general, be unacceptable on the basis of reducing the
potential for bias, it may be considered acceptable with respect to this particular study population.

The second main issue that serves to determine the feasibility of the comparative study is the quality of data from the psychiatric charts and birth records. This was addressed by examining diagnostic data, information on potentially confounding variables, and obstetric data. With regard to diagnostic data, it was shown that for more than half of both cases and controls, the psychiatric chart did not provide explicit information pertaining to the time of first admission with a diagnosis of schizophrenia. As such, one must consider the possibility that subjects who may have actually had a true onset of schizophrenia in childhood could be incorrectly classified as having adult-onset schizophrenia due to the inaccurate or incomplete information in the chart. As it is unlikely that such an error is related to OC exposure in cases and controls, it would probably represent nondifferential misclassification. With respect to the comparative study, such nondifferential misclassification of disease status could introduce a bias toward the null condition. The implications of this misclassification, however, would depend on the effect described by the study. That is, if a strong nonzero effect is described, the nondifferential misclassification would be of a lesser concern.

The assessment of the nature and extent of missing data was relevant in examining the quality of demographic, diagnostic, and obstetric data from the psychiatric charts. Overall, the missing data rate averaged over all of the 30 variables in the data collection form was moderately high, and was significantly higher for controls compared to cases. In terms of diagnostic variables, there was no missing information for almost all subjects. Demographic data for potentially confounding variables generally had low rates of missing data, except for parental education which had very high rates of missing data. Fortunately, there are scales for measuring SES that only require
parental occupation data, such as the Blishen scale (Blishen et al., 1987). Demographic variables associated with OC exposure, such as maternal age and maternal parity, had fairly high rates of missing data, with controls having more than twice the missing data rate as compared to cases for these two variables. Since these potentially confounding variables (i.e. sex, educational/occupational variables) and variables associated with OC exposure (i.e. ethnicity, maternal age, maternal parity) were used to match cases and controls in many previous studies of OCs and schizophrenia, it was thought that these variables should be controlled for in the comparative study. However, other than sex, there was missing data for all variables, so attempts to match on such variables would be problematic for the comparative study. As none of these variables have been established as confounders for the relationship between OCs and childhood-onset schizophrenia vs. adult-onset schizophrenia, it is difficult to say whether there would be a possibility of bias from not being able to control for such variables.

All four of the specific obstetric variables requested on the data collection form had moderately high to very high rates of missing information. For most of these variables, the missing data rate was higher for controls compared to cases. Much of this can be attributed to the fact that Sunnybrook had the lowest proportion of subjects with missing data for variables related to obstetric and developmental history. In fact, there was some kind of data pertaining to the presence or absence of any OC or obstetrical event for all subjects from Sunnybrook. These findings suggest that obstetric data are routinely assessed at Sunnybrook, at least in patients with childhood-onset schizophrenia. More importantly, they suggest that there is a potential for bias since cases and controls come from different facilities and it is apparent that the data collection procedures vary according to the facility. While the potential for bias may arise from the fact that
OC data may be better ascertained or recorded at the sites from which cases were drawn, it could also come from possible differential underreporting of OC data in controls compared to cases, which would be difficult to assess without more comparative data.

The assessment of the quality of OC data also took into account information which was obtainable from hospital birth records. It was found that the proportion of subjects whose birth records could be accessed was higher for cases (31%) than for controls (7%) even though consent to access birth records was given by a slightly higher proportion of controls compared to cases. This was due to the fact that for the cases who provided consent to have their birth records accessed, 100% (8/8) of the birth records were obtained, while for the controls who provided consent to access their birth records, only 25% (5/20) of the birth records were accessible. The accessibility of all birth records for the cases likely reflects the fact that it was not necessary to search for records from many years back (i.e. the earliest would be 1973). The lower rate of accessing birth records for controls, however, is likely due to the greater number of years lapsed since the time birth records were filled out for controls compared to cases, and thus the more difficulties involved in accessing them. For example, it was found that for controls born during the 1950's and '60s, many hospitals placed the birth record within the mother's record; in such cases, the mother's consent in addition to the patient's consent was required to access the birth records. Also, some of the birth records sought for controls had been destroyed since more than ten years had passed since the patient or the patient's mother had been admitted to the hospital. Furthermore, information that may have been required to locate birth records such as the mother's maiden name or date of birth would have been more difficult to obtain for controls who may not know this information and either are not in contact with their mothers or their mothers are
deceased.

The total numbers of cases and controls having OC data from both psychiatric charts and birth records was very low; thus, only a descriptive approach to examining the reliability of the OC data from the psychiatric charts and birth records could be carried out. In 4 of the 8 instances in which OC information for the different reproductive phases could be compared between psychiatric charts and birth records was disagreement observed. The instances of agreement and disagreement were also equal within cases and controls. All instances of discrepancy came from OC data pertaining to the labour/delivery. Due to the small number of comparisons made, and the fairly low prevalence of OCs in these populations, agreement on the absence of OCs does not necessarily provide much information regarding the reliability of OC information from the two sources. It was also shown that there were instances in which information pertaining to a particular gestational phase was restricted to that from the psychiatric charts, or was not available from either charts or birth records, indicating that birth records may not necessarily be complete sources of OC information.

In terms of the general obstetric information compared between charts and birth records, information regarding birthweight was found to be quite reliable within the cases. This finding is consistent with that of Cantor-Graae et al. (1998) who found that recall for birthweight of mothers of adults with schizophrenia was fairly reliable when compared to data from birth records. Duration of labour was not available from either the charts or birth records for the majority of the subjects having both these sources. As there has been evidence to implicate prolonged labour as a specific complication associated with schizophrenia (McNeil & Kaij, 1978; Kendell et al., 1996), the absence of data pertaining to duration of labour could be critical with respect to the results.
obtained in the comparative study. Since the number of subjects having both charts and birth records was very small, one cannot draw any firm conclusions about the reliability of the OC data.

The potential for measurement bias with regard to the ascertainment and reporting of OC information is another important aspect in evaluating the feasibility of the comparative study. The examination of whether there were possible differences in the elicitation of OC data from the psychiatric charts for cases vs. controls was difficult since it was not clear how the OC information was derived for many of the subjects. Even for those subjects whose charts contained OC data which was clearly elicited through an interview, it was not known how many or what type of questions were asked to elicit this information. What can be discerned from these findings is that none of the study sites used a standardized form to routinely collect information pertaining to a patient's obstetrical history, at least not for patients with schizophrenia. Although the Psychosis Clinic at HSC has apparently used a standardized 'Family and Household Form' since 1995 which includes questions pertaining to the patient's obstetrical and developmental history to be filled out by the patient's parent(s), none of the charts of patients seen at HSC who were admitted after 1995 (over half of HSC sample) contained this form. Even if there was a standardized form used by the facility, it still may not be completed. Thus, there is no evidence from the charts to show that for those with OC data, the extent of elicitation of these data (i.e. number of questions asked, etc.) is unequal among cases and controls, but there is also no indication that the OC data is elicited in a systematic way within cases and controls, and even within study sites.

Possible differences in the elicitation of OC data in the birth records among cases and controls were also assessed. Cases and controls were quite similar with regard to having birth records which assessed whether any complications had been experienced, although more of the birth
records of controls tended to have open-ended requests for OC data for particular gestational phases compared to cases. For the OC-related items elicited, cases had a higher mean number of general OC-related items (e.g. birthweight), as well as specific OC-related items (e.g. breech delivery) compared to controls. This suggests the potential for bias in the comparative study in that cases may appear to have a higher incidence of OCs compared to controls, but this may only be due to the fact that there are more items in the birth records of cases compared to controls that elicit OC information.

The potential for recall bias with respect to the OC information reported in the psychiatric charts of cases vs. controls was assessed. An important indicator of the accuracy of recall is the amount of time lapsed between the exposure and the recall (Klemetti and Saxen, 1967). Since it was found that the mean length of time between the OC exposure and the reporting of OC information in the charts was almost twice as long for controls compared to cases, there is a high likelihood that the use of OC data from psychiatric charts would lead to differential misclassification in the comparative study. This finding is not surprising given that controls, by definition, are older as compared to cases at the time of admission for schizophrenia during which the obstetric information would be recorded in the charts.

Another finding relevant to the potential for recall bias was that the OC information in the psychiatric charts was based on maternal recall for a higher proportion of cases compared to controls. It has been suggested that the mother, compared to the patient or father, is by far the most reliable informant with regard to birth history (Lewis et al., 1989), and that maternal recall can be an accurate source of obstetric information with respect to schizophrenia research (O'Callaghan et al., 1990). As such, these results also point to the likelihood of differential
misclassification. The finding is expected on the basis that the cases were children who were still under parental care at the time the OC data were reported. Added to this is the likelihood that some of the controls may have not been in contact with their mothers, or that mothers of older controls may have been deceased at the time that the OC information was sought.

Within the present study, it was relevant to characterize the subject group on a number of demographic variables, particularly since the ascertainment of individuals with childhood-onset schizophrenia was exploratory in nature. It was, however, difficult to completely characterize the subject group due to the presence of missing values. With respect to the sex distribution among cases and controls, the 3:1 male to female sex ratio found for controls is higher than previously reported equal sex ratios in adults with schizophrenia (Jablensky, 1995), while the 1:1 ratio found for cases is lower than the 2:1 male to female sex ratio that has been typically reported in children with schizophrenia (Coleman & Gillberg, 1996). This discrepancy in sex ratios may be due to the ascertainment of unrepresentative patient samples. Also, the inclusion of patients with criminal records from Clarke Metfors may have contributed to the higher male to female sex ratio seen for controls as a male to female ratio of 8:1 was found for patients from this division.

In terms of ethnicity, it was found that the proportion of whites to non-whites was significantly higher among controls compared to cases. The very high percentage of white subjects in the control group compared to the more even distribution of ethnic groups among the cases most likely reflects the increase in the number of non-white babies being born in Canada or the U.S. during the time period in which the cases were born. While none of the controls were black, further analysis reveals that for both Queen St. and Clarke, the highest percentage of potential controls who were excluded due to being born outside of Canada or the U.S. were born in Jamaica.
Thus, although ethnicity appears to be related to subject status, it is most likely related to the period of time during which the cases and controls in this study were born.

With respect to age of onset, the fact that almost 80% of cases were found to have an onset of schizophrenia after the age of 12 appears to be consistent with previous reports (Harris, 1995). For the controls, the mean age of onset of schizophrenia found for males (27 years) was fairly high compared to the typically reported age of onset in the literature (~20 years), while the mean age of onset for females (33 years) was closer to the peak incidence of 30 years often described for women (Coleman & Gillberg, 1996). The higher mean ages of onset found for the controls were likely due to the lack of clear diagnostic data regarding the first admission diagnosis of schizophrenia and the need to use the earliest admission date reported in which a diagnosis of schizophrenia was made to estimate the age of onset.

In carrying out the objectives of the present feasibility study, a number of important issues with regard to the administrative and ethical practices of the various institutions involved were encountered. In particular, the lack of uniformity among the various sites with respect to ethical review procedures and guidelines, as well as clinical services systems available was clearly demonstrated. In terms of ethical review procedures, all facilities with the exception of Youthdale required that the research proposal undergo a formal ethical review process before certain procedures related to the study protocol could be carried out. The fact that the provision of a letter of ethical approval from another institution was sufficient for Youthdale since no formal ethical review process exists at this facility raises the issue of whether the ethical approval for a particular study protocol extended to another facility is effective in acting on the behalf of the patients involved, as well as the investigator if a patient was to be concerned that a breach of
confidentiality was committed.

The impact that ethical guidelines may have on the conduct and findings of research was clearly demonstrated in the present study. While most facilities considered institutional consent to be adequate for the review of patient psychiatric charts and the subsequent contacting of identified subjects, the ethics committee at Whitby felt that the review of patient charts prior to obtaining patient consent would imply a breach of confidentiality. Due to the modified subject ascertainment procedures undertaken at Whitby in which it was necessary to obtain the consent of subjects prior to including them in the study, a large number of eligible subjects were lost from the lack of follow-up. The resulting low number of subjects ascertained from Whitby, all being controls, did not come close to representing the patient load at Whitby. This raises the question of whether more cases would be ascertained from Whitby if the ethical guidelines pertaining to patient confidentiality were less stringent (i.e. similar to the other study sites). As it appears that the strict adherence to ethical guidelines at Whitby is a limiting factor with respect to the feasibility of the comparative study, it must be considered that any potential for risk with the use of less stringent ethical procedures would be far outweighed by the benefits that carrying out the comparative study would provide to schizophrenia research.

The clinical services systems available for the various facilities differed with respect to the method of storing patient records and the use of a coding system. While all control subjects could be systematically drawn from facilities using a diagnostic coding system for the computerized databases, only cases from Sunnybrook and Whitby could be ascertained in this way. The method of obtaining the other case subjects from HSC and Youthdale through manual searches based on the recollection of clinicians most likely did not result in the ascertainment of all eligible cases
from these sites. This is especially the case for Youthdale in which the clinicians attempted to recall patients only from 1996 to 1998. Cases that were recalled from these sites may have likely been more severe or had a longer duration of contact with the facility. With the unsystematic ascertainment of the one case from Clarke based on a referral, it is likely that there are other eligible cases at this site who were missed. Thus, it is very likely that the cases obtained from these sites were not representative of all eligible cases.

The method of storing clinical records also had an effect on the type of patients ascertained. Only adult-onset schizophrenic patients with an inpatient admission were included in the control group while childhood-onset schizophrenic patients having both inpatient and outpatient admissions were included in the case group. This was due to the fact that the computerized patient lists that were drawn up for all facilities except HSC and Youthdale only included inpatient admissions, while outpatients at such facilities could only be ascertained through manual searches. Thus, any potential eligible subjects who only had outpatient admissions from such facilities would have been excluded. Outpatients were included as part of the study population only for HSC and Clarke (children seen at Clarke were admitted as outpatients). Many of the cases from HSC were outpatients as the psychosis clinic provided more short-term inpatient services and usually referred those who required longer term treatment to more chronic care facilities such as Whitby. Depending on the number of excluded outpatients who were eligible for the study, this may have impacted on the study findings if there were differences with regard to the quality of data in outpatient vs. inpatient records. Also, the inclusion of all eligible outpatients in the study population may have increased the numbers of subjects available to meet the sample size requirements for the comparative study.
In addition to the limitations related to administrative and ethical procedures discussed above, there are a number of methodological limitations within the present study indicating that the findings, although suggestive, should not be considered definitive. One potential problem with the design of the study involves the selection of cases and controls. In this study, incident and prevalent cases that had been diagnosed at HSC, Youthdale, and Whitby over a specified time period were selected. For cases such as these who are diagnosed from certain selected facilities, it is not often possible to specify the population from which they arose. As such, the most appropriate controls would come from the same hospitals/facilities as the cases where they would be subject to the same selective factors. Since this was not entirely possible in the present study given that two of the selected sites (i.e. HSC and Youthdale) provide services exclusively to children, the hospitals from which controls were drawn were selected as they were also in the GTA. As it is known that the catchment areas served by the study sites all include Toronto, it is possible that the cases and controls came from this same catchment area, and would have thus been subject to similar selective factors. However, the possibility that bias would be introduced due to selection factors related to cases and controls coming from different facilities should still be considered.

Another limitation of the study design arises from the fact that cases and controls came from populations of different time periods. Since cases were admitted between 1988 to 1998 and controls were admitted between 1993 to 1996, the earliest year of birth for cases would have been 1973, while controls would have been born between the years 1934 to 1978. With such a design, possible changes in the rate of OCs occurring over time could have an effect on the results of the comparative study as the two groups would be coming from populations having different risks for
OCs. Depending on whether there is an increase or decrease in the rate of OCs over time, this could lead to bias in either direction. Thus, strong assumptions about the rate of OCs in Canada remaining constant over say, the last 50 years, would be required to provide support to the validity of the design. The testing of such assumptions, however, may not be possible as any statistical data available would most likely consist of the rates of only certain birth outcomes and would not take into account the majority of other obstetric complications.

The unsystematic ascertainment of cases from the various sites, as discussed above, is another limitation of the study as it involves the potential for selection bias. As a justification for the use of such cases, however, it can be said that for the purposes of this study, the finding of cases for such a rare population was more important than the fact that they may not be representative of the hospital populations. Even so, cases that might have been missed at one of the sites may have been ascertained at another study site. For example, since patients under 18 years of age who are assessed at the Clarke would be referred to one of the hospitals with a child or adolescent psychiatry program, it is likely that most of the other childhood-onset schizophrenia cases, if not ascertained at the Clarke, would have been captured at the other hospitals used in this study. Thus, the incomplete ascertainment of cases at the sites would be unrepresentative of all cases at those sites, but the total childhood-onset schizophrenic sample ascertained could still be quite representative of all childhood schizophrenic patients seen at the hospitals used in the study.

Another problem arises from the use of diagnostic information in the psychiatric chart records to identify case and control subjects. Diagnoses of schizophrenia obtained from hospital records have been shown to have poor reliability in comparison with research diagnoses (Robins et al., 1982; Erdman et al., 1987; Fennig et al., 1994). Moreover, diagnostic variability has been shown
to exist among different hospitals as well as physicians (Kelsey et al., 1986). An attempt was made in this study, however, to minimize the problem of inadequate and unreliable diagnostic data by including as subjects only those whose charts provided a physician confirmed diagnosis of schizophrenia with details of symptoms which supported the diagnosis. While the reliability of the diagnoses made based on such information in the charts was not actually tested in this study, a reasonable approach to doing this would be to have another diagnostician examine a random sample of all reviewed charts, using the same information to determine whether a diagnosis of schizophrenia could be made.

A final limitation of this study comes from the fact that the principal investigator of the study was not blind to the disease status of subjects. This may have influenced the manner in which information was abstracted from the psychiatric charts and birth records. Such a bias in obtaining information could have distorted the present study's findings pertaining to the quality of the OC exposure data in the charts and birth records for cases and controls. The extent of this bias, however, could be lessened by the fact that uniform data collection procedures were used for all subjects.

In summary, based on the different aspects of feasibility addressed, it is unlikely that a multi-site study that compares the OC histories among individuals with childhood-onset schizophrenia vs. adult-onset schizophrenia can be carried out in the Greater Toronto Area. This is mainly due to the lack of adequate cases in the study population of the sites used as well as the low response rate of eligible cases. Even if the comparative study was technically feasible with respect to overall sample size, there are problems related to poor quality of diagnostic and obstetrical data in the psychiatric charts, as well as difficulties in obtaining birth records, especially for control
subjects. It is reasonable to assume that for such a study, OC exposure information can be obtained when either psychiatric charts and/or birth records or psychiatric charts alone are used as sources of OC data. However, the poor quality of OC data in the psychiatric charts, as well as the potential for bias in the ascertainment and reporting of OC data among cases and controls quite clearly indicates that although available, the OC data from the psychiatric charts would not be useful for the comparative study. Within the design of the present study, there is a fairly strong potential for bias due to cases and controls coming from populations of different time periods, the unsystematic ascertainment of cases and controls, and different data collection procedures existing among various facilities.

The above limitations to carrying out the comparative study might be addressed in a number of ways. Possible ways to increase the number of cases for the study would be to also include facilities outside of the Greater Toronto Area, and to ascertain cases from even earlier years. Also, the sample size requirements for cases could be lowered while still maintaining adequate power by increasing the number of controls. More follow-up procedures could be carried out (e.g. sending out a postcard reminder) to increase the response rate and possibly the number of birth records obtained. To deal with the problem of obtaining useable OC data, other possible sources of OC information could be considered. An interview with the mother or a standardized questionnaire that is mailed out could be used to ascertain obstetrical information, and may reduce the possibility of bias resulting from different data collection procedures that exist among various sites.

There are obvious limitations related to the retrospective design of the present study in exploring the question of the relevance of OCs in childhood-onset vs. adult-onset schizophrenia.
Another possible way to examine this question would be to design a case-control study in which cases and controls enter the study as they are diagnosed over time until a sufficient number of subjects meeting the sample size requirements could be obtained. This may resolve the problem of unsystematically ascertaining cases from many years back leading to an unrepresentative sample of cases. Moreover, it would be easier to locate subjects to request their consent to participate in the study if they were prospectively ascertained. The fact that cases and controls are incident diagnosed would also provide assurance that controls did not actually have an onset of schizophrenia in childhood. The only problem with ascertaining incident cases, however, is the usual need for longitudinal follow-up in children before a definitive diagnosis of schizophrenia can be made (McClellan & Werry, 1994). Although there are some clear advantages to using such a prospective design, one important drawback would be the number of years that would be required to carry out the study given that childhood-onset schizophrenia is so rare.

In conclusion, the proposed comparative study of obstetric complication histories of individuals with childhood-onset schizophrenia vs. adult-onset schizophrenia is not necessarily unfeasible in an absolute sense, but would not be feasible based on the assumptions, design, resources, and determinants of feasibility used in the present study. It is expected that the findings from the present study would help to initiate alternative ways to conduct a meaningful comparative study. By using wider recruitment efforts, extending the time period for recruiting cases, increasing the number of controls, and also by using standardized methods, such as interviewing the mother to obtain useable OC data, it is possible that the comparative study could be carried out. In addition to being helpful in designing a comparative study that would be feasible to carry out, the present study could also aid in the design of other studies that involve the use of childhood-onset and
adult-onset schizophrenic subjects, and/or the use of psychiatric charts and hospital birth records. The importance of elucidating the nature of the relationship between OCs and schizophrenia cannot be stressed enough as such findings would certainly have major implications with respect to the prevention and treatment of this disorder that is of a serious public health concern.
REFERENCES


APPENDIX A

DSM-IV Criteria for Schizophrenia

A. Characteristic Symptoms:
   Two or more of the following, each present for a significant portion of time during a 1-month period (or less if successfully treated):
   (1) delusions
   (2) hallucinations
   (3) disorganized speech (e.g. frequent derailment or incoherence)
   (4) grossly disorganized or catatonic behaviour
   (5) negative symptoms (i.e. affective flattening, alogia, or avolition)

Note: Only one Criterion A symptom is required if delusions are bizarre or hallucinations consist of a voice keeping up a running commentary on the person's behaviour or thoughts, or two or more voices conversing with each other.

B. Social/Occupational Dysfunction:
   For a significant portion of the time since the onset of the disturbance, one or more major areas of functioning such as work, interpersonal relations, or self-care are markedly below the level achieved prior to the onset (or when the onset is in childhood or adolescence, failure to achieve expected level of interpersonal, academic, or occupational achievement).

C. Duration:
   Continuous signs of the disturbance persist for at least 6 months. This 6-month period must include at least 1 month of symptoms (or less if successfully treated) that meet Criterion A (i.e. active-phase symptoms), and may include periods of prodromal or residual symptoms. During these prodromal or residual periods, the signs of the disturbance may be manifested by only negative symptoms or two or more symptoms listed in Criterion A present in an attenuated form (e.g. odd beliefs, unusual perceptual experiences).

D. Schizoaffective and Mood Disorder Exclusion:
   Schizoaffective Disorder and Mood Disorder with Psychotic Features have been ruled out because either: (1) no Major Depressive, Manic, or Mixed episodes have occurred concurrently with the active-phase symptoms; or (2) if mood episodes have occurred during active-phase symptoms, their total duration has been brief relative to the duration of the active and residual periods.

E. Substance/General Medical Condition Exclusion:
   The disturbance is not due to the direct physiological effects of a substance (e.g. a drug of abuse, a medication) or a general medical condition.

F. Relationship to a Pervasive Developmental Disorder:
   If there is a history of Autistic Disorder or another Pervasive Developmental Disorder, the additional diagnosis of Schizophrenia is made only if prominent delusions or hallucinations are also present for at least a month (or less if successfully treated).

Source: American Psychiatric Association, 1994
APPENDIX B

August 28, 1998

<Clinician's Name>
Whitby Mental Health Centre
700 Gordon Street
Whitby, Ontario L1N 5S9

Dear <Clinician's Name>:

Re: <Patient's Name, Date of Birth>

I am a student in my fourth year of a Master of Science program in Epidemiology at the University of Toronto. Under the supervision of Dr. Joseph Beitchman, Head of the Child and Family Studies Centre at the Clarke Institute of Psychiatry, I am conducting a research study on the relationship between pregnancy and birth complications and the subsequent development of schizophrenia.

More specifically, my study will determine whether it is feasible to carry out a comparative study of obstetric complication histories of persons with childhood-onset schizophrenia versus adult-onset schizophrenia. My study proposal has been approved by the University of Toronto Department of Psychiatry Review Committee as well as the Whitby Mental Health Centre Ethics Review Committee.

I am writing to you as I require some information on the above named patient who has been given a diagnosis of schizophrenia. My study involves the abstraction of obstetric information from patient psychiatric charts, as well as from hospital birth records. In order to obtain such information, the patient's consent is required. (Enclosed is a copy of the introductory letter as well as the consent form that will be sent to the patient.) Due to the nature of the patient's illness, I am requesting that you provide me with an opinion on whether you feel that the patient is capable of consent or if there would be any contraindications to sending out such a request to the patient.

I can be reached by any of the means below. Please do not hesitate to contact me if you have any questions.

Thank you for your time and consideration.

Yours truly,

Lorena Hsu
c/o Dr. Joseph Beitchman
Clarke Institute of Psychiatry
250 College Street
Toronto, ON M5T 1R8
Telephone: (416) 979-4747, ext. 2495

Enclosures
APPENDIX C

January 13, 1999

Dear <Patient’s Name>:  

We are writing to you to ask your help with a research project. As you are aware, you have been seen at a hospital or clinic in the past for problems related to your mental health. From the psychiatric chart records of the <Site Name>, you have been identified as a potential participant in a multi-site Master’s research project studying the relation between birth history and mental health problems in children and adults. In order to have retrieved this confidential information from your records, the cooperation and consent of the <Site Ethical Review Committee> was obtained.

The causes of mental illness are unknown but there is evidence to suggest that problems during pregnancy and birth may play a role in some forms of mental illness. Currently, little is known about possible differences in the birth histories of children versus adults with mental illness. Determining whether there are differences in the birth histories between these two groups will be important for understanding the causes of mental illness.

To do this study, we need to obtain birth information from your psychiatric chart records, as well as from your hospital birth records. In light of this, we are asking your permission to obtain a copy of your birth records. In order for you to give your consent to participate in this study and allow us to look at your birth records, you (or an authorized person) and a witness must sign the enclosed consent form and return it to us using the envelope provided. One copy of the consent form is for you to keep. Your consent to allow us to examine your birth records will help to further our understanding of the causes of mental illness, and thus may benefit those who suffer from a mental illness.

Please be assured that all information collected from your psychiatric charts as well as your birth records will be kept strictly confidential and that this information will not identify you in any way.

Your participation is entirely voluntary; whether or not you consent to allow us access to the records requested will have no bearing on any services you are now receiving or may receive in the future from the <Site Name>.

If any of this information is not clear or should you wish to discuss it further, the principal investigator of the study may be reached at the telephone number below.

Thank you for your time and consideration.

Yours truly,

Lorena Hsu, M.Sc. Candidate  
Principal Investigator  
University of Toronto  
Telephone: (416) 979-4747, ext. 2495

Joseph H. Beitchman, M.D.  
Project Supervisor  
Head of Child and Family Studies Centre  
Clarke Institute of Psychiatry

Enclosures
APPENDIX D
CONSENT FORM FOR STUDY

Patient's Name__________________________________________

I have been informed that Lorena Hsu, a student in the Master of Science program specializing in Epidemiology at the University of Toronto, is doing a study on mental health and behavioural concerns in children and adults. Under the supervision of Dr. Joseph Beitchman, Head of the Child and Family Studies Centre at the Clarke Institute of Psychiatry, the study will look at how problems experienced during pregnancy and birth may lead to the later development of mental health and behavioural problems in children and adults.

Children (15 years of age and under) who have been seen at a hospital or clinic for psychoses from the period 1988 to 1998, and adults (18 years of age and over) who have been seen at a hospital or clinic for psychoses from the period 1993 to 1996, are being looked at for this study. I understand that I have been asked to participate because I have been seen at a hospital or clinic for psychosis.

I freely give my permission to take part in this study, understanding that it involves: (1) having information looked at and recorded from my medical records, including personal data, pregnancy and birth history, psychiatric history, and information about my parents' education and employment (2) having a copy of my birth records sent from my birth hospital to the investigator of this study, and having information recorded from my birth records.

I understand that the information collected about me will be kept confidential and that information collected will not identify me in any way.

I understand that I do not have to take part in this study if I do not want to and that I may decide not to be in this study at any time without penalty or without in any way affecting the health care I receive. I understand that there are no special risks involved in being in this study, and that, even though I may not gain anything for myself from this, it is expected that other individuals with mental health problems, as well as the field of psychiatry, will gain something from the study.

I understand that I may ask any questions I have before and during the study. If I have any questions about the study, I may contact:

Lorena Hsu Phone: (416) 979-4747, ext. 2495
c/o Dr. Joseph Beitchman
Clarke Institute of Psychiatry
250 College Street
Toronto, Ontario M5T 1R8

By signing this form, I am indicating that I have had sufficient time to consider the request, to ask questions, and have received answers to those questions to my satisfaction, that I understand the purpose and benefits of this study and that I voluntarily agree to participate.

Name (please print) __________________________ Name and City of Hospital of Birth __________________________

Signature of Authorized Person* __________________________ Date __________________________ Witness __________________________

*If the named person is unable to give free and informed consent, the consent of the substitute decision maker in accordance with the hierarchy of the Health Care Consent Act shall be obtained. Every effort, however, should be made to ensure that the subject understands his or her role in the procedures of the study.
APPENDIX E
CONSENT FORM FOR STUDY

Patient's Name ________________________________

I have been informed that Lorena Hsu, a student in the Master of Science program specializing in Epidemiology at the University of Toronto, is doing a study on mental health and behavioural concerns in children and adults. Under the supervision of Dr. Joseph Beitchman, Head of the Child and Family Studies Centre at the Clarke Institute of Psychiatry, the study will look at how problems experienced during pregnancy and birth may lead to the later development of mental health and behavioural problems in children and adults.

Children (15 years of age and under) who have been seen at a hospital or clinic for psychoses from the period 1988 to 1998, and adults (18 years of age and over) who have been seen at a hospital or clinic for psychoses from the period 1993 to 1996, are being looked at for this study. I understand that I have been asked to participate because I have been seen at a hospital or clinic for child psychoses.

I freely give my permission to take part in this study, understanding that it involves: (1) having information looked at and recorded from my medical charts, including personal data, pregnancy and birth history, psychiatric history, and information about my parents' education and employment; (2) having a copy of my birth records sent from my birth hospital to the investigator of this study, and having information recorded from my birth records.

I understand that the information collected about me will be kept confidential and that information collected will not identify me in any way.

I understand that I do not have to take part in this study if I do not want to and that I may decide not to be in this study at any time without penalty or without in any way affecting the health care I receive. I understand that there are no special risks involved in being in this study, and that, even though I may not benefit individually from this, it is expected that in the future, other individuals with schizophrenia, as well as the field of psychiatry, will gain something from the study.

I understand that I may ask any questions I have before and during the study. If I have any questions about the study, I may contact:

Lorena Hsu
C/o Dr. Joseph Beitchman
Clarke Institute of Psychiatry
250 College Street
Toronto, Ontario M5T 1R8

Phone: (416) 979-4747, ext. 2495

By signing this form, I am indicating that I have had sufficient time to consider the request, to ask questions, and have received answers to those questions to my satisfaction, that I understand the purpose and benefits of this study and that I voluntarily agree to participate.

Name (please print) ____________________________ Name and City of Hospital of Birth ________________

Signature of Authorized Person* __________________ Date ____________________ Witness ________________
*If the named person is unable to give free and informed consent, the consent of the substitute decision maker in accordance with the hierarchy of the *Health Care Consent Act* shall be obtained. Every effort, however, should be made to ensure that the subject understands his or her role in the procedures of the study.

Here is a general rule of thumb proposed by University of Toronto Guidelines regarding minors:

a) if the subject is under the age of 7 years, the consent form must be signed by a parent or guardian

b) if the subject is 7 years of age and over, he/she should be informed of the procedures that are allowed by consent of a parent or guardian

c) if the subject is 11 years of age and over, he/she should be specifically asked for consent to the procedures in addition to the parent or guardian

d) if the subject is 14 years of age and over, he/she should be asked to consent in writing (sign the form)
APPENDIX F
HOSPITAL FOR SICK CHILDREN CONSENT FORM

Name:

Date of Birth:

HSC #:

Title of Research Project:
Mental Health Problems

Investigators:
Lorena Hsu, 4th Year Student in Master of Science Program
Department of Public Health Sciences in Epidemiology
Graduate Department of Community Health
University of Toronto

Dr. Joseph Beitchman (Supervisor)
Head, Division of Child Psychiatry
Hospital for Sick Children

(416) 979-4747, ext. 2495
(416) 813-7524

Purpose of the Research:
The purpose of this study is to find out whether a larger study that would compare the birth histories of children and adults with mental health or behavioural problems is useful to do.

Description of the Research:
In this study, children seen at a clinic for childhood psychoses (15 years of age and under) from the period of 1988 to 1998, and adults (18 years of age and older) who have had a psychiatric admission to a facility from the period of 1993 to 1996, are being looked at.

The study involves a review of your records. Information from your psychiatric records, such as your birth history and psychiatric history, as well as some general information about your family, will be looked at and recorded onto a data collection form.

A copy of your birth records will also be accessed from the hospital where you were born. The information from your birth records will also be reviewed and recorded onto a form.

Potential Harms, Injuries, Discomforts, or Inconvenience:
There are no known harms associated with participation in this study.
Potential Benefits:

You will not benefit directly from participating in this study. However, it is expected that other individuals with mental health or behavioural problems, as well as the field of psychiatry, will benefit from the knowledge gained from the study.

Confidentiality:

Confidentiality will be respected and no information that discloses your identity will be released or published without consent unless required by law. For your information, the research consent form will be inserted in the patient health record.

Participation:

Participation in research is voluntary. If you choose not to participate, you and your family will continue to have access to quality care at HSC. If you choose to participate in this study, you can withdraw from the study at any time. Again, you and your family will continue to have access to quality care at HSC.

Consent:

I acknowledge that the research procedures described above have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at The Hospital for Sick Children for me and for other members of my family. As well, the potential harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to me and my care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law.

I hereby consent to participate.

 Name of Patient and Age

Signature (if 16 yrs. or over)

Date

Hospital and City of Birth

Name of Person Who Obtained Consent

Signature

The person who may be contacted about the research is:

who may be reached at telephone #:

Date
Title of Research Project:
Mental Health Problems

Investigators:
Lorena Hsu, 4th Year Student in Master of Science Program
Department of Public Health Sciences in Epidemiology
Graduate Department of Community Health
University of Toronto

Dr. Joseph Beitchman (Supervisor)
Head, Division of Child Psychiatry
Hospital for Sick Children

Purpose of the Research:
The purpose of the study is to find out whether a larger study that would compare the birth histories of children and adults with mental health or behavioural problems is useful to do.

Description of the Research:
In this study, children seen at a clinic for childhood psychoses (15 years of age and under) from the period of 1988 to 1998, and adults (18 years of age and older) who have had a psychiatric admission to a facility from the period of 1993 to 1996, are being looked at.

The study involves a review of your child's records. Information from your child’s psychiatric records, such as birth history and psychiatric history, as well as some general family information, will be looked at and recorded onto a data collection form.

A copy of your child’s birth records will also be accessed from the hospital of birth. The information from your child’s birth records will also be reviewed and recorded onto a form.

Potential Harms, Injuries, Discomforts, or Inconvenience:
There are no known harms associated with participation in this study.
Potential Benefits:

Your child will not benefit directly from participating in this study. However, it is expected that other individuals with mental health or behavioural problems, as well as the field of psychiatry, will benefit from the knowledge gained from the study.

Confidentiality:

Confidentiality will be respected and no information that discloses the identity of the subject will be released or published without consent unless required by law. For your information, the research consent form will be inserted in the patient health record.

Participation:

Participation in research is voluntary. If you choose not to participate, you and your family will continue to have access to quality care at HSC. If you choose on behalf of your child to participate in this study, you can withdraw your child from the study at any time. Again, you and your family will continue to have access to quality care at HSC.

Consent:

I acknowledge that the research procedures described above have been explained to me and that any questions that I have asked have been answered to my satisfaction. I have been informed of the alternatives to participation in this study, including the right not to participate and the right to withdraw without compromising the quality of medical care at The Hospital for Sick Children for my child and for other members of my family. As well, the potential harms and discomforts have been explained to me and I also understand the benefits (if any) of participating in the research study. I know that I may ask now, or in the future, any questions I have about the study or the research procedures. I have been assured that records relating to my child and my child's care will be kept confidential and that no information will be released or printed that would disclose personal identity without my permission unless required by law.

I hereby consent for my child ________________________________ to participate.

Name of Parent

______________________________
Signature

______________________________
Date

Hospital and City of Birth

Name of Person Who Obtained Consent

______________________________
Signature

______________________________
Date

The person who may be contacted about the research is:

______________________________
who may be reached at telephone #:

______________________________
APPENDIX H
HOSPITAL FOR SICK CHILDREN ASSENT FORM

Name:
Date of Birth:
HSC #:

Title of Study:
Mental Health Problems

Investigators:
Lorena Hsu, 4th Year Student in Master of Science Program  (416) 979-4747, ext. 2495
Department of Public Health Sciences in Epidemiology
Graduate Department of Community Health
University of Toronto

Dr. Joseph Beitchman (Supervisor)  (416) 813-7524
Head, Division of Child Psychiatry
Hospital for Sick Children

Why Are We Doing This Study?:
This study will be done to compare the birth histories of children and adults with mental health or behavioural problems.

What Will Happen During the Study?:
During this study, information from your medical records will be looked at and recorded onto a form. This information includes things such as your age and date of birth, any complications that might have happened while your mother gave birth to you, and whether you have visited a hospital before. Your birth records will also be looked at and the information from these records will also be written onto a form. Other than giving permission to look at your birth records, you will not have to do anything else for the study.
Are There Good Things and Bad Things About the Study?:

There are no special risks involved in being in this study. Even though you may not get any special help from being in this study, other people who have mental health or behavioural problems may be helped from the things that are learned from the study.

Who Will Know About What I Did in the Study?:

Your name will be kept a secret so no one else will know any information about you unless you allow us to give this information out, or if the law asks that you give it out. The consent form that your parents sign will be put in your health record.

Can I Decide If I Want to Be in the Study?:

You will decide if you want to be in the study. If you decide that you don't want to be in the study, you and your family will still be able to have the best possible care at the Hospital for Sick Children. If you decide that you want to be in this study, you can leave the study whenever you want to. Again, you and your family will still be given the best possible care at the Hospital for Sick Children.

Assent:

I was present when ________________________ read this form and gave his/her verbal assent.

________________________________________
Name of Person Who Obtained Assent

________________________________________
Signature

________________________________________
Date
APPENDIX I
DATA COLLECTION FORM

Date form completed: _______________ Subject no.: __________

Name of hospital/facility: _______________ Medical records no.: _______________

A. Subject Identifying Information

Gender: __________ Date of birth: _______________ Health card no.: _______________

Address of subject: ____________________________________________________________

Telephone no. of subject: _____________________________________________________

Next of kin/correspondent: __________________________________ Relationship: __________

Address of next of kin/correspondent: __________________________________________

Telephone no. of next of kin/correspondent: _____________________________________

B. Subject Demographic Information

Place of birth: ___________________________ Hospital of birth: _______________________

Maternal age: ____________________________

Ethnic background of subject: ____________________________________________________

Number of siblings: _______________ Subject's birth order: __________________________

Is the subject adopted? _______________ If yes, at what age? __________________________

Subject's level of education: ____________________________________________________

Subject's employment status: ___________________________________________________

Subject's source of income: _____________________________________________________

Mother's occupation and level of education: _______________________________________

Father's occupation and level of education: _______________________________________
C. Confirmation of Diagnosis

I. Psychiatric Admissions

1. Most Recent Psychiatric Admission:

Name of Hospital/Facility: ____________________________
Admission Date: ___________ Discharge Date: ___________ Age on Admission: ___
Diagnosis(es) Given: ______________________________________
Attending Psychiatrist(s): ______________________________________
Follow-up Details: ______________________________________

2. First Psychiatric Admission:

Name of Hospital/Facility: ____________________________
Admission Date: ___________ Discharge Date: ___________ Age on Admission: ___
Diagnosis(es) Given: ______________________________________
Attending Psychiatrist(s): ______________________________________

3. Other Admissions:

______________________________________________________

II. Description of Symptoms

Thought Content:

Perception:

Thought Form:

Speech:
Mood & Affect:

Social/Occupational Functioning:

Other Features:

D. Obstetrical History

I. Obstetrical Information Obtained through Psychiatric Charts

List source(s) of OC information, date recorded, name of respondent filling out form/reporting information, relationship of respondent to subject, and method of obtaining OC information (ie. interview, form, etc.):

Elicitation of Obstetrical Information from Psychiatric Charts:

Did the chart contain a form/questions concerning the patient's obstetrical history?  Yes____ No____

If yes, did the form include an open-ended request for general OC data?  Yes______ No____

If yes, was this for a particular gestational phase(s)?  Yes_______ No_______

Number of general OC-related items elicited:__________

Number of specific OC-related items elicited:__________
General Obstetric Information from Psychiatric Charts:

What was the duration of labour? ____________________________

What was the subject's gestational age? ______________________

Was the subject born on schedule? Yes____ No____

If no, was the subject: Two weeks or more early? Yes____ No____

Two weeks or more late? Yes____ No____

What was the subject's birth weight? ________________________

List all pregnancy, labour/delivery, and neonatal complications/conditions/events experienced by the subject according to gestational period:

I) Pregnancy Complications/Conditions/Events

II) Labour and Delivery Complications/Conditions/Events

III) Neonatal Complications/Conditions/Events
II. Obstetrical Information Obtained from Hospital Birth Records

Name of institution where birth records were obtained: ____________________________

Elicitation of Obstetrical Information from Birth Records:

Did the record include an open-ended request for general OC data? Yes_______ No_______

If yes, was this for a particular gestational phase(s)? Yes_______ No_______

Number of general OC-related items elicited: ______________

Number of specific OC-related items elicited: ______________

General Obstetric Information from Birth Records:

What was the duration of labour? ______________________

What was the subject's gestational age? __________________

Was the subject born on schedule? Yes_______ No_______

If no, was the subject: Two weeks or more early? Yes_______ No_______

Two weeks or more late? Yes_______ No_______

What was the subject's birth weight? ______________

List all pregnancy, labour/delivery, and neonatal complications/conditions/events experienced by the patient according to gestational period:

__________________________________________________________________________

1) Pregnancy Complications/Conditions/Events
II) Labour and Delivery Complications/Conditions/Events

III) Neonatal Complications/Conditions/Events
December 15, 1998

<Birth Hospital>
<Address>
<City>, <Province> <Postal Code>
Attention: Medical Records Dept.

Dear Sir/Madam:

Re: <Patient’s Name>, <Patient’s Date of Birth>

We are writing to you to request a copy of <Patient’s Name> birth records from your facility. The purpose of our request is to use this information for a Master’s research project studying the relation between birth history and mental health problems in children and adults. The study has been granted approval by the University of Toronto Department of Psychiatry Review Committee.

Please find enclosed a signed consent form authorizing release of information from your records to the principal investigator of the study.

The birth records of the above named may be forwarded to:

   Lorena Hsu
   c/o Dr. Joseph Beitchman
   Clarke Institute of Psychiatry
   250 College Street
   Toronto, Ontario  M5T 1R8

If you require additional clarification regarding our information request, please do not hesitate to contact the principal investigator by any of the means below. Your prompt attention to this matter would be greatly appreciated.

Thank you for your time and consideration.

Yours truly,

Lorena Hsu, M.Sc. Candidate
Principal Investigator
University of Toronto
Phone: (416) 979-4747, ext. 2495

Joseph H. Beitchman, M.D.
Project Supervisor
Head of Child and Family Studies Centre
Clarke Institute of Psychiatry

Enclosure