SCHIZOPHRENIA IN CAMBERWELL, 1965-1984

by

David Jonathan Castle MB ChB MSc MRCPsych

submitted in fulfilment of the requirements for the degree of

Doctor of Medicine (MD)

University of Cape Town

May 1995

DECLARATION

I, David Jonathan Castle, hereby declare that the work on which this thesis is based is my original work (except where acknowledgements indicate otherwise) and that neither the whole work nor any part of it has been, is being, or is to be submitted for another degree in this or any other University.

I empower the University to reproduce for the purposes of research either the whole or any portion of the contents in any manner whatsoever.

Signed 6.6.95

David J Castle date

SUPERVISOR

I am most grateful to Professor Robin M Murray, Professor of Psychological Medicine, Kings College Hospital and Institute of Psychiatry, De Crespigny Park, London, SE5 8AF, who acted as overall supervisor of this Thesis.

CONTENTS

ABSTRACT

This Thesis describes the epidemiology of schizophrenia and related disorders in the defined catchment area of Camberwell, SE London, UK, over the period 1965 to 1984. Cases were ascertained through the comprehensive Camberwell Cumulative Psychiatric Case Register. All first-contact patients with a Register diagnosis of any non-affective non-organic psychotic illness were included in the study. Diagnostic uniformity was ensured by rediagnosis of all cases (n=531) using the computerised OCCPI system, which facilitates rediagnosis according to a wide range of diagnostic criteria.

Trends in the incidence of non-affective functional psychoses over the two decades during which the Camberwell Register was operational, are explored. The findings, of a rising rate of illness in Camberwell, are discussed in terms of changes in the demography of the general population over the years, and suggestions offered for discrepancies with other studies of time trends in schizophrenia, particular emphasis being placed on changes in the ethnic composition of Camberwell over this period. A case-control study design is used to explore whether the rising incidence of the illness in the area is due solely or largely to drift into the area of ill individuals, or whether some of the variance can be explained in terms of a pernicious inner-city effect operating during early development (in utero or in early childhood). The findings of an excess of schizophrenia patients actually having been born in the inner city suggests that something about poor households in the inner city might predispose to the illness in later life. This is discussed in the general framework of the neurodevelopmental hypothesis of schizophrenia, which proposes that at least some individuals have a form of illness consequent upon subtle damage to the developing brain.

A major focus of the analyses is gender differences in schizophrenia, and late onset schizophrenia. Early-onset males were particularly likely to fulfil stringent diagnostic criteria for the illness, and to show premorbid dysfunction. The results are interpreted in the neurodevelopmental framework, and reference made to differences in male and female brains in their vulnerability to neurodevelopmental illnesses in general. Taking this theme forward, a form of factor analysis called latent class analysis is used to further explore the notion of different subtypes of schizophrenia, one of which is an early-onset severe male-predominant form (theoretically consequent upon neurodevelopmental deviance). The analyses resulted in a "best fit" model of three subtypes, one an early-onset male-predominant type associated with premorbid dysfunction ("neurodevelopmental" type); a later-onset "paranoid" type; and an affect-laden type exclusive to females ("schizoaffective" type). There were associations with a number of variables of potential importance in terms of aetiology, namely an association of the "neurodevelopmental" type with a family history of schizophrenia and obstetric complications; an association of the "paranoid" type with winter birth; and of the "affective" type with a family history of psychiatric disorder other than schizophrenia (predominantly affective disorder). This typology does not adequately account for those patients with a late- (over 45 years), or very-late onset of illness (over 60). Phenomenological, premorbid, and other differences between early- and late-onset patients are analysed, and the results discussed in the broader framework of the literature on late-onset non-affective psychoses.

PREAMBLE: THE EPIDEMIOLOGY OF SCHIZOPHRENIA

Schizophrenia has fascinated and puzzled researchers for nearly a century since Kraepelin (1896) suggested a dichotomy between "dementia praecox" and manic depressive psychosis; it was Bleuler (1911) who applied the label "schizophrenia", referring to the "splitting" of psychic function which he thought to be of central importance.

Schizophrenia is characterised by certain symptoms, which may usefully be divided into "positive" and "negative". Positive symptoms, which tend to be episodic, include thought intrusion, thought withdrawal, thought broadcast, delusions of control, and auditory hallucinations, characteristically voices commenting on the afflicted individual, or discussing him or her, often in a derogatory manner. These symptoms were suggested by Schneider (1959) to be useful in delineating the illness, though identical phenomena can occur in both mania and organic psychoses.

"Negative" or "deficit" symptoms, such as affective flattening, avolition, and anhedonia, were considered by Kraepelin to reflect a residual state after episodes of positive symptomatology. More recently, it has been suggested that positive and negative symptoms reflect different aetiological processes (Crow, 1986), but attempts to confirm this experimentally have met with mixed success.

The aetiology of schizophrenia:

There is little doubt that schizophrenia runs in families. Gottesman and Shields (1982), in reviewing the literature, suggested an overall risk of schizophrenia in the first degree relatives of a proband with schizophrenia to be around 10%; this compares with a risk of around 1% in the general population. Twin studies (reviewed by Kringlen, 1987; and Kendler, 1993) and adoption studies (see Rosenthal et al, 1971; Kety et al, 1975) have shown that much of this familial aggregation is due to genetic factors. More recent work, including a population-based family study (Kendler et al, 1993) has suggested that schizotypal personality disorder is also genetically related to schizophrenia.

Familial, twin, and adoption studies are in accord in reporting that not all cases of schizophrenia are genetically determined. "Environmental" factors which have attracted attention as possible causes of schizophrenia include obstetric complications (see Lewis & Murray, 1987), early head injury (Wilcox & Nasrallah, 1987), and in utero exposure to influenza infection (reviewed by McGrath & Castle, 1995).

Attempts to explain away at least some of the findings of familial aggregation in schizophrenia in terms of abnormal family interactions, have not revealed consitent or compelling findings. Thus, the theories of Fromm-Reichman ("schizophrenogenic mother"), Lidz ("schizm" and "skew"), and Bateson ("double bind") have never been convincingly experimentally validated (for a review, see Murray, 1979). The abnormal familial interaction patterns in schizophrenia shown by Singer and Wynne (1966) were not replicated in a subsequent rigorous study in the United Kingdom (Hirsch & Leff, 1975), and indeed, any such studies are bedevilled by difficulties in

distinguishing cause from effect.

Having said this, there is little doubt that current life-stresses can precipitate psychotic relapse in predisposed individuals. Brown and Birley (1968) found an excess of significant life events in the 3 month period preceding hospital admission in a group of schizophrenia patients, and went on to show that schizophrenia patients living with relatives who express critical comments, hostility, or overinvolvement, are particulalrly prone to relapse (Brown et al, 1972). This finding of higher relapse in so-called "high expressed emotion" families, has been replicated by a number of investigators, notably Vaughan and Leff (1976). Again, it should be stressed that such factors serve as precipitants of relapse in predisposed individuals, rather than being causal.

Epidemiology of schizophrenia:

Schizophrenia remains a major mental health problem. The annual prevalence in 12 countries was estimated as from 2 to 4 per 1000 population (Jablensky & Sartorius, 1975), and the morbid risk at birth is of the order 1%. The positive symptoms can often be controlled by antipsychotic drugs, but despite these agents, many afflicted individuals experience a decline in their social and occupational functioning which can be devastating to both themselves and their families.

Study of the epidemiology of diseases is vital for the determination of the extent of the problem, secular trends in incidence, and ascertainment of particular high risk groups. Without this knowledge, effective health-care planning and delivery cannot be achieved. Furthermore, epidemiological knowledge can potentially contribute to the search for causes of diseases such as schizophrenia, at least at the level of generating plausible hypotheses on the basis of

distribution of patterns of morbidity in relation to environmental and genetic factors (see Hafner, 1992). Thus, it is important that epidemiological studies of schizophrenia are methodologically rigorous, ensuring complete (or at least unbiased) case-finding, and accurate, reliable diagnosis of illness. Many earlier studies do not meet these standards, as is detailed below.

Problems in schizophrenia epidemiology research:

One of the problems to bedevil much early research in schizophrenia was a lack of diagnostic uniformity, which made comparison between studies almost impossible. For example, a diagnosis of schizophrenia was much more loosely applied in the US than the UK, leading to the quip that the easiest cure for the disease was a trans-Atlantic flight. Indeed, the US/UK diagnostic project (Cooper et al, 1972) investigated rates of schizophrenia and manic depression in the two countries using standardised criteria, and concluded that most of the previously reported difference in rates was due to variations in diagnostic practice. Latterly, the advent of operationalised criteria for schizophrenia (eg. Feighner criteria (Feighner et al, 1972), Research Diagnostic Criteria (RDC; Spitzer et al, 1978), DSM-III (APA, 1980), DSM-IIIR (APA, 1987)) and standardised interviews (eg. Present State Examination (PSE; Wing et al, 1974), Schedule for Affective Disorders and Schizophrenia (SADS; Endicott, 1978), Schedule for the Assessment of Positive Symptoms (SAPS; Andreasen, 1983a), Schedule for the Assessment of Negative Symptoms (SANS; Andreasen, 1983b)) have resulted in far more consistency in schizophrenia research in general. However, one difficulty with reliance on operationalised criteria is that, while showing good reliability, they are not necessarily valid, and their continued widespread use might result in the tacit acceptance that they are. Also, different sets of criteria emphasise different aspects of the illness (eg. 2 weeks duration in RDC vs. 6 months in DSM-IIIR; early onset of illness and family

history of schizophrenia in Feighner's criteria), and this needs to be born in mind when conclusions are drawn.

The second major problem area in epidemiological investigations in schizophrenia is that of case-finding. Most studies have been based on hospital admissions, which are themselves subject to variations in service provision and admission policies. Reliance on admission statistics alone leads to bias from the inclusion of re-admissions. For example, more severely affected patients are more likely to be re-admitted, confounding work in such areas as gender differences in schizophrenia as males tend to have a more severe form of illness, resulting an exaggerated male:female ratio in hospitalised samples. The inclusion of only first admissions is methodologically more sound, but biases still arise. For example, more severely affected patients are more likely to be admitted per se, as are those with a history of violence or disturbed behaviour.

Thorough case-finding can be assured only by covering all caring agencies, or by doing population screens. An example of the former strategy was that employed in the WHO Collaborative Study (see Sartorius et al, 1986), which ascertained all psychiatric contacts with any caring agency in 10 countries. The 5-centre Epidemiological Catchment Area Survey (ECA) in the US (see Keith et al, 1991) is an example of population screening. Of course, these sorts of study require enormous financial and organisational input. Also, diagnostic issues remain troublesome. Thus, while the WHO study used the PSE administered by trained psychiatrists, the ECA resorted to lay interviewers using the Diagnostic Interview Schedule (DIS), which has been shown to be over-inclusive with respect to schizophrenia. Furthermore, such investigations

are either cross-sectional or cover relatively brief periods of time.

Case registers, which record all first contacts with the psychiatric services for a specified area over a specified time-period, are a very useful resource, particularly for the determination of incidence rates for severe mental illness. In countries without a comprehensive health service, it might be anticipated that a number of patients, even with severe mental illness, never come into contact with the mentla health services. There is an added problem for the accuracy of case registers in countries where a substantial proportion of psychiatric practice is in the private sector; private psychiatric facilities are often not linked to case registers. However, in a country like England, with a comprehensive National Health Service, most patients with a severe mental illness such as schizophrenia will eventually have contact with the psychiatric services; for example, Cooper et al (1987), in Nottingham, found the majority of patients with schizophrenia had made contact with the psychiatric services within two years of illness onset. Thus, in practical terms, in countries like England, with a well-developed health service, case registers can be expected to provide an accurate reflection of psychiatric morbidity over prolonged periods.

CHAPTER 1: OVERVIEW AND AIMS

Given the problems in epidemiological research in schizophrenia, and the potential advantages of using a comprehensive case register to address epidemiological issues, I employed the Camberwell Psychiatric Case Register, established by Professor John Wing and colleagues in the 1960's to record contacts with the psychiatric services of the Camberwell catchment area over 2 decades. Regrettably the Register ceased to function in 1984, precluding analysis of trends in schizophrenia in more recent years.

Main aims:

The main theme of my Thesis is an exploration of how a case-register strategy might best be employed to address important current epidemiological issues in schizophrenia research, by exploiting the fact that the sample of patients is not biased by such parameters as admission to hospital, or chronicity.

In particular, I wished to assess:

(1) What biases would have been introduced had the study been based exclusively on patients actually admitted to hospital, and the implications for studies which have been confined to such patients;

(2) Whether the incidence of operationally-defined schizophrenia had changed in inner-city Camberwell in line with a reported decline for England as a whole, and if not, how such a discrepancy can be explained;

(3) Whether previous findings of a particular predisposition of individuals of Afro-Caribbean extraction in Britain, to schizophrenia, could be replicated in an epidemiologically-based sample of patients in whom the illness is operationally defined;

(4) Whether individuals born into a deprived households in the inner city are at increased risk of later development of a schizophrenic illness (relative to neurotic disorders);

(5) To explore gender differences in schizophrenia in a sample of first-contact patients not pre-selected according to age-at-onset, severity of illness, or chronicity; particular areas of interest included:

(i) whether more males than females fulfil stringent diagnostic criteria for schizophrenia;

(ii) whether males are particularly likely to exhibit premorbid dysfunction;

(iii) whether non-affective functional psychoses can usefully be subtyped according to gender;

(iv) whether any such typology has relevance for aetiological models of schizophrenia;

(6) to describe the epidemiology of late-onset schizophrenia in a comprehensive sample of patients of all ages from a defined catchment area;

(7) to explore similarities and differences between patients with an early- and late-onset of schizophrenia.

Operational definitions and the OCCPI system:

One of the major drawbacks of case registers is the reliance on coded clinicians diagnosis, and there is evidence, particularly from the USA, that psychiatric diagnostic habit is often victim to the prevailing dictums regarding diagnosis in general, and diagnostic criteria in particular. Thus, whilst the evolution of sets of operationalised diagnostic criteria have, as detailed in the **Preamble** to this Thesis, undoubtedly lent consistency and uniformity to the application of psychiatric labels to particular patients, the introduction of each new set of criteria potentially results in a shift in diagnostic practice amongst psychiatrists (psychiatry being such an imprecise science, and the features which constitute a diagnosis being so much the subject of debate).

Thus, it seemed imperative to ensure diagnostic uniformity in the sample to be studied, to allow meaningful conclusions to be drawn, and comparisons across studies made. The evolution of the computerised OCCPI system (detailed in Chapter 2 and Appendix 3) for rediagnosing psychiatric patients according to a wide range of diagnostic criteria, was a vital resource for this study. Of course, there remains the difficulty of retrospective gleaning of information from case records, but happily, patients in the catchment area had been admitted to the Maudsley/Bethlem Royal or affiliated hospitals and there is a strong tradition of excellence in psychiatric history-taking and recording in these establishments. Also, it is fair to say that, despite changes in the view of what should constitute a diagnosis of "schizophrenia", all sets of diagnostic criteria are firmly rooted in, and reliant upon, phenomenology, and the description of phenomenological variables has not changed over the years.

Overview of the Thesis:

To place the study in context, **Chapter 2** provides an overview of the Camberwell catchment area is provided, detailing changes in the demography of the area over the years of the study. Particular emphasis is place on socio-economic variables, and on the changes in ethnic composition of the area, as these parameters have particular relevance for the current study, as discussed below.

Chapter 2 also details the methodology employed, namely a rediagnosis of all cases of schizophrenia and related conditions using current operationalised diagnostic criteria. A number of demographic, premorbid, and forensic parameters were also recorded, along with details of substance use. A family history of psychiatric illness in general, and schizophrenia in particular, was also noted.

Chapter 3 serves to introduce the database, providing an overview of the patients, how many were excluded from the study and for what reasons, and how many fulfilled different sets of diagnostic criteria.

A further introduction to the database is served by an analysis of the potential bias which might have arisen had the study been confined only to those patients actually admitted to hospital at first psychiatric contact. Trends in admission practice over the two decades of the study are analysed, parameters predictive of admission explored, and the implications of the results for studies based solely on inpatients, discussed. This also points up one of the methodological strengths of the current study, being as it is based on all contacts with the psychiatric services, and not just those

patients admitted to hospital.

Chapter 4 introduces a discussion of trends in the incidence of non-affective functional psychoses over the two decades during which the Camberwell Register was operational. The Register offered a unique opportunity to explore this important issue in a study designed to preclude the confounding effects of changes in admission policies (all contacts with the services being included), and of changes in diagnostic habit over the years (by the use of uniform diagnostic criteria, as outlined above). The findings, of a rising rate of illness in Camberwell, are discussed in terms of changes in the demography of the general population over the years, and suggestions offered for discrepancies with other studies of time trends in schizophrenia. Particular emphasis is placed on changes in the ethnic composition of Camberwell over this period.

The demography of inner-city Camberwell is again the focus of **Chapter 5**, where a case-control study design is used to explore whether the rising incidence of the illness in the area is due solely or largely to drift into the area of ill individuals, or whether some of the variance can be explained in terms of a pernicious inner-city effect operating during early development (in utero or in early childhood). Thus, cases and controls (controls being the next person on the Register matched for sex and age, but who did not attract a psychotic diagnosis), were analysed regarding place of birth and occupation of their father at the time of the birth, as a measure of the socio-economic environment into which they were born. The findings of an excess of schizophrenia patients actually having been born in the inner city suggests that something about poor households in the inner city might predispose to the illness in later life. This is discussed in the general framework of the neurodevelopmental hypothesis of schizophrenia, which proposes that at least

some individuals have a form of illness consequent upon subtle damage to the developing brain. Such damage might be caused by obstetric complications, early head injury, or exposure of the pregnant mother to the influenza virus; all of these factors might be expected to be more prevalent in deprived inner-city households.

The neurodevelopmental hypothesis is the linking theme to the next three chapters, on gender differences in schizophrenia, and late onset schizophrenia. The literature on gender differences in schizophrenia is overviewed in **Chapter 6**, and an hypothesis detailed that males with severe early-onset illness are the individuals most likely to have a neurodevelopmental form of the illness. This hypothesis is then tested using the Camberwell Register sample, with findings that early-onset males were particularly likely to fulfil stringent diagnostic criteria for the illness, and to show premorbid dysfunction. The results are interpreted in the neurodevelopmental framework, and reference made to differences in male and female brains in their vulnerability to neurodevelopmental illnesses in general.

Using rather more sophisticated statistical techniques, namely a form of factor analysis called latent class analysis, the notion of different subtypes of schizophrenia, one of which is an early-onset severe male-predominant form (theoretically consequent upon neurodevelopmental deviance), is explored further in **Chapter 7**. The analyses resulted in a "best fit" model of three subtypes, one an early-onset male-predominant type associated with premorbid dysfunction ("neurodevelopmental" type); a later-onset "paranoid" type; and an affect-laden type exclusive to females ("schizoaffective" type). The typology is discussed in terms of previous attempts at subtyping schizophrenia. Further exploration of the typology revealed associations with a number

of variables of potential importance in terms of aetiology, namely an association of the "neurodevelopmental" type with a family history of schizophrenia and obstetric complications; an association of the "paranoid" type with winter birth; and of the "affective" type with a family history of psychiatric disorder other than schizophrenia (predominantly affective disorder). The typology is proposed as useful for the further investigation of aetiological parameters in the functional psychoses.

The typology described above does not adequately account for those patients with a late- (over 45 years), or very-late onset of illness (over 60). Such patients have often been ignored in the literature, and the current study was ideally placed to assess the characteristics of these patients, being epidemiologically-based, and having sufficient numbers for statistically robust analysis. Phenomenological, premorbid, and other differences between early- and late-onset patients are analysed, and the results discussed in the broader framework of the literature on late-onset non-affective psychoses.

The **concluding chapter** serves as a Summary of the main findings of the Thesis, and suggests directions for further research.

CHAPTER 2. METHODS: GENERAL

This thesis describes various aspects of the epidemiology of schizophrenia and related disorders in the defined catchment area of Camberwell, in South-East London, over the period 1965-1984. To place the findings in context, a brief description of the demography of the area over this period is provided.

The Camberwell catchment area, 1965-1984:

The Camberwell catchment area is a deprived inner-city area in South-East London, England, which is geographically congruent with the Southern portion of the London borough of Southwark (see figure 2.1). The demography of the area changed considerably over the 20 year period (1965-1984) covered by this study. Appendix 1 gives population numbers for the Camberwell catchment area, by sex and age, for each year of the study; the data are derived from small area statistics from the 1961, 1971, and 1981 censuses (100% samples), with interpolations for intermediate years. The total population declined from 171,000 in 1965 to 118,000 in 1984. Overall, however, there has been remarkably little change in the age-structure of the population in the years under study. In 1965, 38% of males and 35% of females were under 25, and 66% of males and 61% of females under 45. The comparable figures for 1984 were: 37% of males and 35% of females under 25, and 65% of males and 61% of females under 45. The male:female ratio also remained stable over the years (48% male in both 1965 and 1984). National figures for England and Wales are very similar; for example, the 1981 census shows that 38% of males and 34% of females were under the age of 25, and 65% and 60%, respectively, under the age of 45.

NORTH

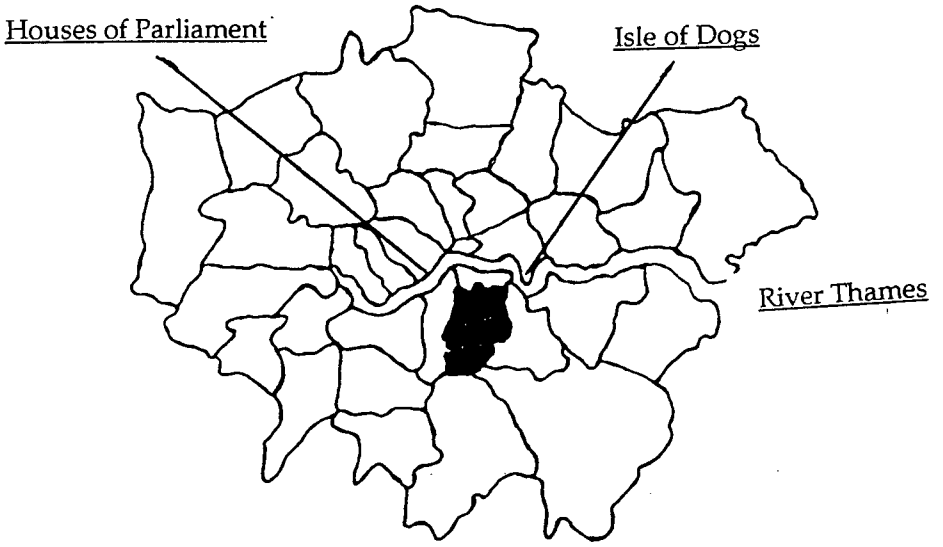

Figure 2.1: Map of Greater-London, showing the extent of the Camberwell catchment area (shaded)

The Camberwell catchment area rates highly on deprivation indices based on such factors as housing tenure and socio-economic status (see Balarajan et al, 1992), and is above average in terms of Jarman indices (SELCA, 1992). An over-representation of individuals in lower socio-economic groupings has been a characteristic of the area. Table 2.1 shows socio-economic groupings for the area in the 1961, 1971, and 1981 censuses. The proportion of individuals in social classes IV and V increased, albeit slightly, over the study period. In contrast, figures for England as a whole show that the proportion of individuals in social classes IV and V declined modestly over this period (see Table 2.1).

In contrast to the decline in the general population over the decades after the 1961 census, there has been a marked growth in the proportion of the population from ethnic minority groups. In particular, there has been an influx into the area of persons born in the Caribbean, the proportion in the general population rising from 2.5% in the 1961 census to 6.6% in the 1981 census. As these individuals came to the UK in their early adulthood, and have subsequently produced children here, the Afro-Caribbean population of Camberwell are generally younger than their (UK-born) Caucasian counterparts.

Sampling frame:

The case-finding strategy was to ascertain all patients with non-affective functional psychoses, from a defined catchment area, who made their first psychiatric contact over a defined period. To achieve this, use was made of the Cumulative Psychiatric Case Register (Wing & Hailey, 1972), which provides a comprehensive list of all persons from the area of Camberwell, who had their first contact with the psychiatric services between 1965 and 1984. A list was generated

Table 2.1: Socio-economic groupings for Camberwell Catchment Area and England as a whole, 1961, 1971 & 1981 censuses

	1961	1966	1971		1981	
Social Class	England	Southwark Borough*	England	Camberwell	England	Camberwell
I	3.8	2.3	5.1	6.2	5.9	5.8
II	15.2	6.2	18.2	6.7	23.0	12.4
III - non manual	) 51.3	18.6	12.3	21.1	12.0	20.0
III - manual		39.3	38.2	36.1	36.1	33.2
IV	20.7	17.8	17.9	15.8	16.8	18.6
V	9.0	15.8	8.3	11.5	6.2	10.0

* the borough into which Camberwell cachment area falls; 1961 small area statistics for SE groupings not available from OPCS

from the Register of all first contacts on the Register in the following diagnostic categories: schizophrenia (equivalent ICD-9 codes 295.0 to 259.9), including schizoaffective disorder (ICD 295.7); "paraphrenia" (ICD 297.2); and "other functional psychoses" (ICD 298.1 to 298.9). The broad range of diagnoses was chosen to avoid preselection according to any specific set of diagnostic criteria or age-at-onset, and to allow for changes in diagnostic habit over time.

The case-records of each patient were obtained from the appropriate hospital or clinic, and all medical, nursing, social work, and occupational therapy notes were scrutinised, as well as all correspondence and accessory information. The quality of the written notes was high, and in most cases a semi-standardised case-summary was also available (Institute of Psychiatry Training Committee, 1973). Patients who had had contact with the psychiatric services prior to 1965 were excluded from further analysis, as were patients in whom there was an obvious organic basis to the illness.

Demographic variables:

For the purposes of the study, a checklist was compiled for completion on each individual. The complete checklist is reproduced as Appendix 2. Specific items of importance to the analyses presented in this dissertation are: sex, age at first psychiatric contact, date of birth, and ethnicity and country of birth of patient and parents. "Ethnicity" categories were Caucasian, Afro-Caribbean, Asian and "other", while "country of birth" categories were UK and Eire, West Indies (Caribbean), Asia, Africa, and "other". These data were recorded directly from the case records; checks on date of contact, date of birth, and country of origin were made from the front sheets of the case records, and the Camberwell Register itself. Checks on ethnicity ratings were made

on a subset of 34 patients, using data from previous direct-interview studies involving these patients; no erroneous ratings were found.

Definitions of illness:

The "Operational Criteria Checklist for Psychotic Illness" or OCCPI, version 2.5 (McGuffin et al, 1991) was completed for each individual. The checklist, reproduced in full as Appendix 3, provides a simple, reliable method of applying multiple operational diagnostic criteria in studies of psychotic illness. Definitions of items follows the Present State Examination (PSE; Wing et al, 1974); the precise definition of each item is given in Appendix 3. The OCCPI 2.5 checklist is allied to a computer software programme, OPCRIT, which generates diagnoses according to operational criteria. For the purposes of the studies conducted for this dissertation, ICD (WHO, 1978) diagnoses were taken as akin to a Register diagnosis of "schizophrenia" (ICD-9 codes 295.0-.9), "schizoaffective disorder" (ICD 295.7), "paraphrenia" (ICD 297.2), or "other non-organic psychosis" (298.1-.9), while RDC (Research Diagnostic Criteria (Spitzer et al, 1978)), DSM-III and DSM-IIIR (Diagnostic and Statistical Manual, 3rd and revised editions (American Psychiatric Association, 1980, 1987)) and Feighner (Feighner et al, 1972) diagnoses were computed using the OPCRIT computer programme. OPCRIT treats missing values as "0".

The author and an independent worker (Dr Simon Wessely, now a senior lecturer and consultant psychiatrist at Kings College Hospital) each rated approximately half the case records. SW was "blind" to the fact that the study was addressing gender issues in schizophrenia. Inter-rater reliability was computed on a random sub-set of 50 case notes which were independently rated by both workers; kappa was 0.82 for RDC diagnoses and 0.76, 0.74, and 0.76 for DSMIII,

DSMIIIR, and Feighner diagnoses, respectively.

Age-at-onset and premorbid variables:

Age-at-onset was recorded as "the earliest age at which medical advice was sought for psychiatric reasons or at which symptoms began to cause subjective distress or impair functioning" (as in OCCPI). Inter-rater reliability (performed by 5 year bands) for "age-at-onset" was excellent (kappa = 0.93). Information relating to marital/cohabiting status at time of contact, and to premorbid social and work adjustment, as well as the presence or absence of abnormal premorbid personality traits was also rated, in accordance with the criteria laid down in the OCCPI. "Premorbid" refers to the period before the onset of illness, as defined above. The criteria for poor premorbid work adjustment take account of poor academic work and of poor performance as a housewife, thus reducing bias relating to early-onset patients (scholars/students) or females (housewives). For the premorbid variables, inter-rater reliabilities (kappa) were: single: 1.0; premorbid work adjustment: 0.65; premorbid social adjustment: 0.64; and personality disorder: 0.60.

CHAPTER 3: DIAGNOSTIC ISSUES AND ADMISSION POLICIES

There were 566 patients on the Register in the appropriate categories. Case records were available on 517 (91%). For six of these patients the case records were of insufficient quality to allow rating, and these were counted as "missing" in further analyses. The number of patients for whom case records were missing differed over the years under study. Thus, in the 1965-1969 cohort, 19 records were missing (14% of the total potential cases in that cohort), 22 (17%) in the 1970-1974 cohort, 11 (8%) in the 1975-1980 cohort, and 3 (2%) in the 1980-1984 cohort. The greater proportion of missing notes in the first decade of the study is due to a number of these notes having been destroyed due to lack of storage space at one of the local hospitals. There is no reason to suspect that this introduced any systematic bias. Specifically, there were no significant differences in the distribution of Register diagnoses, the proportion of males, or the proportion of individuals born outside the UK; also, the age-structure was similar.

Of the 511 available cases, 15 had had previous psychiatric contact elsewhere, or contact before 1965. The Register specifically aimed to exclude such individuals, but the 15 discovered in the "double check", who do not contribute to the incidence rate of schizophrenia, were excluded. In a further six patients, the illness had an obvious organic basis (such as delirium tremens or neurosyphilis), and in a further four, the patient did not receive a psychiatric diagnosis at time of contact. Thus, the final sample comprised 486 valid cases.

Diagnostic criteria fulfilled:

Table 3.1 shows the diagnostic break-down according to RDC, DSM-III, DSM-IIIR and Feighner criteria. The differences in the diagnoses according to the criteria used are of interest in their own right, and have been discussed in detail elsewhere (Farmer et al, 1992). Gender differences in diagnostic criteria fulfilled are presented in Chapter 6. The "no diagnosis" categories are recorded because the OCCPI 2.5 system uses only psychotic diagnostic categories, and the sets of criteria used, do not allocate every case to a diagnostic category. The absence of alcohol and drug-related diagnoses reflects the fact that they are coded separately on the Camberwell Register, and that OPCRIT does not code for them.

ADMISSION POLICIES:

One of the crucial potential advantages of the current study over many of those in the literature is that the sample under consideration consisted of consecutive first contacts rather that relying on admission data. In order to assess the biases which might have arisen had only patients admitted to hospital been considered, the demographic and diagnostic differences between those patients admitted at first psychiatric contact, and those not admitted, were analysed. These analyses are based on the entire sample of 486 valid cases (ie. ICD-9 codes 295, 297.2, 298). Unless otherwise specified, results are presented as risk ratios (RR) with 95% confidence intervals (95%CI).

Trends over time, and demographic variables:

Trends in admission practices over time were assessed by determining the proportion of patients admitted to hospital at first psychiatric contact, by 5-year date bands. The percentage of admitted

RDC	major depression	mania/ bipolar	schizo-affective mania	schizo-affective depression	"broad" schizophrenia	"narrow" schizophrenia		"other"/ no diagnosis
	31 (6.3%)	14 (2.8%)	16 (3.3%)	11 (2.3%)	50 (10.3%)	271 (55.8%)		93 (19.2%)
DSM-III	major depression	bipolar	major affective disorder with psychosis	atypical psychosis	schizophreni-form psychosis	schizophrenia		"other"/ no diagnosis
	8 (1.6%)	1 (0.2%)	44 (9.1%)	181 (37.2%)	74 (15.2%)	158 (32.6%)		20 (4.1%)
DSM-IIIR	major depression	bipolar	schizo-affective disorder	atypical psychosis	schizophreni-form psychosis	schizophrenia	delusional disorder	"other"/ no diagnosis
	10 (2.0%)	1 (0.2%)	59 (12.1%)	94 (19.3%)	53 (10.9%)	196 (40.4%)	51 (10.6%)	22 (4.5%)
Feighner					probable schizophrenia	definite schizophrenia		"other"/ no diagnosis
					87 (17.9%)	157 (32.3%)		232 (49.8%)

Table 3.1: Numbers (percentages) of individuals fulfilling various criteria for functional psychotic illness

patients was 79%, 82%, 77%, and 74% for the 1965-1969, 1970-1974, 1975-1979, and 1980-1984 date bands, respectively (M-H test for trend c^2 1.77; 1df; p=0.18).

Of patients born in the UK/Eire, 80% were admitted at first contact, compared with 75% of those born in the West Indies and 60% of those born in Asia; the differences were not significant, probably because of the small number of Asian-born. Comparison of ethnic Caucasians with ethnic Afro-Caribbeans did not reveal any significant difference in proportion admitted (79% and 78% respectively). The following factors also failed to predict admission to hospital: sex (males 77% females 79%; RR 1.13; 95%CI 0.74-1.74); married/cohabiting status (married/cohabiting 79%; single 78%; RR 0.92; 95%CI 0.59-1.43); and being unemployed (unemployed 78%; employed 79%; RR 0.95; 95%CI 0.60-1.48).

Drug use, police involvement, and violence:

Patients with a history of problem drinking or alcohol dependence were less likely to be admitted than those without such a history (71% vs 81%) but the difference was not statistically significant (RR 0.59; 95%CI 0.33-1.08). A similar but significant trend was seen for patients with a history of cannabis abuse (65% vs 81%; RR 0.44; 95%CI 0.23-0.85).

A history of juvenile delinquency or adult criminality was slightly less common in patients admitted to hospital; again, differences were not significant. However, if police were involved in bringing the patient to hospital, there was a 93% chance of admission, compared to 79% if there was no such history (RR 3.61; 95%CI 1.27-10.26). Violence to others was likely to result in admission (91% vs 78%; RR 2.74; 95%CI 1.22-6.20), while all patients with a history of

violence to self were admitted to hospital vs 80% of those with no such history (c^2 5.40; 1df; p=0.02).

Clinical characteristics:

The age-at-onset distribution of the sample is shown in Figure 3.1; the numbers of admitted patients in each 5-year age-at-onset band is also shown. Overall, age-at-onset did not predict whether the patient was admitted (c^2 14.67; 13df; p=0.327).

Numbers of individuals fulfilling various RDC and DSM-IIIR criteria for subtypes of functional psychosis are shown in Table 3.2, along with the proportions of patients admitted to hospital on first psychiatric contact. For both sets of criteria, the "schizophrenia" category contained the largest number of individuals. In both RDC and DSM-IIIR typology, it was patients with schizo-affective psychoses, though few in number, who had the greatest chance of being admitted to hospital. Patients with DSM-IIIR "delusional disorder" were least likely to be admitted.

Phenomenological variables:

Phenomenological variables, as defined in OCCPI 2.5, were compared in patients admitted to hospital with those not admitted. Results are shown in Table 3.3. Persecutory and grandiose delusions, and any form of auditory hallucination, were significantly ($p<0.05$) more common in patients admitted to hospital. Bizarre behaviour also predicted admission.

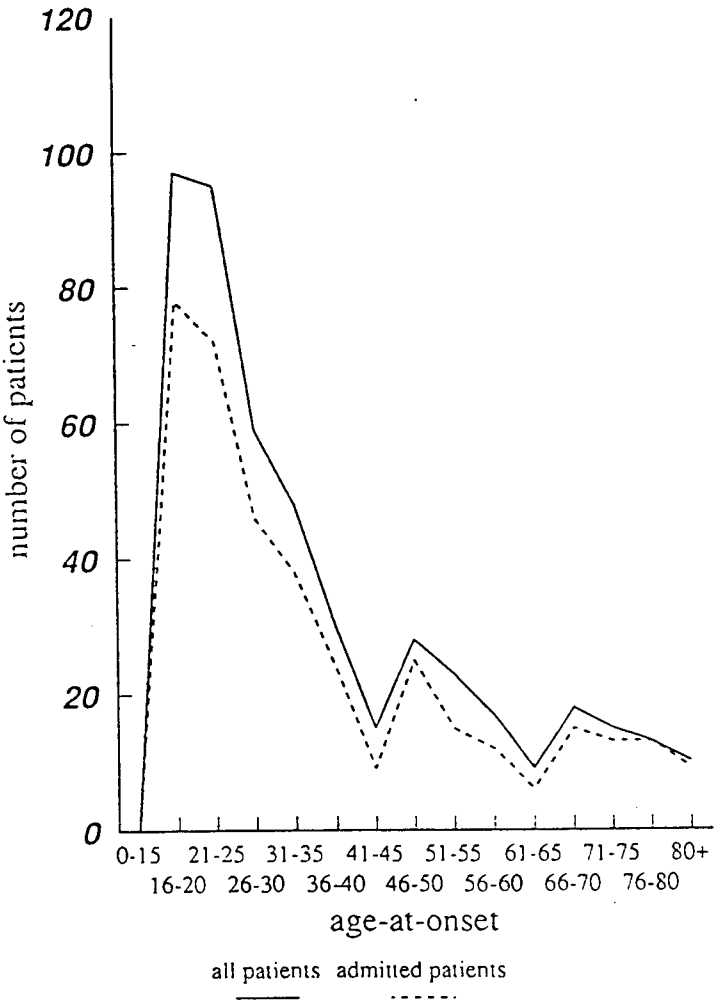

Figure 3.1: Age-at-onset distribution of the entire sample in 5-year age-at-onset bands, and the proportion of admitted patients in each 5-year band

Table 32: Patients admitted to hospital, by diagnostic criteria fulfilled

(A) RDC	SCHIZO-AFFFECTIVE MANIA	SCHIZO-AFFECTIVE DEPRESSED	"BROAD" SCHIZOPHRNEIA	"NARROW" SCHIZOPHRENIA	"OTHER"
NO. OF PATIENTS	16	11	50	271	88
PERCENT ADMITTED	94%	100%	78%	83%	61%
(B) DSM-IIIR	SCHIZO-AFFECTIVE DISORDER	ATYPICAL PSYCHOSIS	SCHIZOPHRENI-FORM PSYCHOSIS	SCHIZOPHRENIA	DELUSIONAL DISORDER
NO. OF PATIENTS	59	94	53	196	51
PERCENT ADMITTED	90%	75%	89%	83%	59%

Table 3.3: Phenomenological variables of patients admitted

VARIABLE	NO. WITH SYMPTOM	% WITH ADMITTED	% SANS ADMITTED	RISK RATIO; 95%CI
BIZARRE BEHAVIOUR	215	86	73	2.18; 1.36-3.47
CATATONIA	27	89	78	2.23; 0.65-7.57
POSITIVE FORMAL THOUGHT DISORDER	107	83	77	1.45; 0.82-2.54
NEGATIVE FORMAL THOUGHT DISORDER	41	88	79	2.06; 0.78-5.39
BLUNTING OF AFFECT	10	80	79	1.08; 0.22-5.21
PERSECUTORY DELUSIONS	368	82	68	2.05; 1.27-3.33
SYSTEMATISED DELUSIONS	139	79	79	1.03; 0.63-1.67
GRANDIOSE DELUSIONS	102	87	77	2.10; 1.12-3.95
DELUSIONS OF REFERENCE	297	88	76	1.23; 0.79-1.91
BIZARRE DELUSIONS	109	82	78	1.27; 0.74-2.19
WIDESPREAD DELUSIONS	235	83	75	1.59; 1.02-2.49
PASSIVITY PHENOMENA	123	81	78	1.25; 0.74-2.09
DELUSIONAL PERCEPTION	17	65	79	0.48; 0.17-1.34
OTHER PRIMARY DELUSIONS	52	71	80	0.63; 0.33-1.20
PERSECUTORY HALLUCINATIONS	279	86	68	3.02; 1.92-4.76
THOUGHT INSERTION	61	72	80	0.66; 0.36-1.22
THOUGHT WITHDRAWAL	33	85	78	1.56; 0.59-4.16
THOUGHT BROADCAST	45	76	79	0.82; 0.40-1.69
THOUGHT ECHO	10	70	79	0.62; 0.16-2.47
3RD PERSON HALLUCINATIONS	157	84	76	1.66; 1.01-2.75
RUNNING COMMENTARY	81	88	77	2.10; 1.04-4.24

DISCUSSION

Trends over time and demographic variables:

Around 20% of patients with a non-affective psychosis were not admitted on first contact with the psychiatric services. This figure is remarkably similar to Shepherd et al (1989), who reported that 20% of schizophrenic patients being admitted to hospital for the first time had had a previous episode of illness for which they had not been admitted. It is not possible, from this study, to tell what proportion of patients were subsequently admitted. A number of studies have found that a significant proportion of schizophrenic patients are never admitted to hospital. For example, Geddes and Kendell (1992) reported that around 8% of schizophrenia patients on the Lothian Psychiatric Case Register had never been admitted, while the ECA study in North America (Keith et al, 1991) claimed that "40% of people with a life-time diagnosis of schizophrenia state that they have ever been admitted to a mental hospital" (pg 48). This wide variation in reported rates is due, inter alia, to differences in case-finding methodology, and in diagnostic criteria used.

The proportion of admitted patients in the current study did not change much over the years. Trends towards community psychiatric care (Prince & Phelan, 1990) as well as the wider use of depot neuroleptic medication (Graham, 1990) might have been expected to lead to a reduction in the number of patients requiring admission. The findings reported here probably reflect a relatively stable service provision. Thus, one can question the generalisability of the findings, as there was no concerted move towards community care in the area in the period under study. Having said this, Tyrer et al (1989) found that, while the development of community psychiatry services can lead to a reduction in the total number of psychiatric admissions, the number of first admissions for schizophrenia remains fairly constant.

The present findings do not support the contention that a reported decline in the incidence of schizophrenia in a number of Western countries (see Chapter 4) is an artifact due to changes in admission policies over time (Graham, 1990; Hafner & Gattaz, 1991). Of course, the findings equally do not support the notion that there has been a decline in the incidence of schizophrenia; in fact, as detailed in Chapter 4, the incidence of schizophrenia in Camberwell rose over the period 1965 to 1984.

As shown in Chapter 4, Afro-Caribbeans in Camberwell have a peculiar susceptibility to schizophrenia; around 20% of the schizophrenia sample were born in the Caribbean, 4 to 6 times the proportion in the general population of Camberwell over the period of the study. It has also been suggested (Dunn & Fahy, 1990) that "Black" patients at the Maudsley are more likely than "Whites" to be admitted compulsorily. It is thus perhaps surprising that in this study, it was, if anything, Caucasian patients who showed a trend towards being admitted. This also serves as evidence against suggestions that the high proportion of Afro-Caribbeans in hospitalised samples of schizophrenia patients is merely due to admission bias.

The figures presented here suggest that Asian patients were less likely to be admitted. Although the findings were not statistically significant, the trend is in keeping with a previous report (Gupta, 1991) of a lower number and duration of admissions in Asian patients with psychosis, in comparison to their Caucasian counterparts.

The fact that gender, age-at-onset, and marital and employment status did not act as predictors of admission is also unexpected. Early-onset male schizophrenia patients tend to have a severe disorder (Castle & Murray, 1991) and one might have expected them to be more likely to be admitted. Furthermore, marriage is purported to have a "protective" effect in schizophrenia, while employment would suggest a relatively high level of functioning in the community. Indeed, these findings are at odds with the experience of groups who have specifically focused on managing acutely ill psychiatric patients outside hospitals. For example, a home-based team in Birmingham (Dean & Gadd, 1990) found that being single and living alone both predicted admission, while being young predicted admission for male (but not female) patients.

Drug use, police involvement, and violence:

Past forensic history had no significant influence on admission, but police involvement in the process of referral was a predictor of admission, as was violence to others. This indicates that it is current behaviour that has the strongest influence on admission policy. The fact that all patients with a history of violence to self were admitted reflects safe psychiatric practice, and is a reassuring finding, as well as being a validation of the efficacy of psychiatric services over many years.

Illness factors:

In terms of phenomenological variables, it was not Schneiderian "first rank" symptoms of schizophrenia (eg. passivity phenomena, thought interference) which were the strongest predictors of admission. Rather, the presence of persecutory delusions and any form of auditory hallucination were more common in those admitted to hospital. Bizarre behaviour was also a

strong predictor of admission. This suggests that florid persecutory ideation and behavioural disturbance were more likely to influence admission practice than textbook "typically schizophrenic" symptoms. This is underlined by the fact that patients with a diagnosis of schizoaffective disorder or DSM-IIIR schizophreniform psychosis were most likely to be admitted. Patients with these conditions tend to have florid symptomatology and often exhibit disruptive behaviour. In contrast, less than two-thirds of patients with DSM-IIIR delusional disorder were admitted. Typically, patients with this disorder exhibit non-bizarre delusions without prominent hallucinations, and are often not behaviourally disturbed (APA, 1987).

The high probability of admission in patients with RDC schizodepression is due, in part at least, to the association with suicidal ideation; over 50% of this group were reported as having been actively suicidal, compared with only 10% of patients with schizophrenia.

CHAPTER 4: TRENDS IN SCHIZOPHRENIA INCIDENCE

Changes in the incidence of a disease over time can afford useful insights in the aetiology thereof. It is thus of considerable interest that workers from a number of Western countries (see Table 4.1) have reported a decline in the treated incidence of schizophrenia in recent decades. However, the validity of these studies has been widely questioned, and it has been suggested that various confounding factors need to be taken into account in interpreting the results (reviewed by Kendell et al, 1993). One consideration is that the advent of operational definitions of schizophrenia may have altered clinicians' concept of the disease, possibly resulting in more reluctance in applying this label. Mortensen et al (1991) have argued for such an effect in the Danish data, and point to a reciprocal increase in cases labelled "schizophrenia borderline states", and "paranoid" and "unspecified" psychoses. Kendell et al (1992) reported from Edinburgh that clinicians' conception of schizophrenia appeared to have narrowed over the 19 years from 1971, especially for males. However, Der et al (1990) found no reciprocal increase in the rate of other psychiatric disorders in their study, suggesting that the effect was not merely due to changes in diagnostic habit. Also, Gupta and Murray (1991) could find no evidence for such an effect in the studies from Scotland, New Zealand and Australia. And in a case register study in Oxfordshire, de Alarcon et al (1990) similarly found no concomitant rise in competing diagnoses to account for all the decline in schizophrenia.

Another factor to consider is that changes in admission policies over the years could be a bias in those studies which have relied on first admission data. Certainly there is a trend in most Western countries to more community care for patients with mental disorders, and the advent of depot neuroleptic medication allows more schizophrenia patients to be treated in the community

Table 4.1: Recent reports of changes in the incidence of schizophrenia over time

AUTHORS (DATE)	PLACE	ASCERTAINMENT	PERIOD	FINDING
Eagles & Whalley (1985)	Scotland	first admissions (rates)	1969-1978	40% decrease
Parker et al (1985)	Australia	first admissions (numbers)	1967-1977	9% decrease
Munk-Jorgensen (1986)	Denmark	male first admissions (rates)	1970-1984	37% decrease
Munk-Jorgensen & Jorgensen (1986)	Denmark	female first admissions (rates)	1970-1984	44% decrease
Dickson & Kendell (1986)	Scotland	first admissions (numbers)	1970-1981	48% decrease
Joyce (1987)	New Zealand	first admissions (numbers)	1974-1984	37% decrease
Eagles et al (1988)	Aberdeenshire, Scotland	first contacts (case register)	1969-1984	54% decrease
Der et al (1990)	England & Wales	first admissions (numbers)	1952-1986	around 50% decrease from mid-1960's
de Alarcon et al (1990)	Oxfordshire, England	first contacts (case register)	1975-1986	significant decline for males only
Harrison & Cooper (1991)	Nottingham, England	first contacts (case register)	1975-1987	rates remained stable
Hafner & Gattaz (1991)	Mannheim, Germany	first admission (case register)	1965 & 1980	almost identical rates

(Graham, 1990). However, two case register studies which included all first contacts with the psychiatric services in Aberdeenshire (Eagles et al, 1988) and Oxfordshire (De Alarcon et al, 1990), also found a decline in the incidence of schizophrenia. Such a decline could not have been a result of changes in numbers of psychiatric beds or of changing admission policies.

Thus, it appears reasonable to accept that there has been a decline in the treated incidence of schizophrenia over the last two decades in a number of Western countries, including England as a whole. However, this effect has not been found universally. Indeed, Hafner and Gattaz (1991) reported no evidence of a decline in schizophrenia in Mannheim from 1965 onwards, while in Yugoslavia the rates also appear to have been static (Folnegovic et al, 1990). Also, routine returns from the Camberwell Register (Wing & Hailey, 1972), which recorded all first-contact psychiatric patients from Camberwell, in South London (see Chapter 2) revealed no decline in the incidence of broadly-defined schizophrenia over the two decades from the mid-1960's.

THE CURRENT STUDY:

The design of the Camberwell Register study provided a unique opportunity to assess trends in operationally defined schizophrenia in a defined catchment area. To this end, data were divided into four five-year time-cohorts, namely: 1965-1969 (1st cohort), 1970-1974 (second cohort), 1975-1984 (third cohort), and 1980-1984 (fourth cohort). Table 4.2 shows the number of individuals who fulfilled ICD criteria (taken as akin to a Register diagnosis of "schizophrenia", "paraphrenia" and "atypical psychosis"), RDC and DSM-III criteria for schizophrenia across the four cohorts. An adjustment was made for missing notes, by ascertaining the percentage of rated patients in each cohort with a register diagnosis of "schizophrenia", "paraphrenia" and "atypical

Table 4.2: Numbers of individuals fulfilling various criteria for schizophrenia

cohort	ICD*	RDC#	DSM-III#
1965-69	132	79 (60%)	41 (31%)
1970-74	133	89 (67%)	39 (29%)
1975-79	143	98 (69%)	48 (33%)
1980-84	133	89 (67%)	45 (34%)

* "ICD" taken as akin to a Register diagnosis of "schizophrenia", "paraphrenia" or "other non-organic psychosis"
# numbers are adjusted for missing notes, according to the percentage of individuals (in parenthesis) with a Register diagnosis of "schizophrenia", "paraphrenia" or "other non-organic psychosis", who fulfilled RDC or DSM-III criteria for schizophrenia

Table 4.3: Annual incidence rates, by cohort, for various criteria for schizophrenia

cohort	ICD*	RDC#	DSM-III#
1965-69	19.9	11.9	6.1
1970-74	20.6	13.8	6.0
1975-79	24.5	16.8	8.2
1980-84	24.9	16.7	8.4
test for trend	0.06	0.06	0.10

* "ICD" taken as akin to a Register diagnosis of "schizophrenia", "paraphrenia" or "other non-organic psychosis"
# numbers are adjusted for missing notes, according to the percentage of individuals (in parenthesis) with a Register diagnosis of "schizophrenia", "paraphrenia" or "other non-organic psychosis", who fulfilled RDC or DSM-III criteria for schizophrenia

psychosis" who fulfilled RDC or DSM-III criteria, and adding this proportion to the total in each category.

Incidence rates for ICD, RDC, and DSM-III schizophrenia were calculated, based on the census figures for the population of Camberwell, and directly standardised to the 1964 age-structure; results are given in Table 4.3. The rate of schizophrenia, however defined, rose over the period under study.

In order to investigate any effect of ethnicity on the results, the proportions of both Caribbean-born and UK-born Afro-Caribbeans, amongst the total number of individuals fulfilling RDC criteria for schizophrenia, were ascertained (Table 4.4). As discussed in Chapter 2,the proportion of the population of the Camberwell catchment area who were born in the West Indies increased from 2.5% in 1961, to 4.9% in 1971, and 6.6% in 1981. Using head of household data from the 1981 census, it was estimated that the total proportion of ethnic Afro-Caribbeans (ie. both Caribbean-born and UK-born) in the general population at that time was around 11.5%. Reference to Table 4.4 shows that the proportion of Caribbean-born individuals amongst the schizophrenia sample was five to six times higher than the proportion in the general population of Camberwell. In the later years of the study, a similar excess is seen for all ethnic Afro-Caribbeans.

Table 4.4: Percentage of all individuals with a register diagnosis of "schizophrenia", "paraphrenia", or "other non-organic psychosis", who fulfilled RDC criteria for schizophrenia, by ethnicity and country of birth

COHORT	INDIVIDUALS BORN IN THE WEST INDIDIES	FIRST- AND SECOND-GENERATION AFRO-CARIBBEANS
1965-69	13%	25%
1970-74	32%	38%
1975-79	30%	38%
1980-84	25%	40%

Table 4.5: Annual rates (rate ratios) of RDC schizophrenia per 100,000 population, by ethnicity and country of birth

COHORT	BY COUNTRY OF BIRTH*			BY ETHNICITY		
	BORN IN WEST INDIES	BORN IN UK	RATE RATIOS (95%CI)	ALL AFRO-CARIBBEANS	ALL OTHER ETHNIC GROUPS	RATE RATIOS (95%CI)
1965-1969	46.7	8.8	5.3 (2.6-10.7)	-	-	-
1970-1974	79.9	9.8	8.2 (4.3-13.2)	-	-	-
1975-1979	70.3	11.8	6.0 (3.6-9.6)	-	-	-
1980-1984	50.8	12.6	4.0 (2.4-6.9)	56.7	9.7	5.9 (3.8-9.2)

* excludes all those born in neither the UK nor the West Indies, and one subject born in the Caribbean but of Asian ethnicity
CI = confidence interval

Using the census data, rates for RDC schizophrenia by country of birth were calculated (Table 4.5). Across all four time bands, rates of schizophrenia for "all individuals born in the West Indies" was significantly greater than "all individuals born in the UK". Of course, in the later years of the study an increasing proportion of the general population of Camberwell were ethnic Afro-Caribbeans born in the UK; this might account for the decline in the rate ratio for "country of birth" from the second to the fourth cohort. Unfortunately, the limitations of the census data allow estimation of rates by ethnicity as such only for the final five years of the study (using "head of household" data from the 1981 census). Table 4.5 shows that for 1908-1984, the rate of schizophrenia for all ethnic Afro-Caribbeans was around six times that for all other ethnic groups combined (the majority of whom would be Caucasian).

DISCUSSION

The results of this investigation reveal that, in Camberwell, there was no decline in the incidence of schizophrenia over the period 1965-1984. Indeed, the rate increased, independent of which diagnostic criteria were used. Thus, the findings are at odds with data for both Scotland (Eagles & Whalley, 1985), and England (Der et al, 1990), and with comparable first-contact samples from Aberdeen (Eagles et al, 1988) and Oxford (De Alarcon et al, 1990). It is, of course, theoretically possible that these earlier findings are artefactual, and only the present correct; however, I believe this to be unlikely, expressly in view of the fact that the use of operational criteria did not alter the trends in the current study.

The strengths of the current study include the inclusion of all contacts with the psychiatric services, excluding bias from changes in admission policies over time, and the application of

uniform operationalised definitions of schizophrenia, precluding bias from changes in diagnostic habit. Case records are not ideal for establishing exact diagnoses, but records were very comprehensive, and the OCCPI has been previously used successfully to rate written case summaries (McGuffin et al, 1984; Farmer et al, 1987).

The widest feasible range of diagnoses on the Register were included, making it unlikely that any substantial number of schizophrenia patients were missed. As an additional check on this, 80% of the 44 patients on the Register in the "paranoia" and "morbid jealousy" categories were screened; none fulfilled RDC criteria for schizophrenia. Also, 56 (75%) of the 75 "manic" patients on the Register between 1971 and 1984 were screened, and only two met RDC criteria for schizophrenia. The inclusion of the manic group was important because it has been suggested (Parker et al, 1985) that, with the advent of lithium prophylaxis for bipolar affective disorder, clinicians might be more likely to apply this diagnosis than one of schizophrenia.

Thus, I believe that it is not possible to explain away the current findings, nor the discrepancy with National data, on methodological grounds. It seems more parsimonious to seek and explanation in terms of the changes in the demography of Camberwell over the two decades since the mid-1960's. Three major factors could be important here, namely:

(i) **Changes in the age structure of the general population:** As outlined in Chapter 2, census data show that the proportion of the general population of Camberwell entering the period of greatest risk for schizophrenia (15-34 years) was fairly stable between 1961 and 1971, but rose slightly in the following decade. However, this could not explain away the findings of an

increase in the incidence of schizophrenia in Camberwell over these years, as the rates for ICD, RDC, and DSM-III schizophrenia presented in Table 4.3 are standardised to the age structure of Camberwell in 1964, obviating any confounding effect of the changing age structure of the population.

(ii) **Changes in the socio-economic structure of the population:** It is well known that schizophrenia is over-represented amongst the lower socio-economic groups, although whether this is due to "drift" of ill individuals, or is a reflection of aetiological factors, remains contentious (see Chapter 5). Whichever is true, any significant change in the socio-economic make-up of the general population of Camberwell could have a bearing on the incidence of the disease over the period under study. As outlined in Chapter 2, there was a slight increase in the proportion of Camberwell residents in social classes IV and V between 1971 and 1981 (27.3% in 1971; 28.6% in 1981; see Table 2.1); this was the period of maximum acceleration in the incidence of schizophrenia. However, the census figures for England as a whole show a modest reduction in the proportion of the population in classes IV and V over this period (26.2% in 1971; 23% in 1981). This discrepancy with the Camberwell figures is compatible with the latter's status as a deprived inner-city area; although this could have had some influence on the results presented here, the differences are modest and cannot be the whole answer for the disparity with national trends for schizophrenia as reported by Der et al (1990).

(iii) **Changes in ethnic composition:** A number of studies have shown increased rates of schizophrenia among Afro-Caribbeans in Britain compared to Caucasians; relative risks of the order of three to six times for foreign-born (Rwegellera, 1977; Dean et al, 1981), and seven to

14 times for UK-born (McGovern & Cope, 1987) Afro-Caribbeans have been reported. A study from Nottingham (Harrison et al, 1988) reported relative risks of "restrictive ICD-9" schizophrenia of 12 times greater in first generation, and 18 times in second-generation Afro-Caribbeans. As the census data reveal that an increasing proportion of the general population of Camberwell is Afro-Caribbean (see Chapter 2), this increase could explain at least part of the discrepancy in the rates of schizophrenia between Camberwell and the rest of the UK.

Because of the inadequacies of the census information, it is difficult to give precise rates of schizophrenia by ethnic grouping. However, on the basis of head-of-household data, it has been estimated that at the time of the 1981 census, 11.5% of the general population of Camberwell were ethnic Afro-Caribbeans (see Chapter 2). Using this figure, an estimated rate of RDC schizophrenia of 9.7 per 100,000 population for all non-Afro-Caribbeans for 1980-1984 was derived. Table 4.5 shows that the rates of RDC schizophrenia for all individuals born in the UK was 8.8 per 100,000 population for 1965-1969. At this time there would have been very few UK-born Afro-Caribbeans in the population at risk entering the age at risk for schizophrenia, as the major influx from the West Indies was in the 1950's and 1960's. However, the 1965-1969 rate for "all individuals born in the UK" is not strictly comparable to the 1980-1984 rate for "all non-Afro-Caribbeans", as the latter includes some immigrants from Africa and Europe who might also have a particular susceptibility to schizophrenia (Rwegellera, 1977; Dean et al, 1981). Thus, it is probable that the rate of schizophrenia for "non-Afro-Caribbeans" remained relatively stable over the two decades from the mid-1960's. The reasons for the failure to show a decline in rates of schizophrenia for this group, in line with the findings of a decline in rates at a National level over the same time period (Der et al, 1990), probably lie in the heterogeneous nature of even the

"non-Afro-Caribbean" population of Camberwell; as outline above, there had also been an influx of other migrants during this period, and migrants generally appear to have a higher than expected susceptibility to schizophrenia (see Chapter 5 for references).

Another pertinent fact here is that Camberwell generally rates highly on measures of social deprivation, and the proportion of the general population of the area in social classes IV and V increased slightly over the two decades from the 1961 census. In contrast, the proportion of the general population of England in these two social classes declined over the same period (see Chapter 2 and Table 2.1). It is well know that there is an association between rates of schizophrenia and levels of social deprivation; the nature of this association, and the relevance for Camberwell, is addressed in the following chapter.

CHAPTER 5: PLACE OF BIRTH AND SOCIAL ORIGINS

Many studies have reported an excess of individuals with schizophrenia in lower socio-economic groups (eg. Redlich et al, 1954; Hollingshead & Redlich, 1954; Goldberg & Morrison, 1963; Silverton & Mednick, 1984). Goldberg and Morrison (1963), in a widely cited study, claimed that although schizophrenia patients were more likely than controls to be categorised as social class V, their fathers showed the same social class distribution as the general population. Such data have led to a general conclusion that individuals with schizophrenia "drift" down the social stratum as a result of their illness or its prodromata. A similar interpretation has also been applied to the finding (eg. Faris & Dunham, 1939; Hare, 1956) of high rates of schizophrenia in deprived inner city areas.

More recently, however, there has been a renewal of interest in an alternative to the "drift" hypothesis, namely that early environmental influences per se are of aetiological importance in schizophrenia. It is now widely accepted that at least some schizophrenia patients have an illness consequent upon some subtle damage to the developing brain; such damage might be genetically or environmentally mediated (Jones & Murray, 1991). The "environmental" factors which have attracted most attention have been obstetric complications (Lewis & Murray, 1987), head injury (Wilcox & Nasrallah, 1987), and prenatal exposure to viral infection (Murray et al, 1992a). All these factors are more likely to be encountered in deprived, overcrowded inner-city areas. Thus, Kety (1980) wrote:

> To the extent that perinatal injuries, malnutrition and infection may play roles in the environmental aetiologies of schizophrenia, their impact would be exaggerated in the lower classes in large cities.

To explore these issues using the Camberwell Register sample, a matched case-control study design was employed. "Cases" were individuals on the Register, who fulfilled RDC criteria for schizophrenia, and "controls" the next non psychotic psychiatric patient on the Register, matched for sex and age (to within 5 years). The hypothesis tested was that, compared to other psychiatric patients, schizophrenia patients would have been preferentially born into low social class families living in the inner city.

The current analyses were confined to those patients born in England and Wales, as the Office of Population Censuses and Surveys (OPCS) has birth records only on such individuals. This restriction also served to preclude bias arising from the inclusion of immigrant groups, known to be at high risk for schizophrenia (Castle et al, 1991; Wessely et al, 1991). Where a control patient was found to have been born outside the UK, the next appropriate control on the Register was chosen instead. Two measures relating to early environment were used, viz. (i) Place of birth; those born in Camberwell (a deprived area in inner London) vs. elsewhere in England & Wales: and (ii) Paternal occupation at birth, as an indicator of the socio-economic status of the household.

Data on place of birth and paternal occupation were obtained directly from the medical records when they were recorded. In the absence of such data, birth certificates were obtained from the OPCS; birth certificates routinely record place of birth and paternal occupation. Allocation of fathers to employment categories was made according to the Registrar General's Classification of Occupations. The allocations were performed "blind" to case/control status by a colleague of the author. For this study, comparisons were made between "non-manual" (categories I, II, and

IIIa) and "manual" (categories IIIb, IV, and V) employment. Roughly half of the paternal occupation data were collected from the medical records for both patients and controls, the rest being from birth records; thus, there was no systematic bias between cases and controls in the recording of paternal occupation at birth of the child. As a check on the medical records, birth certificates were drawn on 20 random patients on whom data had been recorded from the medical records. Despite a few minor dissimilarities (eg. exact description of job), no errors were found in allocation to being born in Camberwell vs. elsewhere, or in fathers being recorded as being in "manual" or "non-manual" employment.

Data on paternal occupation at birth were available for 128 matched case-control pairs. The distribution is shown in Figure 5.1. The fact that the majority of fathers in both groups were in non-manual employment is consistent with the inner-city status of Camberwell (see Chapter 2). The major discrepancy between the distributions for cases and controls was a relative paucity of fathers of cases in class IIIa (non-manual), and an excess in class IIIb (manual).

Regarding place of birth, data were available for 155 case-control pairs for being born in Camberwell vs. elsewhere (for a further 6 pairs it was known that patients/controls were born in inner London or elsewhere, but unclear whether they were born in Camberwell). Table 5.1 shows the discordant pairs, risk ratios, and 95% confidence intervals for: (i) paternal occupation; (ii) being born in Camberwell vs. elsewhere; and (iii) being born in inner London or elsewhere. It can be seen that the schizophrenia patients were more likely to have had a father in "manual" employment at the time of their birth than the controls. They were also more likely to have been born in inner London; the odds ratio was even higher when comparison was made between those

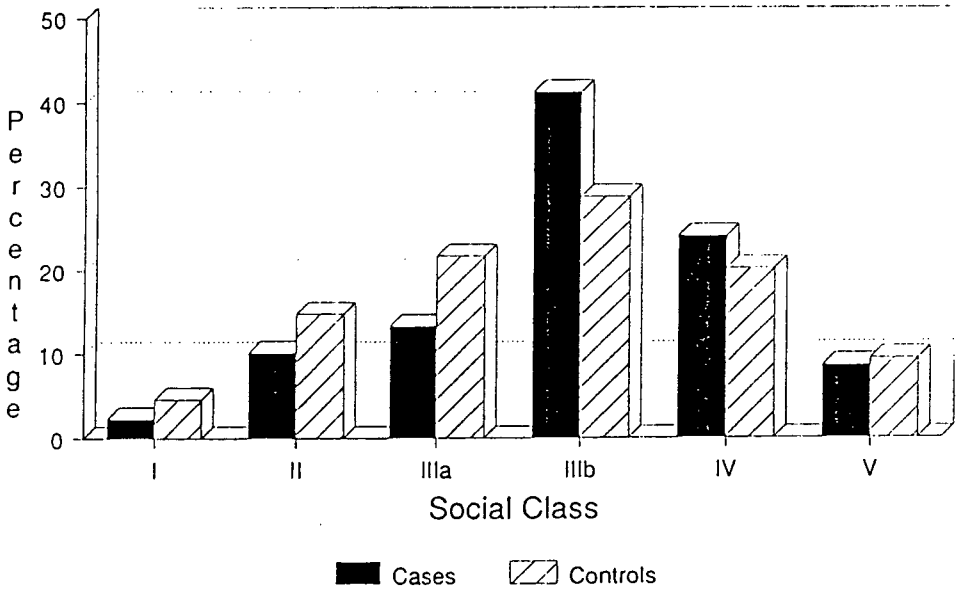

Figure 5.1: Paternal social class distribution for 128 matched case-control pairs

TABLE 5.1: Odds ratios (95% confidence intervals) for discordant matched pairs

MATCHED PAIR	NOS. OF DISCORDANT MATCHED PAIRS	ODDS RATIO	95% CONFIDENCE INTERVALS
(1) Paternal social class		2.1	1.2-3.7
father of case "manual", father of control "non-manual"	38		
father of case "non-manual", father of control "manual"	18		
(2) Place of birth (Camberwell)		2.3	1.3-4.1
case born C'well, control born elsewhere	42		
Control born Camberwell, case born elsewhere	18		
(3) Place of birth (inner London)		2.1	1.2-3.7
case born inner London, control born elsewhere	35		
control born inner London, case born elsewhwere	19		

born inside or outside Camberwell.

Conditional logistic regression analyses were performed to assess potential confounding. The statistical package EGRET was used throughout. There were 117 case/control pairs for whom both place-of-birth and paternal occupation data were available. For these pairs, the risk ratio for paternal occupation was much the same as for the original 126 pairs (RR 2.0; 95%CI 1.1 - 3.7). Controlling for being Camberwell-born reduced the risk ratio to 1.7 (95%CI 0.9 - 3.2).

Being of Afro-Caribbean ethnicity was a risk factor for schizophrenia (RR 16.0; 95%CI 2.1 - 120.7). Controlling for ethnicity reduced the odds ratio for both paternal occupation (RR 1.6; 95%CI 0.9 - 2.8) and being born in Camberwell (RR 2.1; 95%CI 1.1 - 3.9).

DISCUSSION

In case-control studies, it is important to be aware of two potential methodological pitfalls, namely recall bias and selection bias. Recall bias is unlikely to have been a problem in the current study in that the relevant variables (place of birth and paternal occupation at birth of the child) are fairly objective variables which, in any event, were, where possible, extracted from the birth certificate of the patient. Having been recorded at the time of the birth, recall bias does not pertain to the birth certificates. For those patients for whom data were extracted from the case records, it is unlikely that any systematic recording bias would have operated between cases and controls; furthermore, a reliability check on these data, checking against birth certificates (as described under "Methods" above), attested to their accuracy.

Selection bias is potentially more problematic in this study in that cases and controls might have been expected to seek help differentially according to social class. Thus, although most patients with schizophrenia would be expected to come into contact with the psychiatric services irrespective of social class, the same cannot be assumed for the controls. One design feature of this study, however, attempted to reduce the possibility of any systematic bias in the controls by including a wide range of "non-schizophrenia" diagnoses, and not focusing on a single diagnostic category amongst which patients' help-seeking behaviour might possibly be biased by such factors as social class. Also, the variable of interest was the social class of the father at the time of the birth of the child, rather than the social class of the patient him- or herself.

Thus, the results presented here suggest that individuals who develop schizophrenia are more likely than non-psychotic controls to have been born into socially deprived households. Here social deprivation is indicated by lower socio-economic status of fathers, as well as the fact that inner London boroughs (and Camberwell in particular) rate highly on measures of deprivation based on factors such as housing tenure and socio-economic status (see Chapter 2).

This inner city-birth effect is consonant with a number of other studies. In Norway, Astrup and Odegaard (1961) found higher rates of schizophrenia amongst those born in cities, and, while migrants generally showed lower rates, migrants from cities had higher rates than those from rural areas. Machon et al (1983), in a high risk sample, found that an excess of individuals who later manifested schizophrenia had been born in urban areas. More recently, in England and Wales, Takei et al (1992) found schizophrenia patients to be significantly more likely than other psychiatric patients to have been born in cities, while Lewis et al (1992), using Swedish data,

found that individuals with schizophrenia were particularly likely to have been brought up in urban centres. Dauncey et al (1993) reported that schizophrenia patients were especially likely to live in socio-economically deprived areas in Nottingham, and that this pattern had been present from early in life.

Many studies have examined the social class of schizophrenia patients, but few have investigated the socio-economic grouping of their fathers. The best known, though not the best study (Goldberg & Morrison, 1963), reported that fathers of individuals with schizophrenia had the same occupational distribution as the general population. However, the studies of Hollingshead and Redlich suggested that the fathers of individuals with schizophrenia were themselves from lower socio-economic backgrounds, while Turner and Wagenfeld (1967) reported fathers of schizophrenia patients to be over-represented in the lower socio-economic groups. In reviewing these studies, Kohn (1975) concluded that

> The weight of evidence lies against the drift hypothesis providing a sufficient explanation of the class-schizophrenia relationship. In all probability, lower class families produce a disproportionate number of schizophrenics.

The findings presented here are in line with this conclusion, and as such, they challenge the conventional wisdom that the excess of schizophrenics in deprived areas and the maldistribution of these individuals with regard to social class, is due entirely or predominantly to "drift". Individuals who later manifest schizophrenia are disproportionately likely to have suffered the disadvantages of social deprivation in utero and in early life. One explanation could be that their fathers have some genetic "loading" for schizophrenia, insufficient to manifest the illness, but

sufficient to make them less "competitive" in socio-economic terms. An alternative, which I favour, is that some environmental factor of aetiological importance in schizophrenia is more likely to affect those born into households a) of lower socio-economic status, and b) in the inner city.

CHAPTER 6: GENDER DIFFERENCES IN SCHIZOPHRENIA

Schizophrenia has an earlier onset in males than females, by about 5 years in most studies (see Lewine, 1988). Differences in help-seeking behaviour between males and females with schizophrenia, or by their families, cannot explain away these findings; however "onset" is defined (first treatment, first hospitalisation, first symptoms), the sex differences in age at onset are robust (Loranger, 1984; Riecher et al, 1989; Hafner et al, 1991). Gender differences in onset are not an artifact due to definition of illness, being found even if stringent DSM-III (APA, 1980) criteria are employed (Loranger, 1984; Shimizu et al, 1988). There is also consistency across cultures, in that an analysis of data from 11 centres of the WHO "Determinants of Outcome" study (Hambrecht et al, 1992) found that females had a later onset than males in all centres.

Furthermore, the age-at-onset distribution curves for schizophrenia differ between men and women. In a study of 392 consecutive first admissions with a diagnosis of schizophrenia or paranoid disorder from a defined catchment area (the "ABC study"), Hafner and colleagues (1991) found that males showed a single marked peak in the early 20's, while for females there was a "second peak" of onset in the 45-54 year age group. This finding was echoed in the distribution of pooled data from the WHO "Determinants of Outcome" study (Hambrecht et al, 1992). Thus, it appears that, not only do females have a mean age-at-onset of illness later than males, but that the age-at-onset distribution curves for males and females are very different in shape. This has profound implications for any theory aimed at explaining gender differences in schizophrenia (see Castle & Murray, 1993). One possibility is that some factor associated with being female serves to delay the onset of the illness. The factor to attract most attention has been oestrogen; thus, the oestrogen hypothesis proposes that during the reproductive years, women

are somehow "protected" by the antidopaminergic action of oestrogens, and that the slight peak in the incidence of female schizophrenia in the 46-55 year age-range is the result of removal of such protection at the menopause (see Hafner et al, 1991; Riecher-Rossler & Hafner, 1993). An alternative explanation is that the gender differences in age-at-onset are a clue to subtypes of schizophrenia to which men and women are differentially prone (see Castle & Murray, 1991; Goldstein et al, 1990a; Murray et al, 1992).

"DEMENTIA PRAECOX" SUBTYPE:

Randall (1983), and subsequently Weinberger (1987), have articulated a view that schizophrenia is a neurodevelopmental illness, consequent upon insult to the developing brain. Jakob and Beckmann (1986) and Falkai et al (1990) found heterotopia of pre-alpha cells in the entorhinal cortex of schizophrenic brains, suggesting arrest of neuronal migration, and implying the abnormalities have their origin in foetal life. More recent findings of distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurones in frontal and lateral temporal lobes (Akbarian et al, 1993a; 1993b) lend support to this conclusion.

It has been proposed elsewhere (Castle & Murray, 1991; Murray et al, 1992) that the excess of males amongst early-onset schizophrenics is a reflection of a male propensity to a severe early-onset form of the illness, akin to Kraepelin's (1896) original conception of "dementia praecox", and consequent upon neurodevelopmental deviance. In support of this hypothesis, evidence was cited of a tendency to worse premorbid functioning (eg. Zigler & Levine, 1973; Zigler et al, 1977; Klorman et al, 1977; Lewine, 1981; Childers & Harding, 1990; Foerster et al, 1991) and lower premorbid IQ and poorer school performance (Offord, 1974; and reviewed by Aylward et

al, 1984) amongst males than females who subsequently develop schizophrenia.

Castle and Murray (1991) also cited evidence of more structural brain abnormalities in male schizophrenia patients than in their female counterparts, finding 10 studies (6 CT and 4 MRI) which showed schizophrenic males more likely than females to exhibit structural brain abnormalities. Flaum et al (1990) reviewed neuroimaging studies of individuals with schizophrenia, which reported gender effects; most had small sample sizes and lacked statistical power, but of the six studies which found a gender effect, males had larger ventricle/brain ratios (VBR) than females in five. In three of their own four studies, Flaum et al (1990) found males had significantly larger ventricles than controls, but that there was no such effect for females. More recently, Lewine et al (1993) analysed neuroradiologists' findings in a sample of 108 patients fulfilling DSM-IIIR criteria for schizophrenia (82 male) and 150 healthy controls; the schizophrenic men had a significantly higher rate (26.8%) of anomalies than schizophrenic women (15.4%), or control men and women (10.2% and 9.9%, respectively). On a related theme, Andreasen et al (1993) have shown that in male, but not female, schizophrenia patients, the normal positive correlation between IQ and the volume of various brain structures (eg. temporal lobe) is lost. Once again, this implies greater abnormality in males than females with schizophrenia. Not all neuroimaging studies of schizophrenia patients have found such a gender difference (eg. Nasrallah et al, 1990; Gur et al, 1991), and studies have not been designed specifically to address this issue; however, the weight of evidence suggests more structural brain abnormalities in males than females with schizophrenia.

Other characteristics of schizophrenia in males, such as more negative symptoms (reviewed by Bardenstein & McGlashan, 1990), and generally worse outcome (for reviews, see Seeman, 1986; Goldstein, 1988; Angermeyer et al, 1989, 1990) are consonant with the notion that males are more prone to a severe form of the illness (see Table 6.1). In aetiological terms, males with schizophrenia, expressly those with an early onset of illness, appear more likely than females to have a history of those obstetric complications implicated in the aetiology of the condition (see Lewis et al, 1989; Castle & Murray, 1991; and O'Callaghan et al, 1992). The propensity of males with schizophrenia to early insults such as obstetric complications is consonant with the fact that an excess of males, and an association with obstetric complications, have been reported to be features of other "neurodevelopmental" disorders (eg. autism). The reasons for the particular vulnerability of males to such disorders are complex, but study of gender differences in rates of cerebral maturation, and of cerebral organisation and structure might provide some of the answers (see McGlone, 1980; Diamond, 1989; Lewine et al, 1990). The role of sex hormones on brain maturation should be considered in this regard (reviewed by DeLisi et al, 1989; see Seeman & Lang, 1990; and Hafner et al, 1991).

Female MZ twins have higher concordance rates for schizophrenia than do male MZ twins (Rosenthal, 1970; Kringlen, 1987), and four recent studies (Bellodi et al, 1986; Goldstein et al, 1990b; Wolyniec et al, 1992; Sham et al, 1993a) have now shown that the relatives of female schizophrenia probands have a greater risk of developing schizophrenia than do relatives of their male counterparts. This might be interpreted as evidence of more "environmental" schizophrenia in males (eg. as a consequence of obstetric complications), but such reasoning is probably too simplistic. Indeed, it appears that schizophrenia patients with an early onset (ie. "dementia

Table 6.1: Gender differences in schizophrenia

	Males	Females
Age-at-onset distribution	early peak with uniform decline	more even distribution throughout adult life
Symptomatology	more likely to exhibit "typical" and "negative" symptoms	more likely to exhibit "atypical" and affective symptoms
Season of admission	no clear seasonal pattern	cyclical pattern as mania
Premorbid functioning	more likely to show poor premorbid social & occupational functioning, and low premorbid IQ	less likely to have been socially, occupationally, or intellectually compromised
Neuropathology	more likely to exhibit structural brain changes	less likely to exhibit structural brain changes
Course of illness	tends to be worse in terms of hospitalisation, and social & occupational functioning	generally better treatment, social and occupational outcome

praecox" type) illness might be particularly likely to have a family history of the disorder (eg. Albus et al, 1993; Sham et al, 1993a). What is increasingly clear is that neurodevelopmental deviance does not necessarily imply "environmental" causation; indeed, Jones and Murray (1991) have suggested that "the genetics of schizophrenia is the genetics of neurodevelopment". Furthermore, evidence from the obstetric literature shows how obstetric complications can often be seen as a consequence of earlier (possibly genetically mediated) cerebral insult (see O'Callaghan et al, 1992). Thus, this form of schizophrenia could itself be aetiologically heterogeneous, some cases being largely genetically mediated, some largely "environmentally" mediated, and some having an admixture of both genetic and environmental factors.

SCHIZOPHRENIA AND AFFECTIVE DISORDER:

Reviewers have tended to conclude that there is no definitive evidence for an overall sex difference in the prevalence of schizophrenia (eg. Hafner, 1987; Lewine, 1988). However, when diagnostic criteria of increasing stringency (eg. RDC, DSM-IIIR) are applied to cohorts of schizophrenia patients, more females than males are excluded (eg. Lewine et al, 1984; Katchnig & Lenz 1988). Jones et al (1993) have shown that stringent diagnostic criteria for schizophrenia, such as DSM-IIIR (APA, 1987), define a form of illness associated with early onset and negative symptoms; as outlined above, males are more likely to fulfil such stringent criteria. The converse of this is that 41% of females but only 14% of males who met PSE/CATEGO (Wing et al, 1974) broad criteria for schizophrenia were reassigned by DSM-IIIR to affective disorder (Jones et al, 1993). Bardenstein and McGlashan (1990) have recently reviewed gender differences in schizophrenia, and schizoaffective and affective disorders, and concluded that, in comparison with their male counterparts, females with schizophrenia are "more likely to receive

differential diagnoses of atypical, affective, or manic depressive illness", and that females are over-represented amongst patients with a diagnosis of schizoaffective disorder. For example, Tsuang et al (1976) found 71% of their "atypical" group to be female, similar to the proportion amongst a comparison group with bipolar disorder, while in the Chestnut Lodge series (see Bardenstein & McGlashan, 1990), 66% of 87 patients with schizoaffective disorder were female (compared with 48% of those with schizophrenia, and 69% with bipolar disorder). Similarly, women are more susceptible to so-called "cycloid" psychoses, characterised by discrete episodes of florid psychosis of abrupt onset which tend to resolve with good return of function between episodes (Cutting et al, 1976); there is some evidence that such patients respond to the prophylactic effect of lithium (Perris 1974).

Recent reviews of the relationship between schizophrenia and affective disorder (eg. Levitt & Tsuang, 1988; Taylor, 1992), have pointed out the complexity of the association, and the considerable overlap in families. Similarly, studies of familial loading in "schizoaffective" psychoses are difficult to compare because of variability in diagnostic criteria (see Pope & Yurgelun-Todd, 1993). However, a number of studies suggest that patients with "atypical" and "schizoaffective" psychoses show higher than expected familial loading for affective disorder. For example, Tsuang et al (1976) found that the siblings of their patients with "atypical schizophrenia" showed a low risk for schizophrenia (1.1%) but a high risk for affective illness (7.4% vs. 6.9% in bipolars and 1.9% in schizophrenic comparison groups). In reviewing the specificity of "schizophrenic" symptoms, Pope and Lipinsky (1978) found 15 studies where familiality was compared in "good-prognosis" and "poor prognosis" schizophrenia patients. Those in the good prognosis groups (mostly "atypical", "schizoaffective" or "schizophreniform"

psychoses) typically showed two to three times as much familial affective illness as schizophrenia, while the poor prognosis groups showed a two- to three-fold difference in the opposite direction. A recent family interview study (Pope & Yurgelun-Todd, 1993) found high rates of affective disorder in the relatives of patients with schizoaffective illnesses, but not in relatives of those with schizophrenia. Also, Sham et al (1993b), in a Danish data set, found that, compared to their male counterparts, females with schizophrenia had a higher rate of manic depression in their relatives.

Another line of evidence in support of the notion that some females with schizophrenia have a form of illness with links with affective disorder, is the demonstration of gender differences in season of admission. Although the demonstration of an excess of admissions for psychosis in summer months is best established for affective psychosis, studies from a number of countries have shown a similar pattern in patients with schizophrenia (see Takei et al, 1992). This observation led Hare (1988) to suggest that "schizophrenia and mania may have some aetiological factor in common", while Crow (1986) stated that "seasonality effects suggest an underlying aetiological unity [in the functional psychoses]". Few studies have determined gender effects in seasonality of admission. Takei et al (1992) examined season of first admission in 17,770 patients with schizophrenia and 20,845 with affective disorder in England and Wales between 1976 and 1986 and demonstrated a cyclical seasonality with an excess of summer admissions in female, but not male, schizophrenic patients; a similar cyclical pattern was seen in manic patients of both sexes. The finding of a cyclical pattern in female, but not male, schizophrenia patients has been replicated in an independent large data set from Scotland (Takei & Murray, 1993).

THE CURRENT STUDY:

The Camberwell Register sample allowed an investigation of gender differences in an epidemiologically based sample not preselected by hospitalisation (and hence severity), restrictive diagnosis (the diagnoses included being very broad), or age-at-onset (patients across all ages at onset were included).

Figure 6.1 shows the age-at-onset distribution for all non-affective non-organic psychotic patients. Mean age-at-onset was 31.2 years for males and 41.1 years for females. Males exceeded females in those patients with an onset of less than 35 years, whereafter a female preponderance was seen.

Diagnosis and gender:

According the RDC, 20% of females but only 6% of males were in the affective disorder spectrum (major depression, bipolar disorder, schizoaffective disorder). The results were similar when DSM-IIIR criteria were applied, with 20% of females and 9% of males being diagnosed as having a psychotic affective disorder. In DSM-IIIR, females were also somewhat more likely to have an "atypical psychosis" or "schizophreniform psychosis" label (22% vs 19% of males).

Effects of diagnostic stringency:

Table 6.2 shows the numbers of patients fulfilling various criteria for schizophrenia, by sex; male:female ratios are also shown. Following DSM-IIIR criteria, the data were analysed in two groups according to age-at-onset, namely less than 45 years, and 45 years and over. Surprisingly, a higher proportion of older than younger patients met the various operational criteria. In the group with age-at-onset under 45 years, increasing the stringency of diagnosis resulted in a more

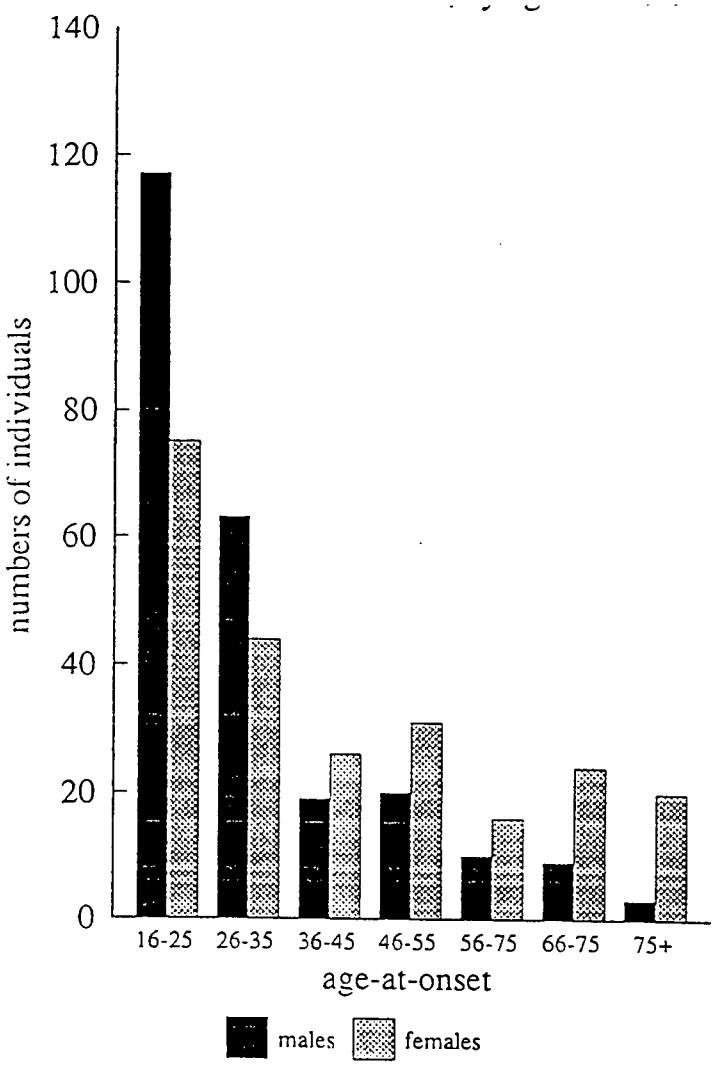

Figure 6.1: Age-at-onset distribution for all non-affective non-organic psychotic patients, by gender

emphatic male preponderance. This was particularly so for those criteria with a 6-month duration-stipulation, namely DSM-III, DSM-IIIR and Feighner criteria. In contrast, the male:female ratio in the later-onset group was far less affected by increasing stringency of diagnosis.

Incidence:

Rates of schizophrenia by gender were determined by 5-year date-bands across the study period. The male:female ratio of the general population of Camberwell was fairly uniform throughout the period under study, showing a slight female preponderance, as detailed in Chapter 2. The male:female rate ratios were thus much the same over the 20 years, and results are shown for the whole group. Figure 6.2 shows annual rates for DSM-IIIR schizophrenia, by sex. It will be noted that the distribution for males shows a peak in the under-25's, while for females the distribution is far more even over the years.

To explore these findings further, rates for schizophrenia as defined by a range of different criteria were determined, and the incidence rate ratios calculated with and without an age-at-onset stipulation (Table 6.3). Incidence rate ratios were calculated using person-time data; approximate 95% confidence limits were calculated according to the method described by Rothman (1986). Hypothesis testing of the differences between two rate ratios was derived from the formulae for the mean and variance of the number of cases in a binomial distribution; test statistics were translated into p values using the tables for the standard normal distribution (Rothman, 1986).

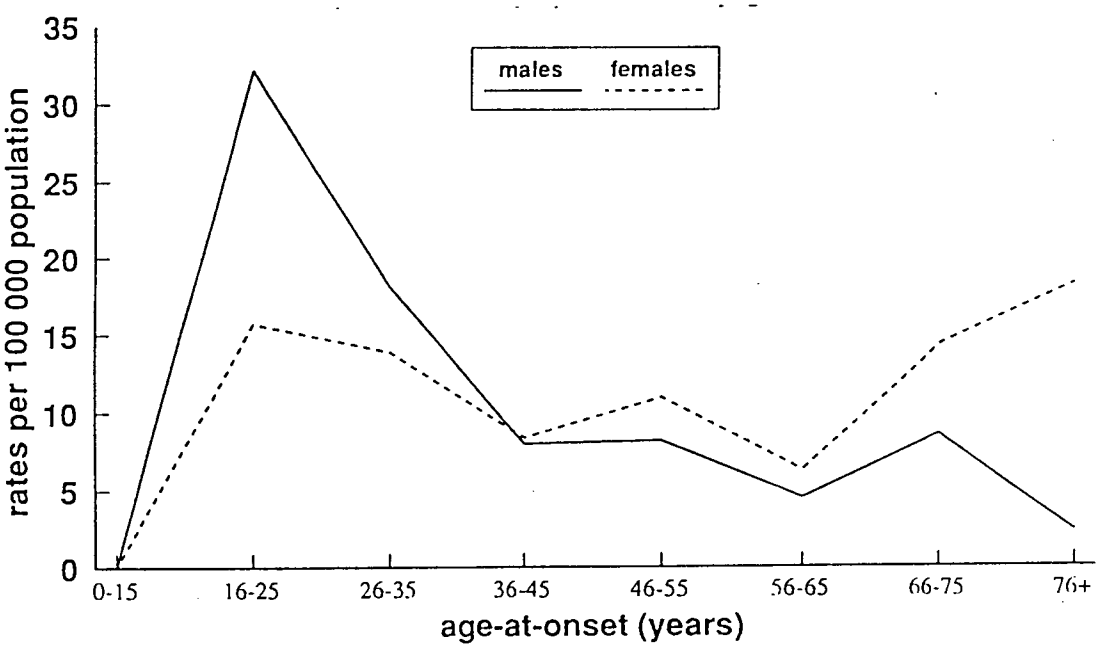

Figure 6.2: Rates for DSM-IIIR schizophrenia, by gender

Table 6.2: Numbers of patients fulfilling various criteria for schizophrenia, by sex and age-at-onset.

CRITERIA	ONSET	MALE*	FEMALE*	M:F RATIO
ICD	< 45 > 44	195 44	141 90	1.4:1 0.5:1
RDC	< 45 > 44	127(65%) 37(84%)	82(58%) 75(83%)	1.6:1 0.5:1
DSM III	< 45	108(55%)	50(35%)	2.2:1
DSM III R	< 45 > 44	86(44%) 22(50%)	41(29%) 47(52%)	2.1:1 0.5:1
Feighner	< 40	96(49%)	39(28%)	2.5:1

* percentages in brackets reflect proportion of non-affective psychotic individuals (ICD "schizophrenia", "atypical psychosis" and "paraphrenia") fulfilling various criteria for schizophrenia.

TABLE 6.3: Rates (rate ratios) of Schizophrenia per 100,000 population, by sex

CRITERIA	ONSET	MALE	FEMALE	IRR* (95% ci)	X-STATISTIC; p value
ICD	< 45 yrs > 44 yrs all ages	25.2 10.4 19.2	17.8 17.1 17.6	1.41 (1.13 - 1.75) 0.50 (0.34 - 0.71) 1.13 (0.94 - 1.35)	3.86; p < 0.001 2.76; p = 0.002 1.37; n.s.
RDC	< 45 yrs > 44 yrs all ages	16.4 8.7 13.7	10.4 14.3 11.9	1.58 (1.20 - 2.08) 0.61 (0.41 - 0.90) 1.16 (0.92 - 1.42)	3.26; p < 0.001 2.48; p = 0.006 1.29; n.s.
DSM III	< 45 yrs	13.9	6.3	2.20 (1.57 - 3.07)	4.73; p < 0.001
DSM III R	< 45 yrs > 44 yrs all ages	11.1 5.2 9.0	5.2 9.0 6.7	2.14 (1.47 - 3.10) 0.58 (0.35 - 0.96) 1.34 (1.01 - 1.78)	4.10; p < 0.001 2.14; p = 0.016 2.07; p = 0.020
Feighner	< 40 yrs	14.8	6.0	2.49 (1.72 - 3.61)	4.98; p < 0.001

* IRR = Incidence Rate Ratio

For those criteria with no age-at-onset stipulation, overall rate ratios for the two sexes showed a slight male excess, significant only for DSM-IIIR criteria. The rate ratios were similar to the sex ratios shown in Table 6.2; in the younger group increasing stringency of diagnosis resulted in much higher male:female rate ratios, while little difference was made to the rate ratios in the older group. In consequence, whenever an age-at-onset stipulation was made (45 years for all criteria other than those of Feighner, where it was 40 years), the incidence of schizophrenia was higher in the resulting young males than young females; for the older onset groups, the reverse was the case.

Pre-morbid functioning:

Data relating to personality disorder, marital status, and premorbid social and work adjustment for all non-affective psychotics are shown in Table 6.4. In the early-onset group, males were significantly more likely to be single, to have poor premorbid social and work adjustment, and to show premorbid personality disorder (the OCCPI criteria for personality disorder are broad, including schizoid, schizotypal and paranoid types). None of these premorbid parameters distinguished males from females in the later-onset group.

Comparison of the early- and late-onset non-affective psychotics by sex in terms of premorbid dysfunction revealed that, for both sexes, the younger group were more likely to be unmarried (males RR 0.15; 95%CI 0.07-0.30; females RR 0.47; 95%CI 0.27-0.82) and to have a poor work record (males RR 0.08; 95%CI 0.02-0.25; females RR 0.28; 95%CI 0.15-0.52). However, only for males were the younger group significantly more likely to have exhibited poor premorbid social adjustment (RR 0.26; 0.12-0.56), and to have had premorbid personality disorder (RR 0.27;

Table 6.4: Premorbid social and occupational adjustment by sex and age-of-onset, for all non-affective psychotics

PARAMETER	ONSET	MALE	FEMALE	RISK RATIO; 95%CI
single*	< 45 > 44	147 (75%) 14 (31%)	76 (53%) 33 (35%)	0.37; 0.23-0.59 1.17; 0.55-2.53
poor work adjustment	< 45 > 44	107 (55%) 4 (9%)	62 (44%) 16 (18%)	0.64; 0.41-0.98 2.08; 0.65-6.65
poor social adjustment	< 45 > 44	103 (53%) 10 (23%)	41 (29%) 19 (21%)	0.36; 0.23-0.57 0.89; 0.37-2.13
personality disorder	< 45 > 44	53 (27%) 4 (9%)	19 (13%) 7 (8%)	0.41; 0.23-0.73 0.83; 0.23-3.01

* "single" = never married or cohabited.

Table 6.5: premorbid social and occupational adjustment by sex and age-at-onset, DSMIIIR schizophrenics only

PARAMETER	ONSET	MALE	FEMALE	RISK RATIO; 95%CI
single*	< 45 > 44	70 (82%) 7 (32%)	23 (56%) 21 (45%)	0.27; 0.12-0.63 1.73; 0.59-5.02
poor work adjustment	< 45 > 44	53 (62%) 3 (14%)	24 (58%) 11 (23%)	0.85; 0.39-1.82 1.83; 0.45-7.41
poor social adjustment	< 45 > 44	54 (64%) 7 (32%)	11 (27%) 16 (34%)	0.21; 0.09-0.48 1.11; 0.37-3.26
personality disorder	< 45 > 44	30 (35%) 2 (9%)	8 (20%) 7 (15%)	0.44; 0.18-1.08 1.75; 0.33-9.21

* **"single" = never married or cohabited**

95%CI 0.09-0.78).

To show the effect of increasing diagnostic stringency on premorbid characteristics, these parameters were analysed in patients fulfilling DSM-IIIR criteria; these criteria define a severe form of schizophrenia, but do not have an age-at-onset stipulation, allowing comparison of early- and late-onset groups (Table 6.5). In comparison with the broad group of non-affective psychotics (Table 6.4), the DSM-IIIR group were more likely to exhibit poor premorbid functioning irrespective of sex or age-at-onset; however, differences were not statistically significant. Among early-onset patients, the levels of significance of the gender differences in premorbid parameters were lower for the DSM-IIIR group than for the broad group (statistical significance was not reached at the 5% level for work adjustment or personality disorder). In the later-onset group males and females did not differ significantly in terms of any of the premorbid parameters.

Comparison of early- and late-onset individuals with DSM-IIIR schizophrenia showed early-onset males were more likely than their later-onset counterparts to be single (0.10; 0.03-0.29), and to show poor premorbid social (RR 0.27; 0.09-0.72) and work (0.10; 0.03-0.36) adjustment, and personality disorder (0.18; 0.04-0.84. For females, the early- and late-onset DSM-IIIR groups differed significantly (5% level) only in terms of work adjustment (RR 0.22; 0.08-0.54).

Very-early-onset patients:

It will be noted from Figure 6.1 that there is a massive excess of males amongst those individuals with an onset below the age of 25. The application of stringent criteria dramatically increased

the male:female ratio in this group (from 1.6:1 for all non-organic non-affective psychotics, to 3.4:1 for DSM-IIIR schizophrenics). Incidence rates for the broadly defined group were 25.5 per 100,000 for males and 16.1 per 100,000 for females (RR 1.59; 95%CI 1.18-2.12); for the DSM-IIIR defined group, the rates were 12.0 per 100,000 for males and 3.4 per 100,000 for females (RR 3.56; 95%CI 2.04-6.20).

Table 6.6 shows that in terms of premorbid functioning, those with onset before 25 years were severely impaired; on all parameters they showed more abnormality than the total group with age at onset less than 45 (see Table 6.4). Males were significantly (5% level) more likely to be single, and to show impaired social adjustment. There was a trend towards males being more likely than their female counterparts to have premorbid personality dysfunction, and to be occupationally impaired.

When premorbid functioning was analysed in only those very-early-onset patients fulfilling DSM-IIIR criteria for schizophrenia, both males and females showed more impairment than for the broadly defined very-early-onset group (Table 6.7). Furthermore, the differences between the sexes were less marked for the very-early-onset DSM-IIIR schizophrenics than for the whole group with onset before age 25.

Table 6.6: Premorbid social and occupational adjustment by sex, for all non-affective psychotics < 25 years age-at-onset

PARAMETER	MALE	FEMALE	RISK RATIO; 95%CI
single*	106 (91%)	56 (76%)	0.38; 0.15-0.95
poor work adjustment	74 (63%)	35 (47%)	0.62; 0.33-1.14
poor social adjustment	69 (59%)	27 (37%)	0.45; 0.24-0.85
personality disorder	36 (31%)	15 (20%)	0.49; 0.24-1.01

* single = never married or cohabited

Table 6.7: Premorbid social and occupational adjustment by sex, for DSM III R schizophrenics < 25 years age-at-onset only

PARAMETER	MALE	FEMALE	RISK RATIO; 95%CI
single*	60 (94%)	24 (92%)	0.41; 0.06-2.69
poor work adjustment	47 (73%)	12 (47%)	0.47; 0.15-1.55
poor social adjustment	43 (67%)	10 (39%)	0.36; 0.11-1.19
personality disorder	24 (38%)	7 (27%)	O.95; 0.29-3.08

* single = never married or cohabited

DISCUSSION

Diagnosis and gender:

In accord with expectations from the literature (detailed above), females with broadly defined functional psychosis were more likely than their male counterparts to be re-labelled as "affective" or "atypical/schizophreniform" on application of more stringent operational criteria. The implications of this are that some females commonly given a clinical diagnosis of "schizophrenia" in fact have a variant of an affective disorder. This is discussed in more detail below.

Diagnostic stringency and premorbid variables:

Earlier studies (Lewine et al, 1984; Katschnig & Lenz, 1988) have found that the application of more stringent criteria to cohorts of schizophrenic hospital patients results in a marked excess of males. The current study shows conclusively that this is a reflection of a higher incidence of severe schizophrenia in men. However, the incidence was higher in males only among those patients with an age-at-onset of less than 45; the effect was even more dramatic in those whose illness first manifested before the age of 25.

All the operationalised criteria used in this study exclude patients with a strong affective component to their illness. RDC criteria stipulate an illness-duration of 2 weeks, while DSM-III, DSM-IIIR and Feighner criteria stipulate 6 months. Thus, males with an early age-at-onset (and particularly those with an onset before 25 years) appear to be particularly prone to a severe form of schizophrenia, characterised by long duration and lack of affective symptomatology. Furthermore, these patients were more likely than their female counterparts to have remained single, to have poor premorbid social and employment records, and to exhibit premorbid

personality disorder. These premorbid characteristics also differentiated early-onset from later-onset males.

Of course, some of these factors (particularly marital status) might reflect gender differences in the general population, but in the absence of a non-patient control group I could not directly investigate this possibility. However, the available literature (eg. Foerster et al, 1991) supports the notion that males with schizophrenia are particularly deviant with respect to premorbid functioning.

I believe that these findings are incompatible with the notion, detailed above, that the relatively benign nature of schizophrenia in women is merely a reflection of later disease-onset due to the putative "protective" effects of oestrogen. Indeed, were that the case, early-onset males and females would be equally likely to fulfil stringent criteria for the illness. The fact that early-onset males were particularly prone to a form of disease characterised by lack of affective symptoms, long illness duration, and premorbid dysfunction, lends support to the hypothesis that men are particularly vulnerable to a subtype of schizophrenia, akin to Kraepelin's original (1896) conception of "dementia praecox", consequent upon neurodevelopmental deviance (Castle & Murray, 1991; detailed above). The fact that so many of the young males were "single" could merely reflect the demography of the general population, although criteria did not stipulate "married".

In the later-onset patients (>44 years), increasing the stringency of diagnosis had little effect on the sex-ratio, which continued to show a female preponderance. Thus, in later onset patients,

males and females are proportionally equally likely to have a severe form of schizophrenia, without prominent affective features and with long illness-duration. Although a higher proportion of late- than early-onset non affective psychotics met RDC and DSM-IIIR criteria, late onset patients were less likely than their early-onset counterparts to be unmarried, or to be premorbidly occupationally or socially (for males only) compromised. Males and females in this group were equally unlikely to have exhibited premorbid social dysfunction or a poor work record. Personality disorder, despite being broadly defined in the OCCPI, distinguished between the early- and late-onset males; this did not hold for females. In short, later-onset patients tended not to show the premorbid deficits thought to be characteristic of the "dementia praecox" form of schizophrenia. Of course, part of the explanation could lie in the later onset of illness per se.

Gender differences in premorbid functioning were less marked in those patients fulfilling stringent criteria for schizophrenia. This probably reflects the fact that stringent criteria define a form of illness inherently more likely to be associated with poor premorbid functioning. Thus, even though young males were more likely to fulfil such criteria, females who did meet the criteria were more likely than those who did not, to exhibit these premorbid characteristics. Young DSM-IIIR schizophrenic females, though few in number, do show some of the deficits thought characteristic of "dementia praecox" schizophrenia.

The very-late-onset group are particularly interesting, and are discussed further in Chapter 8. The inclusion of this very-late-onset group caused the group mean age-at-onset to be higher than that reported in previous epidemiological studies of schizophrenia (eg. Hafner, 1987), and is probably responsible for the large differential between males and females (usually reported as around 5

years; eg. Loranger (1984)). The fact that so many very-late-onset patients met stringent criteria for schizophrenia reflects the florid symptomatology and long illness-duration in many such patients (see Castle & Howard, 1992).

CHAPTER 7: A GENDER-BASED TYPOLOGY OF SCHIZOPHRENIA

The analyses presented in Chapter 6 show that males in this representative catchment-area sample had an earlier mean age-at-onset than their female counterparts. Young males were particularly likely to fulfil stringent criteria for schizophrenia, and to exhibit premorbid social and occupational dysfunction. These findings are in line with the predictions outlined above, that young men are differentially prone to a severe, early-onset form of the illness, associated with premorbid dysfunction. To explore these findings further, a rather more sophisticated form of statistical analysis, latent class analysis, was employed.

A GENDER-BASED LATENT CLASS TYPOLOGY OF SCHIZOPHRENIA:

Latent class analysis, a form of factor analysis, involves the construction of latent variables to explain the associations between observed or manifest variables, dealing with categorical manifest variables and assuming a categorical latent variable (Green, 1951; Lazarsfeld & Henry, 1968).

In the latent class analysis described here, the example of Goldstein et al (1990) was followed, in using simultaneous latent class models (Clogg & Goodman, 1985), with gender-specific latent classes. These models are specified by restricting the conditional probability of being male at unity in some latent classes, and at zero in others. Interest is focused on the number of latent classes in each gender, and the extent to which the latent classes of the two genders correspond to each other. A sequence of latent class models were fitted, ranging from one to three latent classes per gender, with and without the restrictions of total homogeneity on the within-class conditional probabilities. The program MLLSA (maximum likelihood latent structure analysis) developed by Clogg (1977) was used throughout.

Variables considered: latent class analysis:

The variables for the analysis were chosen to provide a coverage of aetiological (genetic, "environmental"), premorbid, and phenomenological parameters, as well as gender and age-at-onset. The variables were: (1) family history of schizophrenia in first or second degree relatives (FH), (2) winter birth, i.e. December to April (WB), (3) poor premorbid social adjustment (SA), (4) restricted affect (RA), (5) persecutory delusions (PD), (6) dysphoria (DS), (7) early onset, i.e. 25 years or younger (EO), and (8) male sex (MS). The variables are defined in OCCPI 2.5. As such, the variables approximate those used by Goldstein et al (1990).

There were 447 patients with non-affective functional psychosis, for whom all the manifest variables for use in Stage 1 of the latent class analysis had been recorded. The distributions of the eight chosen manifest variables are given in Table 7.1. Summary statistics for pairwise relationships are given in Table 7.2; with the size of association being measured by product moment (Pearson's) correlation coefficients, and the statistical significance assessed by chi-squared tests for 2X2 tables. The most significant positive associations were between male sex and poor premorbid social adjustment, early onset and poor premorbid social adjustment, and the most significant negative association was between early onset and paranoid delusions.

Table 7.1: The Distributions of the Manifest Variables

	Present (1)	Absent (0)
Family History (FH)	35	412
Restricted Affect (RA)	48	399
Persecutory Delusion (PD)	346	101
Poor Social Adjustment (SA)	165	282
Dysphoria (DS)	213	234
Early Onset (EO)	166	281
Winter Birth (WB)	196	251
Male Sex (MS)	227	220

Table 7.2: Pairwise Product Moment Correlations of the Manifest Variables

FH	1							
RA	.060	1						
PD	.038	-.020	1					
SA	.053	.169***	-.086*	1				
DS	-.095*	.045	.044	.069	1			
EO	.086	.197***	-.282****	.237****	.027	1		
WB	.078	-.030	-.008	-.069	.015	-.017	1	
MS	-.046	.183***	-.050	.215****	-.145**	.164***	.022	1
	FH	RA	PD	SA	DS	EO	WB	MS

* p<.1, ** p<.01, *** p<.001, **** p<.0001 (chi-squared test of independence with Yate's correction).

To these data, the following six latent class models were fitted.

M1. One latent class per gender, with total homogeneity.

M2. One latent class per gender, totally unconstrained.

M3. Two latent classes per gender, with total homogeneity.

M4. Two latent classes per gender, totally unconstrained.

M5. Three latent classes per gender, with total homogeneity.

M6. Three latent classes per gender, totally unconstrained.

Two global measures of goodness-of-fit, the Pearson (X^2) and likelihood ratio (L^2) chi-squared statistics, and their associated degrees of freedom (d.f.), were obtained for each model using MLLSA (Table 7.3). Both X^2 and L^2 were very large for M1, which was therefore excluded from further consideration. In any event, the clinical interpretation of M1, that there is one disorder identical in the two genders, is contrary to the literature on gender difference in schizophrenia reviewed above.

The interpretation of M2 is that there are two subtypes, one of which occurs solely in men, and the other in women. In contrast, M3 suggests the existence of two subtypes which occur in men and women in different proportions. These two models differ only slightly in d.f., but enormously in both X^2 and L^2, with M3 providing a much better fit to the data. M2 was therefore excluded from further consideration.

The next comparison is between M3 and M4. The interpretation of M4, like that of M2, suggests that there is no relationship between the subtypes in men and women. Here the evidence from X^2 and L^2 as to whether M3 or M4 is the best statistical fit, is not consistent, the difference in

Table 7.3: Global Goodness of Fit Test Statistics for Models 1-6

Model	X^2	L^2	d.f.
M1	465.18	325.85	247
M2	419.39	265.42	240
M3	264.18	222.99	238
M4	250.41	176.96	225
M5	245.34	204.51	230
M6	260.68	157.67	214

L^2 (46.03) is significant, suggesting M4 to be a better fit.

M5 postulates the existence of three subtypes which occur in both genders in different proportions. The parameter restrictions in M5 make it more parsimonious than M4 (by 5 d.f.), so that a slightly worse goodness-of-fit is acceptable for M5. However, the evidence from X^2 and L^2 point to opposite directions; X^2 favours M5 while L^2 favours M4.

Finally, M6 is a model with three subtypes in men and three unrelated subtypes in women. Comparing M5 and M6, which differ by 16 d.f., the difference in X^2 is 15.34 in favour of M5, but the difference in L^2 is 46.84 in favour of M6. Hence, the global goodness-of-fit statistics are not consistent with each other, a reflection of the large number of cells in the contingency table, many of which would be expected to be empty. Thus, instead of relying solely on global test statistics the expected cell counts and residuals were examined, revealing that the fit of M3 was poorer that of the other three models. However, the degrees of freedom for M4, M5, and M6, which fit the data almost equally well, are 225, 230, and 214 respectively, showing that M6 is far less parsimonious than the other two models. M4 and M5 are statistically very similar.

Table 7.4 shows that M4 is characterised by the existence of a subtype (classes 1 and 3) with a high frequency of positive family history, early onset, restricted affect and poor premorbid adjustment, and a male to female ratio of 2 to 1. Interestingly, within this type, more males (class 1) than females (class 3) have restricted affect and poor premorbid adjustment, but more females than males have positive family history. The second possible subtype (classes 2 and 4) has a higher frequency of persecutory delusions, and a female excess. The two subtypes do not

Table 7.4: Parameter Estimates for M4

MODEL 4	Males		Females	
	X=1	X=2	X=3	X=4
P(X)	.22	.29	.11	.38
P(FH=1|X)	.11	.03	.14	.08
P(RA=1|X)	.30	.06	.13	.03
P(PD=1|X)	.65	.83	.43	.90
P(SA=1|X)	.72	.29	.44	.21
P(DS=1|X)	.50	.34	.56	.55
P(EO=1|X)	.78	.20	1.0	.08
P(WB=1|X)	.36	.51	.53	.40
P(MS=1|X)	(1)	(1)	(0)	(0)

Legend

The latent categorical variable, X, takes values 1, 2, 3, 4, each representing a latent class. The parameters P(X) are the probabilities of the different values of X, i.e. the probabilities of the latent classes. The parameters P(FH=1|X), P(RA=1|X), etc, are the conditional probabilities of the manifest variable taking a value of 1, given the value of the latent categorical variable, i.e. the within class conditional probabilities of the manifest variables. The parameters in brackets, i.e. the conditional probabilities of being male within the latent classes, are fixed constants.

differ much with regard to dysphoria. Confusingly, winter birth appears to be more frequent in class 2 and 3 than in class 1 and 4, i.e. it appears to be more frequent in the males of the second subtype and the females of the first subtype.

M5 is easier to interpret (Table 7.5). First, there is a subtype (classes 1 and 4) with a high frequency of positive family history, early onset, restricted affect, and poor premorbid adjustment, and a male to female ratio of just over 2 to 1. This subtype is very similar to the first subtype in M4. The second subtype (classes 2 and 5) has a high frequency of persecutory delusions and winter birth, a low frequency of early onset, and a male to female ratio of about one. This subtype is similar to the second subtype in M4. The third subtype (classes 3 and 6) has a very high frequency of dysphoria and persecutory delusions, a very low frequency of family history of schizophrenia and restricted affect, and very few men.

Thus, M5 can be considered a special case of M4, and that is the model which was taken forward to Stage 2 of the latent class analysis.

Stage 2 of the latent class analysis:

Each of the 447 subjects was assigned to one of the classes in M5, and correlations explored between the type of illness and a range of family history, premorbid, phenomenological, and treatment response characteristics. All variables were dichotomous, being scored 1 if the characteristic was present and 0 if absent. Ratings on all items were performed before the latent class typology was derived.

Table 7.5: Parameter Estimates for M5

MODEL 5	MALES			FEMALES		
	X=1	X=2	X=3	X=4	X=5	X=6
P(X)	.29	.22	.00	.13	.23	.13
P(FH=1|X)	.10	.07	.01	.10	.07	.01
P(RA=1|X)	.22	.03	.00	.22	.03	.00
P(PD=1|X)	.61	.88	.93	.61	.88	.93
P(SA=1|X)	.60	.20	.23	.60	.20	.23
P(DS=1|X)	.50	.31	.98	.50	.31	.98
P(EO=1|X)	.74	.09	.16	.74	.09	.16
P(WB=1|X)	.41	.51	.28	.41	.51	.28
P(MS=1|X)	(1)	(1)	(1)	(0)	(0)	(0)

Legend

The latent categorical variable, X, takes values 1, 2, 3, 4, 5, 6 each representing a latent class. The parameters P(X) are the probabilities of the different values of X, i.e. the probabilities of the latent classes. The parameters P(FH=1 | X), P(RA=1 | X), etc, are the conditional probabilities of the manifest variable taking a value of 1, given the value of the latent categorical variable, i.e. the within class conditional probabilities of the manifest variables. The parameters in brackets, i.e. the conditional probabilities of being male within the latent classes, are fixed constants.

The "premorbid" variables were:

(1) Family history (other): psychiatric disorder other than schizophrenia in first or second degree relative severe enough to warrant psychiatric referral.

(2) Alcoholism in parents: if either parent was considered (rater judgement) to have problem drinking or alcohol dependence.

(3) Obstetric complications: rated according to the composite scale of Lewis et al (1989); this scale has been used previously to rate Maudsley case records (see Lewis & Murray, 1987).

(4) Developmental problems: rated according to the scale devised by Foerster et al (1991), adapted for use with case records; the scale covers speech, motor and reading difficulties, and enuresis/encopresis. A single composite "developmental score" was obtained.

(5) Premorbid personality disorder: rated broadly, as in OCCPI 2.5 (McGuffin et al, 1991; see Appendix 3); most patients rated positively for this item showed features of paranoid, schizoid and/or schizotypal personality disorder.

(6) Single marital status: subject had never married or lived as married.

(7) Poor premorbid work adjustment: as in OPCCPI 2.5; allowance is made for standard of housework, to minimise gender bias.

(8) Unemployment: at illness-onset; full-time students and those engaged in housework full-time were rated as employed.

(9) Offending history: any convictions up to and including time at first contact; rated from criminal records office and hospital case records (see Wessely et al, 1994).

(10) Prodromal phase: of at least 6 months as in DSM-IIIR (American Psychiatric Association, 1987).

To reduce the number of "phenomenological" variables, as defined in OPCCPI 2.5, were grouped as follows:

(1) Depressive symptomatology: any one of slowed activity, agitated activity, loss of energy/tiredness, loss of pleasure, poor concentration, excessive self-reproach, suicidal ideation, initial insomnia, early morning wakening, excessive sleep, loss of appetite, loss of weight, increase in appetite and increase in weight.

(2) Manic symptomatology: any one of excessive activity, reckless activity, pressured speech, increased self-esteem, thoughts racing, distractibility, reduced need for sleep, elevated mood and irritable mood.

(3) Unspecified affective symptomatology: affective symptoms predominated or schizophrenic symptoms occurred at the same time as affective symptoms (rater judgement).

(4) Schneiderian first rank symptoms: any one of thought insertion, thought withdrawal, thought broadcast, thought echo, third person auditory hallucinations, running commentary, delusional perception and delusions of passivity.

(5) Thought disorder: if speech was difficult to understand or incoherent, or if positive formal thought disorder was present.

(6) Negative symptomatology: any one of paucity of thought or speech, blunted affect, or rapport difficulty.

(7) Paranoid delusion: any one of well-organised delusions, grandiose delusions, delusions of influence, and wide-spread delusions.

(8) Non-Schneiderian auditory hallucinations: any one of persecutory/jealous hallucinations, abusive/accusatory/persecutory voices and other (non-affective) auditory hallucinations.

(9) Inappropriate affect: as described in OCCPI 2.5.

(10) Bizarre delusion: as in OCCPI 2.5.

(11) Bizarre behaviour: as in OCCPI 2.5.

(12) Catatonia: as in OCCPI 2.5.

The only variable on "treatment response" was:

(1) Response to neuroleptics: if schizophrenic symptoms responded to neuroleptics (rater judgement), as in OCCPI 2.5.

The frequency distributions of the above binary variables in the three subtypes were calculated, and the differences tested using chi-squared tests of homogeneity. The correlations are shown in Tables 7.6 a-c. Among "premorbid" variables, Type A is characterised by a relatively high frequency of obstetric complications, developmental problems, premorbid personality disorder, single marital status, poor premorbid work adjustment, positive offending history, and long prodromal phase. Indeed, all positive "premorbid" features were commoner in Type A than in Types B or C, with the exception of family history of psychiatric disorder other than schizophrenia (mostly affective disorder), which was commonest in Type C.

In terms of the "phenomenological" variables, the subtypes did not differ significantly in first rank symptoms, auditory hallucinations or bizarre delusions. This is to be expected since these are the symptoms typical of schizophrenia. Type A had the highest frequencies of thought disorder, negative symptoms, manic symptomatology, inappropriate affect, bizarre behaviour and catatonia. The high rate of "manic" symptoms probably reflects the broad definition used; for example, "distractibility" could also be a sign of acute schizophrenic psychosis. Type B had the highest frequency of paranoid delusions. Type C had the highest frequencies of depressive

symptomatology and unspecified affective symptoms. Differences in response to neuroleptic treatment were only marginally significant, with Type A being the least and Type C the most frequently responsive.

In summary, then, the results suggest three types of illness, viz.:

(1) Classes 1 and 4 of M5 are characterised by early onset, poor premorbid adjustment, restricted affect, and male preponderance. This form is associated with premorbid social maladjustment, personality disorder and positive offending history, and has a high frequency of restricted and inappropriate affect, negative features, thought disorder, and catatonia. Furthermore, it has the highest rates of a family history of schizophrenia and of a history of obstetric complications, aetiological factors which have been implicated in the neurodevelopmental abnormality in schizophrenia (see Murray et al, 1992). Winter birth, on the other hand, does not appear to be particularly common. The identification of this subtype using latent class analysis, is in line with expectations from the literature on gender differences in schizophrenia (as reviewed above), and accords well with the results of the classical analyses of gender differences in this sample, as detailed above.

It should be emphasised that none of the variables included in this analysis are direct measures of structural brain abnormalities, and thus the proposed "neurodevelopmental" aetiology is presumptive. However, some support for this assumption comes from studies showing an association between poor premorbid functioning (and negative symptomatology) and structural brain abnormalities in schizophrenia (see Weinberger et al, 1980; Pearlson et al, 1985, 1989; Orel et al, 1991), as well as the fact that schizophrenic males (and expressly young males) appear most

likely to show such abnormalities on neuroimaging investigations (see above). To address this question definitively, a prospective study including measures of structural brain abnormalities would be required.

(2) Classes 2 and 5 of M5 are characterised by later onset, paranoid delusions, and an almost equal sex ratio. It is generally a milder illness with much less restricted affect, negative features and thought disorder. It is proposed that these classes represent a "paranoid" subtype, similar to the paranoid subtype of Tsuang and Winokur (1974), and to P cluster of Farmer et al (1983). In line with these previous studies, the "paranoid group" showed a lower familial risk for schizophrenia. The season of birth effect in this group, with 52% of patients having a date of birth between December and April, is intriguing. In an extensive review of the literature, Bradbury and Miller (1985) found no consistent schizophrenic subtype to be more prone to the seasonality effect. However, Opler et al (1984) and Takei et al (1992) reported more winter birth effect in patients with later onset of illness.

(3) Classes 3 and 6 of M5 are characterised by dysphoria, paranoid delusions, a negligible familial risk of schizophrenia, and an absence of men. It is proposed that these classes represent a "schizoaffective" subtype (see below).

DISCUSSION

Limitations of the current study:

Data were obtained retrospectively from hospital case notes, rather than directly from the patients. Although the quality of the case notes were generally high, certain items, particularly those concerning the distant past, or distant relatives, were likely to be inadequately recorded. However, there is no reason to suspect any systematic reporting bias. Adequate information was not always available to rate all the OCCPI items. For these reasons, the decision was made to measure characteristics dichotomously, rather than on a more graded scale. No doubt this resulted in some loss of information, but it was still preferable to the use of a scale whose validity was uncertain. However, while the data may lack precision, they are at least unbiased, since ratings were made before the latent class analysis, and without knowledge of the proposed typology.

Interpretation and relationship to previous attempts at subtyping schizophrenia:

Bearing these limitations in mind, the results suggest that broadly defined schizophrenia is a mixture of two, and possibly three, fairly distinct conditions.

With regard to the separation between Types A and B, it is interesting that, historically, Kraepelin was uncertain about the relationship between paranoid psychosis and dementia praecox. "The most criticism has always been directed against the inclusion of the paranoid forms in dementia praecox.... how wide the circle of paranoid cases must be drawn, which we are justified in regarding as expressions of that disease" (Kraepelin, 1919). However, without multivariate statistical methods, he was unable to find a clear separation between paranoid psychosis and the

rest of schizophrenia: "Everywhere the same basic disturbances recur again and again.... not all of these characteristics can be demonstrated in each and every case. Nevertheless the survey of a large number of complete observations teaches us that we never find a picture which does not show a link by very gradual transitions with all the others...." (Kraepelin, 1909).

This is not the first attempt, since Kraepelin, to investigate a potential separation between "paranoid" and "non-paranoid" schizophrenia. Tsuang and Winokur (1974) classified a group of schizophrenic patients into hebephrenic and paranoid subtypes by clinical judgment, and found that hebephrenics had earlier onset, more flat affect and thought disorder, higher familial morbidity, and worse outcome. Farmer et al (1983) performed a hierarchical cluster analysis, and found two reasonably distinct clusters, an H type characterised by family history of schizophrenia, poor premorbid adjustment, early onset, bizarre behaviour, blunted affect, and incoherent speech, and a P type with well organised delusions.

Are Type A and Type B two distinct illnesses, or are they more and less severe forms of the same disorder? Farmer et al (1984) claimed that the rates of both H and P subtypes were significantly higher in the cotwins of both MZ and DZ H type probands when compared to cotwins of MZ and DZ P type probands. It was therefore suggested that the two subtypes were not genetically distinct conditions, but were more likely to represent varieties of disorder that occupy "different positions on the same multifactorial continuum of liability."

In contrast, I suggest that Type A is a "neurodevelopmental" disorder distinct from Type B (see above). However, it is probable that there is a degree of overlap in the aetiologies (genetic and/or

environmental) of the 2 subtypes (as discussed in Chapter 6).

A "schizoaffective" subtype?

While patients with prominent dysphoria undoubtedly exist ("Type C"), it is not clear whether they constitute a group distinct from the first two types. However, the fact that the patients in this group often had a family history of psychiatric disorders other than schizophrenia (most of which would have been affective disorders) suggests aetiological differences from the first two subtypes. In one of the few published studies to compare schizophrenic patients with and without a family history of affective disorder, Kendler and Hays (1983) found that those patients with a family history of depression were more likely than those without such a history to develop a depressive syndrome during follow-up. Also, Owen et al (1989) found that schizophrenic patients with a family history of affective disorder were less likely to have structural brain abnormalities than are other schizophrenic patients.

Previous attempts at subtyping schizophrenia have not identified such a group of patients. This may be due to patient selection: while the current analyses involved the broad "ICD-9" conception of schizophrenia and related disorders, others (eg. Tsuang & Winokur, 1974) have used restrictive criteria (e.g. those of Feighner et al, 1972) which could have excluded such patients. The delineation of this subtype is in line with the findings of gender differences in diagnosis outlined in the classical analyses above, of a female propensity to fulfil criteria for affective and "atypical" psychoses. As such, the results are consonant with suggestions (detailed above) that some late-onset females who are diagnosed as having schizophrenia, have a form of illness related to affective disorder in aetiology.

CHAPTER 8: LATE ONSET SCHIZOPHRENIA

Despite the plethora of epidemiological investigations in schizophrenia, late-onset illness has all too often been ignored. The reasons (until recently) for this lack of interest in late-onset schizophrenia lie, in part at least, in the tacit acceptance (expressly in the US, and embodied in DSM-III criteria for schizophrenia), that schizophrenia cannot manifest for the first time after 44 years of age (APA, 1980). The European tradition has been somewhat different, and ICD-9 (WHO, 1980) does not have an age-at-onset stipulation for schizophrenia; furthermore, paraphrenia, akin to Roth's (1955) concept of "late paraphrenia" as a paranoid delusional illness with onset usually after the age of 60, is recognised in ICD-9, though it has been dropped from ICD-10 (WHO, 1993).

It is thus not surprising that most of the published investigations of the epidemiology of late-onset schizophrenia are to be found in the European literature. The bulk of the studies have been of the prevalence of late-onset schizophrenia in hospitalised samples. Fewer investigators have tried to assess the prevalence in community samples, and there have been even fewer incidence studies specifically of late-onset illness. An excess of females amongst late-onset schizophrenics has been widely reported, but few studies have addressed this matter directly.

Studies of prevalence and age-at-onset distribution of late-onset schizophrenia have recently been reviewed by Harris & Jeste (1988). They noted a marked inconsistency in the reported findings, due, inter alia, to differing case-finding methodology, and a failure to employ standardised diagnostic criteria. On the basis of those 8 studies which reported the occurrence of late onset schizophrenia among schizophreniA patients of varying ages, Harris and Jeste estimated (weighted

means based on sample size) that around 23% of schizophrenic patients could be considered to have a late onset of illness (generally onset > 40 years); the range was 15.4% to 32.0%. The mean proportion of late onset schizophrenics amongst populations of elderly patients with schizophrenia, was 31%.

Ten of the studies reviewed by Harris and Jeste reported on differences in the proportion of schizophrenics with age-at-onset before and after age 60 years. The weighted means showed that around 14% of late-onset (usually >40 years) schizophrenia patients first manifest the illness after 60. Six of the studies gave a further breakdown of age-at-onset. Amongst the late-onset patients (onset > 40), a mean of 57.5% had an onset between 40 and 50 years, 30.2% between 50 and 60, and 12.3% after 60. This translates as around 13% (40-50 years), 7% (50-60 years) and 3% (> 60 years) of all patients with schizophrenia.

It is important to note that almost all of the studies reviewed by Harris and Jeste are based on unselected samples of patients, and are thus not true prevalence studies. Also, most are based on patients admitted to hospital. There have been very few studies of the community prevalence of late-onset schizophrenia. Post (1966) has outlined the difficulties inherent in such studies, pointing to the fact that Kay et al (1964), in a community study, identified no patients fulfilling Roth's (1955) criteria for late paraphrenia among 309 persons over 65 years of age in Newcastle, while it was later found that at least 8 patients from that population had been hospitalised or institutionalised with late paraphrenia. In community surveys, Parsons (1964) found a prevalence of late paraphrenia of 1.7% of over-65's in a Welsh town, and Williamson et al (1964) 1% in a Scottish borough. More recently, Christenson and Blazer (1984) found that 4% of 997 elderly

persons exhibited symptoms of pervasive persecutory delusions. From the 5-site ECA study in the US, Keith et al (1991) reported one-year prevalence rates for schizophrenia to be 0.6% for 45-64 year-olds, falling to 0.2% amongst the over-65's. The rate for 18-29 year-olds was 1.2%, and for those aged 30-44, 1.5%. As the ECA figures are based solely on self report by the interviewed subjects, they must be viewed with some caution.

An alternative approach, which avoided diagnostic issues, has been used by Tien (1991), who established incidence rates for hallucinations, by age and sex, in the ECA study. Between the ages of 18 and 60, the incidence of visual hallucinations was slightly higher in males than females, but after 60 years (and expressly after 80) there was an emphatic rise in the rates for females. For males, there was a much more modest rise at around 70 years of age. Auditory hallucinations showed a different distribution, with a peak for males at 25-30 years; females showed a later peak at 40-50, with a subsequent rise after 70. Of course, hallucinations are not pathognomonic for schizophrenia, but they are often manifestations of the illness. Thus, these data potentially provide an insight into sex effects in the ageing brain, and have implications for our understanding of age and sex effects in schizophrenia itself.

Few investigators have specifically assessed the <u>incidence</u> of late-onset schizophrenia. Kay (1972), using first admission data from England and Wales for 1966, found rates of schizophrenic illnesses (including paranoia and paranoid states) over 65 years of age to be between 10 and 15 per 100,000 for males, and between 20 and 25 per 100,000 for females.

Of course, incidence rates determined by hospital admission data are necessarily biased, and almost certainly underestimate the true incidence of the disease. Even though there have been claims that practically all individuals with schizophrenia are eventually admitted to hospital, the available data do not support that this assumption, as discussed in Chapter 3. For example, Geddes and Kendell (1992) reported that 8% of schizophrenia patients on the Lothian Psychiatric Case Register, in Scotland, had never been admitted to a psychiatric hospital. In the ECA study, a massive 40% of patients who received a life-time diagnosis of schizophrenia reported they had never had a psychiatric admission (Keith et al, 1991). There are reasons to suspect that individuals with late-onset schizophrenia are particularly likely not to be admitted. Such individuals often have a long history of eccentricity and social isolation, yet are not usually educationally or occupationally compromised (eg. Kay & Roth, 1961; Post, 1966). Thus, it might be expected that many individuals in this group could carry on functioning in the community even when deluded; the lack of friends and other social contacts would militate against them coming to the notice of the psychiatric services. Indeed, in the survey of community elderly by Christenson and Blazer (1984) quoted above, only half of those individuals exhibiting pervasive persecutory delusions perceived the need for help, and very few had had psychiatric contact.

One way in which some of the bias arising from the use of hospitalised patient populations can be avoided, is the use of psychiatric case registers, which record all contacts with the psychiatric services, not just admissions. The author is aware of only one study which has employed such a register specifically to examine the incidence of late-onset schizophrenia. In this study, Holden (1987) estimated annual rates of late paraphrenia of 17 to 24 per 100 000 population, depending on whether "organic" cases were included or not; one problem with the study is the very small

sample size, resulting in wide confidence limits.

Gender differences in late-onset schizophrenia have been widely reported. An extensive discussion of gender differences in schizophrenia is provided in Chapter 6. Suffice to say here that a female excess is seen in almost all studies of late onset schizophrenia which have included both sexes. The female:male ratio in the over-40's ranges from 5:3 (Bland, 1977) to 1.9:1 (Bleuler, 1943); in very-late-onset cases (onset >60), the female preponderance is even more marked, ranging from 3:1 (Roth, 1955) to 45:2 (Herbert & Jacobsen, 1967). Figure 8.1 shows first admission rates for schizophrenia, by sex, for England in 1984. It will be noted that there is a dramatic excess of males under age 40, while females predominate in the later-onset patients. The male:female ratio peaks at 2.1:1 in the 20-24 year age group, reaches unity at around the age of 40, and declines to 0.6:1 at around 65 years.

The large study of Bland (1977) suggested an increase in the female:male ratio with increasing age at first hospitalisation, but the data presented in figure 8.1 are equivocal in this respect. Again, one of the difficulties with these studies is that they are based almost exclusively on hospitalised samples, leading to conclusions being drawn on relatively severely affected patients, as outlined above.

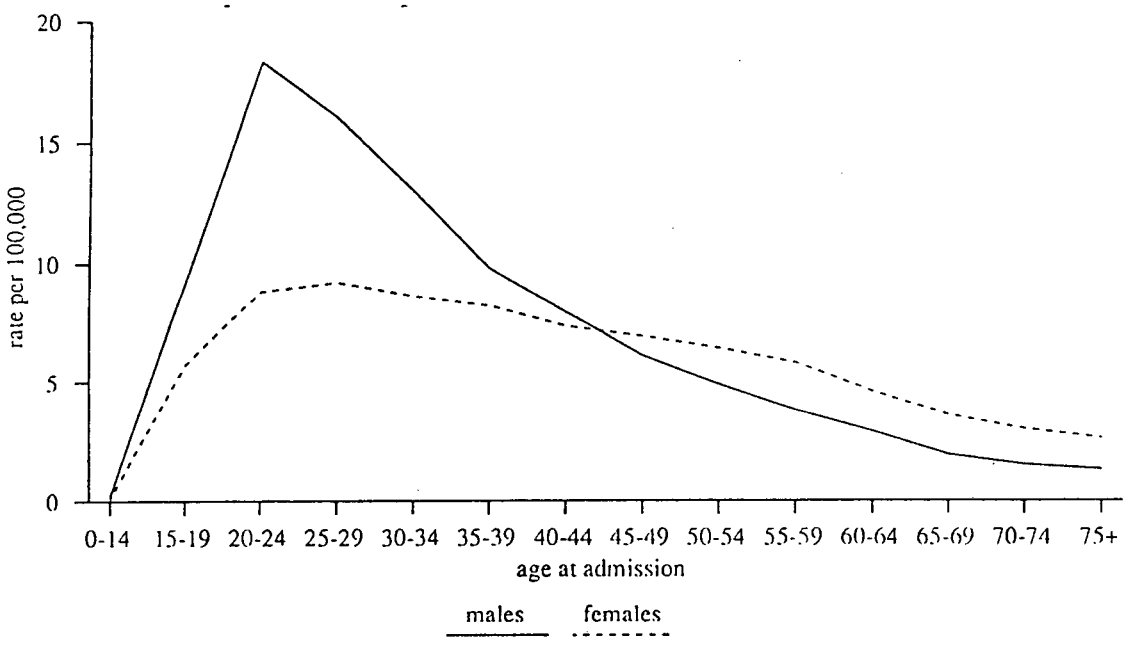

Figure 8.1: First-admission rates for schizophrenia, by gender (England, 1984)

THE CURRENT STUDY:

The methodological problems pertaining to most previous investigations of late-onset schizophrenia, as outlined above, were circumvented by using the Camberwell Register sample. Thus, a broad range of diagnostic groups across all ages at onset were included in the analyses. There was also no hospitalisation bias, although there is reason to suspect, for the reasons given above, that patients with a late onset of illness might be particularly unlikely to make contact with the psychiatric services.

Incidence rates:

Figure 8.2 shows annual incidence rates for broadly defined schizophrenia and related disorders, as well as for those individuals fulfilling DSM-IIIR criteria for schizophrenia. The DSM-IIIR rates were adjusted for missing notes using the appropriate proportion of patients in the total sample fulfilling DSM-IIIR criteria in each 10-year age-at-onset band. Contrary to expectation, a higher proportion of patients with onset of illness over 44 years fulfilled DSM-IIIR criteria for schizophrenia (52%), compared with younger-onset patients (38%). This is underlined by the fact that later-onset patients were also more likely to have had an illness lasting more than 6 months (53% of over-44's vs. 36% of patients with onset before 45 years). The distribution by age-at-onset was much the same irrespective of stringency of diagnosis. The highest rates were in the 16-25 year age group, with a slight 2nd peak in the 46-55 year group, and a third (more emphatic) peak in the over-65's.

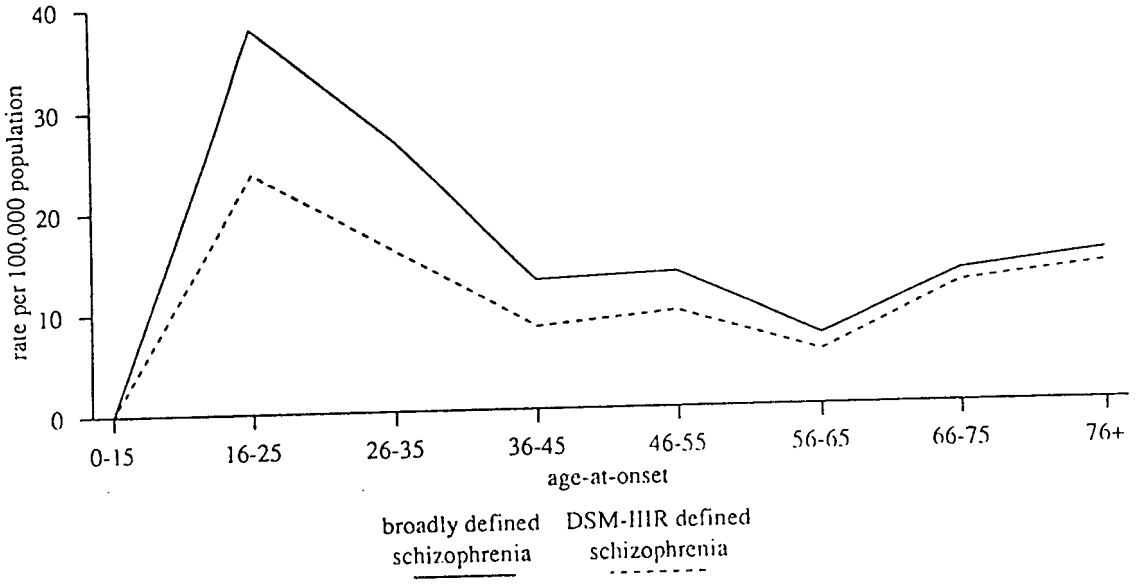

Figure 8.2: First-contact rates for broadly defined and DSM-IIIR defined schizophrenia

Phenomenological and demographic issues:

The data on diagnostic criteria are somewhat misleading, in that a closer analysis of phenomenological variables revealed distinct differences between patients with an early and those with a late (>44 yr) onset of illness. The differences are detailed in Table 8.1 a,b (all ratings as in OCCPI 2.5; Appendix 3). Specifically, formal thought disorder, passivity phenomena, thought interference, and negative symptoms (paucity of thought/speech, restricted affect) were more common in patients with an onset of illness under 45 years of age, while persecutory delusions, expressly in an elaborately organised form, and any form of auditory hallucination were more common in the late-onset group. Indeed, the only symptoms not significantly differently distributed between early- and late-onset patients were delusional perception, bizarre delusions, and delusions of reference.

In terms of premorbid parameters, patients with an onset of illness after 45 years of age fared better than their early-onset counterparts. Comparison of the two groups on levels of educational achievement were not meaningful as opportunities and expectations regarding schooling and tertiary education have changed markedly in the latter half of this century, a fact underlined by fully 84% of the later-onset group not having had any education beyond the age of 14 years. However, OCCPI 2.5 criteria for premorbid work adjustment are not prejudiced by educational achievement, and the early- and late-onset groups differed markedly in this regard; 50% of the former but only 15% of the latter were judged to have had poor premorbid work adjustment (RR 0.17; 95%CI 0.10-0.29). Similarly, 22% of late- vs. 43% of early-onset patients were rated (OCCPI criteria) as having shown poor premorbid social adjustment (RR 0.37; 95%CI 0.23-0.58). Consonant with this finding, 66% of the later-onset group were currently or had been married,

Table 8.1 (a): Prevalence of symptoms more common in early-onset patients

	PERCENTAGE IN EARLY-ONSET PATIENTS (n=336)	PERCENTAGE IN LATE-ONSET PATIENTS (n=134)	RISK RATIO; 95%CI
Positive formal thought disorder	27.4	10.4	0.31; 0.17-0.56
Negative formal thought disorder	11.0	2.2	0.18; 0.05-0.61
Inappropriate affect	17.8	4.4	0.21; 0.09-0.51
Restricted affect	13.1	3.7	0.26; 0.10-0.66
Passivity delusions	29.5	17.2	0.48; 0.29-0.79
Catatonia	8.0	2.2	0.31; 0.10-0.89
Primary delusions other than delusional perceptn	13.7	4.4	0.29; 0.12-0.69
Thought insertion	15.2	7.5	0.44; 0.22-0.90
Thought withdrawal	12.5	2.4	0.32; 0.11-0.93
Grandiose delusions	24.1	14.9	0.55; 0.32-0.94

Table 8.1 (b): Prevalence of symptoms more common in late-onset symptoms

	PERCENTAGE IN EARLY-ONSET PATIENTS (n=336)	PERCENTAGE IN LATE-ONSET PATIENTS (n=134)	RISK RATIO; 95%CI
Persecutory delusions	71.4	93.3	4.11; 2.17-7.77
Organised delusions	19.6	54.5	4.80; 3.13-7.42
Persecutory delusions with hallucinations	58.6	73.9	1.92; 1.25-3.00
Third person auditory hallucinations	28.9	42.5	1.71; 1.17-2.67
Accusatory or abusive voices	45.5	61.2	1.85; 1.23-2.77
Running commentary	14.6	22.4	1.72; 1.04-2.84

the proportion in the early-onset group being only 33% (RR 0.26; 95%CI 0.17-0.40).

Gender differences:

The mean age-at-onset of illness for the broadly defined schizophrenia group was 31.2 years for males and 41.1 years for females. Figure 8.3 shows the proportion of males and females in each 10-year age-at-onset band. Nearly half the male patients had an onset of illness before the age of 25 years; thereafter there was a monotonous decline, with only 12% of male patients first manifesting their illness between the ages of 46 and 65, and 4% after 65 years of age. In contrast, less than a third of the females had manifested their illness by the age of 25, and the overall age-at-onset distribution was more even over the years, with 20% having an onset of illness between 46 and 65 years, and fully 18% after 65.

The dramatic differences in age-at-onset distribution between the sexes is also seen in figure 8.4, which shows male:female ratios by 10-year age-at-onset bands. The ratio is > 1 under the age of 35, whereafter the ratio declines dramatically to 0.15 (3 males to 20 females) in the over 75's.

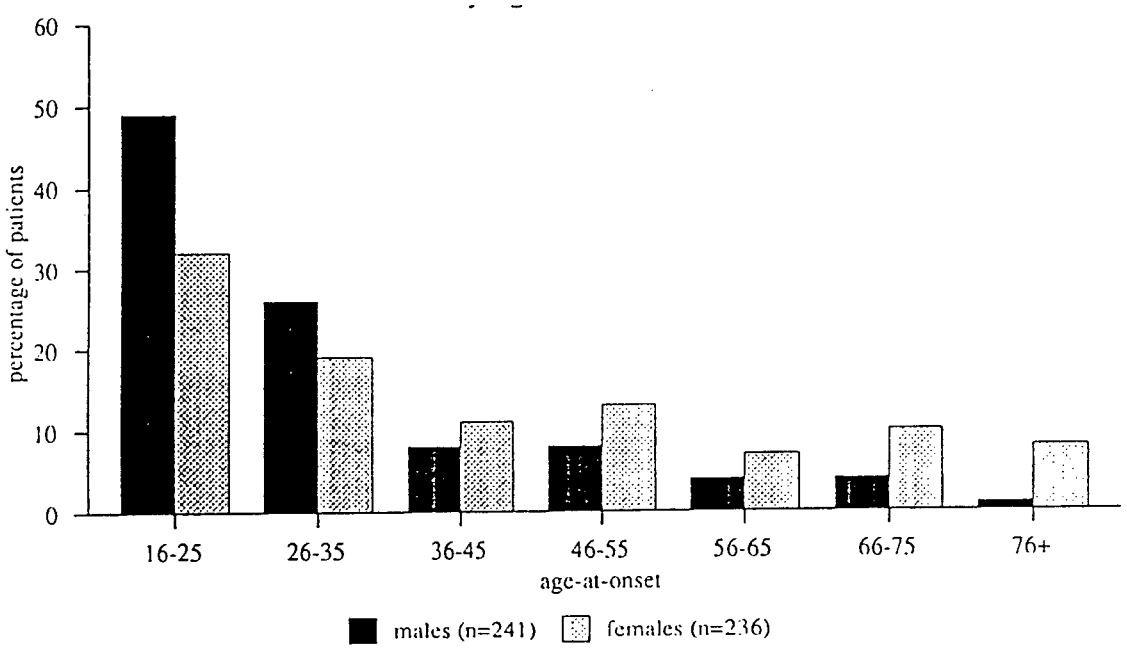

Figure 8.3: Proportions of male and female schizophrenia patients, by age-at-onset

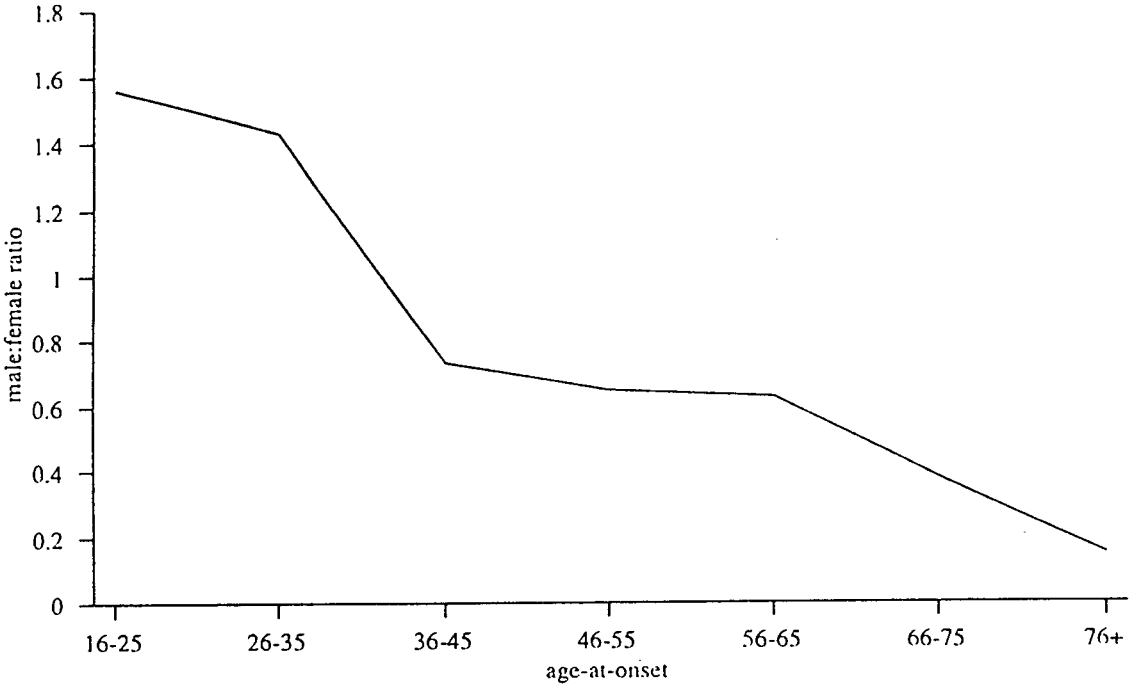

Figure 8.4: Male:female ratio of schizophrenia patients, by age-at-onset

DISCUSSION

Twenty-eight percent of the patients had an onset of illness over the age of 44 years, and 12% over 64. These figures are rather higher than the proportions estimated by Harris and Jeste (1988) detailed above. Of interest is the high proportion of late-onset patients who fulfilled stringent DSM-IIIR criteria for schizophrenia. Few other studies have reported on how many late-onset schizophrenics meet operationalised criteria for schizophrenia, but Rabins et al (1984) found that 21 of 35 (60%) of their group of patients with onset after 44 years met DSM-III criteria for schizophrenia after the age-at-onset stipulation was removed. Thus, the manifestation of stringently defined schizophrenia is by no means confined to younger ages. The incidence curves for schizophrenia in the current sample underline this fact. Even when only those patients fulfilling DSM-IIIR criteria are considered, the annual incidence rate for late-onset schizophrenia was 12.6 per 100 000 population, half that for the 16-25 year age-group.

The phenomenological differences between early- and late-onset patients are largely in keeping with previous reports. For example, in a comparative case-note study, Pearlson et al (1989) found that, compared to their early-onset counterparts, schizophrenics with an onset of illness after the age of 44 were more likely to be deluded and to experience hallucinations; in contrast, they were much less likely to exhibit formal thought disorder or affective blunting. Such findings suggest that it is premature to consider early- and late-onset schizophrenics homogeneous, and there are implications for the understanding of the aetiology of this group of conditions.

The fact that late-onset patients were more likely than those with early onset to have shown good premorbid adjustment in occupational terms is also consonant with the literature (eg. Post, 1966).

Previous investigators (eg. Kay & Roth, 1961; Post, 1966) have noted that many very-late-onset schizophrenics have been rather socially isolated throughout their lives. The finding that it was the early-onset group who were particularly likely to have exhibited poor premorbid social adjustment places such reports in context, and underscores data from many sources (see Murray et al, 1992 for a review) that early-onset schizophrenics have a pernicious form of the illness which is particularly likely to be associated with premorbid dysfunction. These results are directly in line with the conclusions drawn in Chapter 6 and 7.

Gender differences:

A later onset of schizophrenia in females is a remarkably consistent finding across studies, the difference being usually of the order of 5 years (see Lewine, 1988). Most studies examining this question have confined themselves to younger patients; certainly few have included those with an onset after the age of 60. The wide sex-differential in age at onset in the current study is due to the inclusion of the late- and very-late-onset groups, amongst whom there is a marked female preponderance. A full discussion of gender differences in the current sample is provided in Chapters 6 and 7.

SUMMARY & CONCLUDING REMARKS

Over many years, schizophrenia research has been bedeviled by fundamental methodological problems, in particular the sampling frame used (very few studies being epidemiologically sound in this respect), and diagnostic criteria applied. I believe that the strategy used in the current study addressed both of these crucial areas of potential bias, in that the sample included all first contacts with the psychiatric services from a defined catchment area, and a very broad diagnostic group were ascertained, with a wide range of operational criteria of differing stringency and emphasis being applied. Another advantage of the study design was that it allowed assessment of changes over a 20-year period. The large number of patients generated allowed statistically robust analyses to be performed, even on sub-groups of patients.

Diagnostic uniformity was ensured by the re-diagnosis of all patients with a non-affective non-organic psychosis who made their first contact with the psychiatric services of Camberwell over a period of two decades. As far as I am aware, this is the first time this strategy has been applied to such a large group of patients over such a protracted period. The study thus gives an insight into the features which dictate whether particular patients fulfil certain diagnostic criteria for psychotic illness, as has been discussed in full elsewhere (Farmer et al, 1992). The relevance for our understanding of gender differences in schizophrenia has been addressed extensively in this Thesis (see below).

An indication of potential **admission bias** in studies of schizophrenia patients was given by analyses of those demographic and illness factors which predicted admission to hospital. The decision to admit a psychiatrically ill patient will depend, inter alia, on (a) the mental state, and social characteristics of the patient; (b) the past psychiatric history; (c) the place and time that the initial assessment takes place; and (d) the availability of alternatives to hospitalisation. The current study was able to address only the first group of variables. Thus, patients presenting for the first time with a non-organic non-affective functional psychosis were more likely to be admitted if: (i) there was police involvement, and/or violence to self or others; (ii) they met criteria for schizo-affective psychosis; (iii) they exhibited paranoid/grandiose delusions and auditory hallucinations; (iv) they were behaving bizarrely.

This knowledge is important for accurate conclusions to be drawn from studies exclusively of hospitalised patients. For example, the data suggest that the association between violence and schizophrenia would be exaggerated in hospitalised samples. On the other hand, some true findings might simply be dismissed as due to admission bias. In this context, it might have been expected that Afro-Caribbeans would be more likely to be admitted than Caucasians, and the fact that this was not so supports the notion that previous findings of an excess of Afro-Caribbeans amongst inpatients with schizophrenia is not explicable on the basis of admission bias.

The sampling strategy used in this study provided a unique opportunity to investigate **trends** in the treated incidence of schizophrenia over time. In particular, the uniform and thorough ascertainment of all contacts with the psychiatric services (not just patients admitted to hospital), and the use of standardised operationalised diagnostic criteria, enabled the avoidance of the most

important design faults associated with many previous studies of this issue.

Furthermore, the discrepancy with National hospital admission figures for England over the same period, could be dissected in terms of likely biases. The finding of high rates of schizophrenia in Afro-Caribbean migrants as the most likely explanation for this discrepancy, is in accord with an ever-widening literature on psychosis in migrants and ethnic minorities. The use of operational diagnostic criteria was critical in these analyses, as has been underlined by those (eg. Littlewood & Lipsedge, 1982) who believe that many migrants exhibit short-lived acute psychotic reactions which should not be labelled "schizophrenia".

Future research needs to focus on what accounts for the peculiar susceptibility of such groups to psychotic breakdown; an encouraging line of work is to look at other characteristics of ethnic minorities, in particular socio-economic disadvantage, as potential confounding variables (eg. Boddington, 1992).

The well known fact that individuals with schizophrenia are over-represented in **lower socio-economic groups** in deprived inner-city areas has usually been interpreted as evidence of "social drift" of ill individuals. The findings presented in this Thesis, that schizophrenia patients were more likely than non-schizophrenia patients to have born into deprived households in inner London, suggests that social deprivation in utero or in early childhood might be aetiologically important in some cases of schizophrenia.

There is now a great deal of evidence that at least some individuals with schizophrenia have an illness consequent upon neurodevelopmental deviance, cerebral insult being sustained very early in life but manifesting symptoms only as the brain matures (Weinberger, 1987; Murray et al, 1992). Possible environmental causes of such brain insult include obstetric complications, low birth weight, and maternal viral infections. Regarding the latter, three studies (Machon et al, 1983; O'Callaghan et al, 1992; Takei et al, 1992) have shown that city-born, as opposed to rural-born, schizophrenia patients are particularly liable to have been born in the winter months, when respiratory viral infections are especially prevalent. Research should now be directed to establish whether it is overcrowding within households, and within cities, with consequent greater exposure to viral infection during pregnancy, which mediates the increased risk of schizophrenia in those born into working class households in the inner city.

Gender differences in schizophrenia are increasingly being recognised as providing potential clues to the aetiology of this group of disorders. Again, most previous studies in this area have been on hospitalised samples, biasing towards more severely affected (male) patients. Diagnostic issues and gender have not hitherto been systematically addressed in an epidemiologically-based sample. The gender analyses presented here are based on a large representative catchment-area sample of patients not preselected according to age-at-onset or any specific set of diagnostic criteria.

Different analytical approaches suggested that gender differences in the sample can be interpreted in terms of a differential susceptibility of men and women to subtypes of schizophrenia. The most robust subtype is a severe early-onset illness associated with premorbid dysfunction,

negative symptomatology, a family history of schizophrenia, and obstetric complications; a presumed neurodevelopmental aetiology in this group could be investigated with neuroimaging and neuropathological studies.

A paranoid subtype, with prominent paranoid ideation but less premorbid dysfunction and lower family loading for schizophrenia, was also delineated, in line with a number of other typological investigations of schizophrenia. A novel finding in the current study was an association of this subtype with winter birth, suggesting some season environmental aetiological factor (possibly a virus) might be operating in some such individuals.

Finally, the finding of a group of females with prominent affective symptomatology and a family history of psychiatric illness other than schizophrenia (mostly affective disorder), lends support to the notion that some females usually labelled "schizophrenic" have an illness with links to affective disorder.

Further research should address these issues in prospectively collected series of patients, where phenomenological and premorbid variables can be collected, accurate obstetric and family histories ascertained, and neuroimaging studies performed.

As a caveat, the typology does not adequately explain those patients with a very late onset of illness ("late paraphrenia"). Recent findings (reviewed by Castle & Howard, 1992) that a substantial proportion of such patients have structural brain abnormalities, and mild cognitive deficits (Holden, 1987; Hymas et al, 1989), suggests that organic brain dysfunction serves as a "final common pathway" in many patients in this group (see Murray et al, 1992).

Schizophrenia of **late onset** has all too often been ignored by schizophrenia researchers. This study reinforces the fact that the onset of a non-affective "functional" psychosis in later life is by no means rare. Furthermore, the study shows that there are differences between patients with an early and alate onset of illness,,both in terms of illness presentation, and premorbid functioning. This challenges the widely held view that schizophrenia of late onset is merely a milder form of the same illness as that presenting at earlier ages.

Further examination of this group of patients, and consideration of age at onset in schizophrenia research in general, is long overdue. The research challenge offered by late-onset schizophrenia is exciting. Here is a neglected region of schizophrenia, whose exploration does not need to await the development of new research procedures and in which the observed combined effects of neurodevelopment and degeneration, rather than neurodevelopment alone might provide new ideas about the aetiology of all schizophrenia. I trust that, in the rush to employ new technologies such as magnetic resonance imaging and positron emission tomography in this group of patients, the epidemiological context will not be forgotten.

ACKNOWLEDGEMENTS

In the conduct of this study, a number of individuals gave help and support. Dr Simon Wessely rated around half of the case records, and provided general guidance. Dr Pak Sham's help in the technicalities of the latent class analysis, was indispensable. Sandie Sari and Jenny Marchant gave friendship and technical assistance with the figures and tables. Anna Waterreus aided the arduous task of collating and checking the references. Professor Frances Ames gave useful advice and enduring support. Professor Robin Murray provided the original inspiration for the study, and without his help and encouragement it would never have been completed. The vision of Professor John Wing in establishing the Camberwell Register should also be acknowledged.

Publications which have arisen from these data include:

Castle D, Wessely S, Der G & Murray RM. "The incidence of operationally defined schizophrenia in Camberwell, 1965 to 1984"
British Journal of Psychiatry 1991; 159: 790-794

Wessely S, **Castle D**, Der G & Murray RM. "Schizophrenia and Afro-Caribbeans: A case control study" British Journal of Psychiatry 1991; 159: 795-801

Farmer A, Wessely S, **Castle D** & McGuffin P. "Methodological issues in using a polydiagnostic approach to define psychotic illness"
British Journal of Psychiatry 1992; 161: 824-830

Wessely S & **Castle D**. "How valid are psychiatric case notes for assessing criminal convictions?"
Journal of Forensic Psychiatry 1992; 3: 359-363

Castle DJ, Scott K, Wessely S & Murray RM. "Does social deprivation during gestation and early life predispose to later schizophrenia?"
Social Psychiatry and Psychiatric Epidemiology 1993; 28: 1-4

Castle DJ, Wessely S & Murray RM. "Sex and schizophrenia: Effects of diagnostic stringency and associations with premorbid variables"
British Journal of Psychiatry 1993; 162: 658-664

Castle DJ, Sham P, Wessely S & Murray RM. "The subtyping of schizophrenia in men and women: A latent class analysis" Psychological Medicine 1994; 24: 41-51

Sham P, **Castle DJ**, Wessely S & Murray RM. "The subtyping of schizophrenia in men and women: Further exploration of a latent class typology"
Schizophrenia Research (in press)

Williams J, Farmer AE, Wessely S, **Castle D** & McGuffin P. "Heterogeneity in schizophrenia: An extended replication of the hebephrenic-like and paranoid-like subtypes" Psychiatry Research 1993; 49: 199-210

Castle DJ, Phelan M, Wessely S & Murray RM. "Which patients with non-affective functional psychosis are not admitted at first psychiatric contact? An analysis of 484 patients" British Journal of Psychiatry 1994; 165: 101-106

Wessely S, **Castle D**, Douglas A & Taylor P. "The criminal careers of incident cases of schizophrenia" Psychological Medicine 1994; 24: 483-502

Howard R, **Castle DJ**, Wessely S & Murray RM. "A comparative study of 470 cases of early-onset and late-onset schizophrenia" British Journal of Psychiatry 1993; 163: 352-357

Castle DJ & Murray RM. "The epidemiology of late onset schizophrenia"
Schizophrenia Bulletin 1993; 19: 691-700

REFERENCES

Akbarian, S.; Bunney, W.E.; Potkin, S.G.; Wigal, S.B.; Hagman, J.O.; Sandman, C.A.; and Jones, E.G. Altered distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase cells in frontal lobe of schizophrenics implies disturbances of cortical development. Archives of General Psychiatry, 50: 169-177, 1993a

Akbarian, S.; Vinuela, A.; Kim, J.J.; Potkin, S.G.; Bunney, W.E.; and Jones, E.G. Distorted distribution of nicotinamide-adenine dinucleotide phosphate-diaphorase neurones in temporal lobe of schizophrenics implies anomalous cortical development. Archives of General Psychiatry, 50: 178-187, 1993b

Albus, M.; Hueber, S.; Kraus, G.; and Lechleuthner, T. Influence of gender, age at onset and family loading on the course of schizophrenia, schizoaffective and bipolar disorders. Schizophrenia Research, 9: 129, 1993

American Psychiatric Association. Diagnostic and Statistical Manual for the Classification of Psychiatric Diseases (3rd ed). Washington DC: APA, 1980

American Psychiatric Association. Diagnostic and Statistical Manual for the Classification of Psychiatric Diseases (3rd ed, revised). Washington DC: APA, 1987

Andreasen, N.C. The Scale for Assessment of Positive Symptoms. Iowa City, Iowa: University of Iowa, 1983a

Andreasen, N.C. The Scale for Assessment of Negative Symptoms. Iowa City, Iowa: University of Iowa, 1983b

Andreasen, N.C.; Flaum, M.A.; Swayze, V.W.; Tyrrell, M.S.; and Arndt, S. Positive and negative symptoms in schizophrenia: a critical appraisal. Archives of General Psychiatry, 47: 615-621, 1990

Andreasen, N.C.; Flaum, M.A.; Swayze, V.W.; Harris, G.; Cizadlo, T; and Gupta, S. "Gender differences in the brain in schizophrenia". Presented at the American Psychiatric Association Meeting, San Francisco, California, May 1993

Angermeyer, M.C.; Goldstein, J.M.; and Kuhn, L. Gender differences in schizophrenia: rehospitalisation and community survival. Psychological Medicine, 19: 365-382, 1989

Angermeyer, M.C.; Kuhn, L.; and Goldstein, J.M. Gender and the course of schizophrenia: differences in treated outcomes. Schizophrenia Bulletin, 16: 293-307, 1990

Astrup, C.; and Odegaard, O. Internal migration and mental illness in Norway. Psychiatry Quarterly 34: 116-130, 1961

Aylward, E.; Walker, E.; and Bettes, B. Intelligence in schizophrenia: Meta-analysis of the research. Schizophrenia Bulletin, 10: 430-459, 1984

Balarajan, R., Yuen, P.; and Machin, D. Deprivation and general practitioner workload. British Medical Journal, 304: 116-130, 1992

Bardenstein, K.K.; and McGlashan, T.H. Gender differences in affective, schizoaffective, and schizophrenic disorders. A review. Schizophrenia Research, 3: 159-172, 1990

Bellodi, L.; Bussoleni, C.; Scorza-Smeraldi, R.; Grazzi, G.; Zacchetti, L.; and Smeraldi, E. Family study of schizophrenia: Exploratory analysis for relevant factors. Schizophrenia Bulletin, 12: 120-128, 1986

Bland, R.C. Demographic aspects of functional psychoses in Canada. Acta Psychiatrica Scandinavica, 55: 369-380, 1977

Bleuler, E. Dementia Praecox or the group of schizophrenias. (1911) Translated by J. Zinkin. New York: International University Press, 1950.

Bleuler, E. Late schizophrenic clinical pictures. (1943, in German) Fortschritte der Neurologie-Psychiatrie, 15: 259-290, 1972

Bradbury, T.N.; and Miller, G.A. Season of birth in schizophrenia: A review of evidence, methodology, and aetiology. Psychological Bulletin, 98: 569-594, 1985

Brown, G.W.; Birley, J.L.T.; and Wing, J.K. Influence of family life on the course of schizophrenic disorders. British Journal of Psychiatry, 121: 241-258, 1972

Brown, G.W.; and Birley, J.L.T. Crises and life changes and the onset of schizophrenia. Journal of Health Society and Behaviour, 9: 203-214, 1968

Castle, D.J. Some current controversies in the epidemiology of schizophrenia. Current Medical Literature - Psychiatry, 4: 3-7, 1993

Castle, D.J.; and Howard, R. What do we know about the aetiology of late-onset schizophrenia? European Psychiatry, 7: 99-108, 1992

Castle, D.J.; and Murray, R.M. The neurodevelopmental basis of sex differences in schizophrenia. Psychological Medicine, 21: 565-575, 1991

Castle, D.J.; and Murray, R.M. The epidemiology of late-onset schizophrenia. Schizophrenia Bulletin, 19: 691-700, 1993

Childers, S.E.; and Harding, C.M. Gender, premorbid social functioning, and long-term outcome in DSM-III schizophrenia. Schizophrenia Bulletin, 16: 309-318, 1990

Christenson, R.; and Blazer, D. Epidemiology of persecutory ideation in an elderly population in the community. American Journal of Psychiatry, 141: 59-67, 1984

Clogg, C.C. Unrestricted and restricted maximum likelihood latent structure analysis: A manual for users. University Park, PA: Population Issues Research Office, 1977

Clogg, C.C.; and Goodman, L.A. Simultaneous latent structure analysis in several groups. In: Tuma, N.B., ed. Sociological Methodology. San Francisco: Josey-Bass, 1985, pp. 81-110

Cooper, J.E.; Kendell, R.E.; Gurland, B.J.; Sharpe, L.; Copeland J.R.M.; and Simon, R. Psychiatric diagnosis in New York and London. Maudsley Monograph no. 20. London: Oxford University Press, 1972

Crow, T.J. The continuum of psychosis and its implication for the structure of the gene. British Journal of Psychiatry, 149: 419-429, 1986

Cutting, J.C.; Clare, A.W.; and Mann, A.H. Cycloid psychosis: Investigation of the diagnostic concept. Psychological Medicine, 8: 637-648, 1976

De Alarcon, J.; Seagroatt, V.; and Goldacre, M. Trends in schizophrenia. Lancet, 335: 852-853, 1990

Dean, C.; and Gadd, E.M. Home treatment for acute psychiatric illness. British Medical Journal, 301: 1021-1023, 1990

Dean, G.; Walsh, D.; and Downing, H. First admissions of native-born and immigrants to psychiatric hospitals in south-east England. British Journal of Psychiatry, 139: 506-512, 1981

DeLisi, L.; Dauphinais, D.; and Hauser, P. Gender differences in the brain: Are they relevant to the pathogenesis of schizophrenia? Comprehensive Psychiatry, 30: 197-208, 1989

Der, G.; Gupta, S; and Murray, R.M. Is schizophrenia disappearing? Lancet, 335: 513-516, 1990

Diamond, M.C. Sex and the cerebral cortex. Biological Psychiatry, 25: 823-825, 1989

Dickson, W.E.; and Kendell, R.E. Does maintenance lithium therapy prevent recurrence of mania under ordinary clinical conditions? Psychological Medicine, 16: 521-530, 1986

Dunn, J.; and Fahy, T.A. Police admissions to a psychiatric hospital: Demographic and clinical differences between ethnic groups. British Journal of Psychiatry, 156: 373-378, 1990

Eagles, J.M.; Hunter, D.; and McCance, C. Decline in the diagnosis of schizophrenia among first contacts with the psychiatric services in north-east Scotland, 1969-1984. British Journal of Psychiatry, 152: 793-798, 1988

Eagles, J.M.; and Whalley, L.J. Decline in the diagnosis of schizophrenia among first admissions to Scottish mental hospitals from 1969-1978. British Journal of Psychiatry, 146: 151-154, 1985

Endicott, J. A diagnostic interview: The schedule for affective disorder and schizophrenia. Archives of General Psychiatry, 35: 837-841, 1978

Everitt, B.S. An Introduction to Latent Variable Models. London: Chapman & Hall, 1984

Everitt, B.S. A Monte Carlo investigation of the likelihood ratio test for number of classes in latent class analysis. Multivariate Behavioural Research, 23: 531-538, 1988

Falkai, P.; Bogerts, B.; and Ovary, I. "Developmental Neuropathology in Schizophrenia" Presented at the World Psychiatric Association, Oslo, Norway, August 1990

Faris, R.E.L.; and Dunham, H.W. Mental Disorders in Urban Areas. Chicago: Chicago University Press, 1939

Farmer, A.E.; McGuffin, P.; and Gottesman, I.I. Twin-concordance for DSM III schizophrenia. Archives of General Psychiatry, 44: 634-641, 1987

Farmer, A.E.; McGuffin, P.; and Spitznagel, E.L. Heterogeneity in schizophrenia: a cluster-analytic approach. Psychiatry Research, 8: 1-12, 1983

Feighner, J.P.; Robins, E; Guze, S.B.; Woodruff, R.; Winokur, G.; and Munoz, R. Diagnostic criteria for use in psychiatric research. Archives of General Psychiatry, 26: 57-63, 1972

Flaum, M.; Arndt, S.; and Andreasen, N.C. The role of gender in studies of ventricle enlargement in schizophrenia: A predominantly male effect. American Journal of Psychiatry, 147: 1327-1332, 1990

Foerster, A.; Lewis, S.W.; Owen, M.J.; and Murray, R.M. Premorbid personality in psychosis: Effects of sex and diagnosis. British Journal of Psychiatry, 158: 171-176, 1991

Folnegovic, Z.; Folnegovic-Smalc, V.; and Kulran, Z. The incidence of schizophrenia in Croatia. British Journal of Psychiatry, 156: 363-365, 1990

Geddes, J.R.; and Kendell, R.E. A case control study of schizophrenic patients who have never been admitted to hospital. Paper presented at Royal College of Psychiatrists Annual Meeting, Dublin, 24th-27th July 1992

Goldberg, E.M.; and Morrison, S.L. Schizophrenia and social class. British Journal of Psychiatry, 109: 785-802, 1963

Goldstein, J.M. Gender differences in the course and outcome of schizophrenia. American Journal of Psychiatry, 145: 684-689, 1988

Goldstein, J.M.; Santangelo, S.L.; Simpson, J.C.; and Tsuang, M.T. The role of gender in identifying subtypes of schizophrenia: a latent class approach. Schizophrenia Bulletin, 16: 263-275, 1990a

Goldstein, J.M.; Faraone, S.V.; Chen, W.J.; Tolomiczencko, G.S.; and Tsuang, M.T. Sex differences in the familial transmission of schizophrenia. British Journal of Psychiatry, 156: 819-826, 1990b

Gottesman, I.; and Shields, J.A. Schizophrenia and Genetics: A Twin Study Vantage Point. New York: Academy Press, 1972

Graham, P.M. Trends in schizophrenia. Lancet, 335: 852, 1990

Green, B.F. A general solution of the latent class model of latent structure analysis and latent profile analysis. Psychometrika, 16: 151-166, 1951

Gupta, S. Psychosis in migrants from the Indian subcontinent and English-born controls. A preliminary study on the use of psychiatric services. British Journal of Psychiatry, 159: 222-225, 1991

Gupta, S. and Murray, R.M. The changing incidence of schizophrenia: Fact or artefact? Directions in Psychiatry, 11: 1-8, 1991

Gur, R.E.; Mozley, P.D.; Resnick, S.M.; Shtasel, D.; Kohn, M.; Zimmerman, R.; Harman, G.; Atlas, S.; Grossman, R.; Erwin, R.; and Gur, R.C. Magnetic resonance imaging in schizophrenia: I. Volumetric analysis of brain and cerebrospinal fluid. Archives of General Psychiatry, 48: 407-412, 1991

Hafner, H. The epidemiology of schizophrenia. Triangle, 31: 133-154, 1992

Hafner, H. Epidemiology of schizophrenia. In: Hafner, H.; Gattaz, W.F.; and Janzarik, W., eds. Search for the Causes of Schizophrenia. Heidelberg: Springer-Verlag, 1987. pp. 66-69

Hafner, H. and Gattaz, W.F. Is schizophrenia disappearing? (letter). European Archives of Psychiatry and Neurological Sciences, 240: 374-376, 1991

Hafner, H.; Behrens, S.; De Vry, J.; and Gattaz, W.F. An animal model for the effects of estradiol on dopamine-mediated behaviour: Implications for sex differences in schizophrenia. Psychiatry Research, 38: 125-134, 1991

Hambrecht, M.; Maurer, K.; Hafner, H.; and Sartorius, N. Transnational stability of gender differences in schizophrenia European Archives of Psychiatry and Neurological Sciences, 242: 6-12, 1992

Hare, E.H. Mental illness and social conditions in Bristol. Journal of Mental Science, 102: 349-357, 1956

Hare, E.H. Temporal factors and trends, including birth seasonality and the viral hypothesis. In: Nasrallah, H.A., ed. Handbook of Schizophrenia, Vol. 3. Amsterdam: Elsevier, 1988. pp. 345-377

Harris, M.J.; and Jeste, D.V. Late-onset schizophrenia: an overview. Schizophrenia Bulletin, 14: 39-55, 1987

Harrison, G.; and Cooper, J.E. Why isn't schizophrenia disappearing in Nottingham? Schizophrenia Research, 4: 259, 1991

Harrison, G.; Owens, D.; Holten, A.; Neilson, D.; and Boot, D. A prospective study of severe mental disorder in Afro-Carribbean patients. Psychological Medicine, 18: 643-657, 1988

Herbert, M.E.; and Jacobsen, S. Late paraphrenia. British Journal of Psychiatry, 113: 461-469, 1967

Hirsch, S.R.; and Leff, J.P. Abnormalities in the Parents of Schizophrenics. Maudsley Monograph No. 22. Oxford: Oxford University Press, 1975

Holden, N.L. Late paraphrenia or the paraphrenias? A descriptive study with a 10-year follow-up. British Journal of Psychiatry, 150: 635-639, 1987

Hollingshead, A.B.; and Redlich, F.C. Schizophrenia and social structure. American Journal of Psychiatry, 110: 695-701, 1954

Hymas, N.; Naguib, M.; and Levy, R. Late paraphrenia - a follow-up study. International Journal of Geriatric Psychiatry, 4: 23-29, 1989

Jakob, H.; and Beckmann, H. Prenatal developmental disturbances in the limbic allocortex in schizophrenics. Journal of Neural Transmission, 65: 303-326, 1986

Jones, P.B.; and Murray, R.M. The genetics of schizophrenia is the genetics of neurodevelopment. British Journal of Psychiatry, 158: 615-623, 1991

Jones, P.B.; Bebbington, P.; Foerster, A.; Lewis, S.; Murray, R.; Sham, P.C.; and Toone, B. Sex differences in the diagnosis and phenomenology of schizophrenia. British Journal of Psychiatry, in press, 1993

Katschnig, H; and Lenz, G. Are sex differences in age at onset of schizophrenia related to phenomenological subtypes? Schizophrenia Research, 1: 111-112, 1988

Kay, D.W.K. Schizophrenia and schizophrenia-like states in the elderly. British Journal of Hospital Medicine, 8: 369-376, 1972

Kay, D.W.K.; and Roth, M. Environmental and hereditary factors in the schizophrenias of old age ('late paraphrenia') and their bearing on the general problem of causation in schizophrenia. Journal of Mental Science, 107: 649-686, 1961

Kay, D.W.K.; Beamish, P.; and Roth, M. Old age mental disorders in Newcastle Upon Tyne. British Journal of Psychiatry, 110: 146-158, 1964

Keith, S.J.; Regier, D.A.; and Rae, D.S. Schizophrenic disorders. In: Robins, L.N., and Regier, D.A., eds. Psychiatric Disorders in America. New York: The Free Press, 1991

Kendell, R.E.; Malcolm, D.E.; and Adams, W. The problem of detecting changes in the incidence of schizophrenia. British Journal of Psychiatry, 162: 212-218, 1993

Kendler, K.S. Twin studies of psychiatric illness: Current status and future directions. Archives of General Psychiatry, 50: 905-915, 1993

Kendler, K.S.; and Hays, P. Schizophrenia subdivided by family history of affective disorder: A comparison of symptomatology and course of illness. Archives of General Psychiatry, 40: 951-955, 1983

Kendler, K.S.; McGuire, M.; Gruenberg, A.M.; O'Hare, A.; Spellman, M.; and Walsh, D. The Roscommon family study: III. Schizophrenia-related personality disorders in relatives. Archives of General Psychiatry, 50: 781-788, 1993

Kety, S.S. The syndrome of schizophrenia. British Journal of Psychiatry 136: 421-436, 1980

Kety, S.; Rosenthal, D.; Wender, P.H.; Schulsinger, F.; and Jacobsen, B. Mental illness in the biological and adoptive families of adopted individuals who have become schizophrenic. In: Fieve, R.R.; Rosenthal, D.; and Bull, H., eds. Genetic Research in Psychiatry. Baltimore: Johs Hopkins University Press, 1975

Klorman, R.; Strauss, J.S.; and Kokes, R.F. Pre-morbid adjustment in schizophrenia: III. The relationship of demographic and diagnostic factors to measures of pre-morbid adjustment in schizophrenia. Schizophrenia Bulletin, 3: 214-225, 1977

Kohn, M.L. Social class and schizophrenia: A critical review and reformulation. In Annual Review of the Schizophrenic Syndrome (ed. R Cancro). New York: Brunner/Mazel, 1975

Kraepelin, E. Psychiatrie: ein Lehrbuch fur Studirende und Aertze. Leipsig: Barth, 1896

Kraepelin, E. Psychiatrie: ein Lehrbuch fur Studirende und Aertze, 8th ed. Leipzig: Barth, 1909

Kraepelin, E. Dementia Praecox and Paraphrenia. Translated by R.M. Barclay from Psychiatrie, 8th ed. Edinburgh: Livingston, 1919.

Kringlen, E. Contribution of genetic studies on schizophrenia. In: Hafner, H.; Gattaz, W.F.; and Janzarik, W., eds. Search for the Causes of Schizophrenia. Heidelberg: Springer-Verlag, 1987. pp. 123-143

Lazarsfeld, P.L.; and Henry, N.W. Latent structure analysis. Boston, Massachusetts: Houghton Mifflin, 1968

Levitt, J.L.; and Tsuang, M.T. The heterogeneity of schizoaffective disorder: Implications for treatment. American Journal of Psychiatry, 145: 926-936, 1988

Lewine, R.J. Sex differences in schizophrenia: Timing or subtypes? Psychological Bulletin, 90: 432-444, 1981

Lewine, R.J. Gender and schizophrenia, In: Nasrallah, H.A., ed. Handbook of Schizophrenia, Vol 3. Amsterdam: Elsevier, 1988. pp. 379-397

Lewine, R.J.; Burbach, D.; and Meltzer, H.Y. Effect of diagnostic criteria on the ratio of male to female schizophrenic patients. American Journal of Psychiatry, 141: 84-87, 1984

Lewine, R.J.; Gulley, L.R.; Risch, S.C.; Jewart, R.; and Houpt, J.L. Sexual dimorphism, brain morphology, and schizophrenia. Schizophrenia Bulletin, 16: 195-203, 1990

Lewine, R.J.; Hudgins, P.; Brown, F.; Caudle, J.; and Risch, S.C. Gender differences in qualitative brain morphology findings in schizophrenia. Schizophrenia Research, 9: 202, 1993

Lewis, G.; David, A.S.; Andreasson, S.; and Allebeck, P. Schizophrenia and city life. Lancet, 340: 137-140, 1992

Lewis, S.W.; and Murray, R.M. Obstetric complications, neurodevelopmental deviance, and schizophrenia. Journal of Psychiatric Research, 21: 413-421, 1987

Lewis, S.W.; Murray, R.M.; and Owen, M.J. Obstetric complications in schizophrenia: Methodology and mechanisms. In: Schultz, S.C.; and Tamminga, C.A., eds. Schizophrenia: Scientific Progress. New York: Oxford University Press, 1989.

Loranger, A.W. Sex differences in age at onset of schizophrenia. Archives of General Psychiatry, 41: 157-161, 1984

Machon, R.A.; Mednick, S.F.; and Schulsinger, F. The interaction of seasonality, place of birth, genetic risk and subsequent schizophrenia in a high-risk sample. British Journal of Psychiatry, 143: 383-388, 1983

McGlone, J. Sex differences in human brain asymmetry: A critical survey. Behaviour and Brain Science, 3: 215-263, 1980

McGovern, D.; and Cope, R.V. First psychiatric admission rates of first and second-generation Afro-Caribbeans. Social Psychiatry, 22:139-149, 1987

McGrath, J.; and Castle, D.J. Does influenza cause schizophrenia? A five year review. Australian and New Zealand Journal of Psychiatry, 29: 23-31, 1995

McGuffin, P.; Farmer, A.E.; Gottesman, I.I.; Murray, R.M.; and Reveley, A.M. Twin concordance and operationally defined schizophrenia. Archives of General Psychiatry, 41: 541-545, 1984

McGuffin, P.; Farmer, A.E.; and Harvey, I. A polydiagnostic application of operational criteria in psychotic illness: Development and reliability of the OPCRIT system. Archives of General Psychiatry, 48: 764-770, 1991

Mortensen, P.B.; Munk-Jorgensen, P.; and Stromegren, E. Is schizophrenia disappearing (letter) European Archives of Psychiatric Neurological Science, 240: 374, 1991

Munk-Jorgensen, P. Decreasing first-admission rates of schizophrenia among males in Denmark 1970-1984: changing diagnostic patterns? Acta Psychiatrica Scandinavica, 73: 645-650, 1986

Munk-Jorgensen, P.; and Jorgensen, P. Decreasing rates of first admission diagnoses of schizophrenia among females in Denmark 1970-1984. Acta Psychiatrica Scandinavica, 74: 379-383, 1986

Murray, R.M. Schizophrenia. In: Hill, P.; Murray, R.; Thorley, A. Essentials of Postgraduate Psychiatry. London: Academic Press, 1979. pp. 319-390

Murray, R.M.; O'Callaghan, E.; Castle, D.J.; and Lewis, S.W. A neurodevelopmental approach to the classification of schizophrenia. Schizophrenia Bulletin, 18: 319-332, 1992

Nasrallah, H.A.; Schwarzkopf, S.B.; Olson, S.C.; and Coffman, J.A. Gender differences in schizophrenia on brain MRI scans. Schizophrenia Bulletin, 16: 205-210, 1990

O'Callaghan, E.; Gibson, T.; Colohan, H.A.; Buckley, P.; Walshe, D.G.; and Larkin, C. Risk of schizophrenia in adults born after obstetric complications and their association with early onset of illness: A controlled study. British Medical Journal, 305: 1256-1259, 1992

Offord, D.R. School performance of adult schizophrenics, their siblings and age-mates. British Journal of Psychiatry, 125: 12-19, 1974

Opler, L.A.; Kay, S.R.; Rosado, V.; and Lindenmayer, J-P. Positive and negative syndromes in chronic schizophrenic inpatients. Journal of Nervous and Mental Disease, 172: 317-325, 1984

Orel, O.; Cannon, T.D.; Hollister, J.M.; Mednick, S.A.; and Parnas, J. Ventricular enlargement and premorbid deficits in school-occupational attainment. Schizophrenia Research, 4: 49-52, 1991

Parker, G.; O'Donnall, M.; and Walter, S. Changes in the diagnoses of the functional psychoses associated with the introduction of lithium. British Journal of Psychiatry, 146: 377-382, 1985

Parsons, P.L. Mental health of Swansea's old folk. British Journal of Preventative and Social Medicine, 19: 43-47, 1964

Pearlson, G.D.; Garbacz, D.J.; Moberg, P.J.; Ahn, H.S.; and de Paulo, J.R. Symptomatic, familial, perinatal, and social correlates of computer axial tomography (CAT) changes in schizophrenia and bipolars. Journal of Nervous and Mental Disease, 173: 42-50, 1985

Pearlson, G.D.; Kim, W.S.; Kubos, K.L.; Mobrg, P.J.; Jayaram, G.; Bascom, M.J.; Chase, G.A.; Goldfinger, A.D.; and Tune, L.E. Ventricle-brain ratio, computed tomographic density, and brain area in 50 schizophrenics. Archives of General Psychiatry, 46: 690-697, 1989

Perris, C. A study of cycloid psychosis. Acta Psychiatrica Scandinavica. Supplement 235, 1974

Pope, H.G.; and Lipinsky, J.F. Diagnosis in schizophrenia and manic depressive illness. Archives of General Psychiatry, 35: 811-828, 1978

Pope,H.G.; and Yurgelun-Todd, D. A family interview study of schizophrenia, schizoaffective disorder, and major mood disorder: updated findings. European Psychiatry, 8: 1-5, 1993

Post, F. Persistent Persecutory States of the Elderly. Oxford: Pergamon Press, 1966

Prince, M.J.; and Phelan, M.C. Trends in schizophrenia. Lancet, 335: 851-852, 1990

Rabins, P.; Paulker, S.; and Thomas, J. Can schizophrenia begin after age 44? Comprehensive Psychiatry, 25: 290-293, 1984

Randall, P.L. Schizophrenia, abnormal connection, and brain evolution. Medical Hypotheses, 10: 247-280, 1983

Redlich, F.C.; Hollingshead, A.B.; Roberts, B.H.; Robinson, H.A.; Freedman, L.Z.; and Myers, J.K. Social structure and psychiatric disorders. American Journal of Psychiatry, 109: 729-734, 1953

Riecher-Rossler, A.; and Hafner, H. Schizophrenia and oestrogens - is there an association? European Archives of Psychiatry and Clinical Neuroscience, 242: 323-328, 1993

Riecher, A.; Maurer, K.; Loffler, W.; Fatkenheuer, B.; an der Heiden, W.; and Hafner, H. Schizophrenia - a disease of young single males? European Archives of Psychiatry and Neurological Sciences, 239: 210-212, 1989

Rosenthal, D. Genetic Theory and abnormal behaviour. New York: McGraw Hill, 1970

Rosenthal, D.; Wender, P.H.; Kety, S.S.; and Welner, J. The adopted-away offspring of schizophrenics. American Journal of Psychiatry, 128: 307-311, 1971

Roth, M. The natural history of mental disorder in old age. Journal of Mental Science, 101: 281-301, 1955

Rothman, K. Modern Epidemiology. Boston: Little, Brown, 1986

Rwegellera, G.G.C. Psychiatric morbidity among West Africans and West Indians living in London. Psychological Medicine, 335: 851-852, 1977

Sartorius, N.; Jablensky, A.; Korten, A.; Ernberg, G.; Anker, M.; Cooper, J.E.; and Day, R. Early manifestations and first-contact incidence of schizophrenia in different cultures. Psychological Medicine, 16: 909-928, 1986

Schneider, K. Clinical Psychopathology. Translated by M.W. Hamilton. London: Grune and Stratton, 1959

Seeman, M.V. Current outcome in schizophrenia: Women vs men. Acta Psychiatrica Scandinavica, 73: 609-617, 1986

Seeman, M.V.; and Lang, M. The role of estrogens in schizophrenia gender differences. Schizophrenia Bulletin, 16: 185-194, 1990

Sham, P.C.; Bebbington P.; Jones P.B.; Russell, A.; Gilvarry, K.; Wilkins, S.; Lewis, S.; Toone, B.; and Murray, R. The Camberwell Functional Psychosis Family Study. 2.Age at onset, gender, and familial morbidity in schizophrenia. Schizophrenia Research, 9: 124, 1993a

Sham, P.C.; MacLean, C.; and Kendler, K.S. A typological model of schizophrenia based on age at onset, sex, and familial morbidity Acta Psychiatrica Scandinavica, in press, 1993b

Shepherd, M.; Watt, D.; and Falloon, I. The natural history of schizophrenia: A five year follow-up study of outcome prediction in a representative sample of schizophrenics. Psychological Medicine, monograph supplement 15. Cambridge: Cambridge University Press 1989

Shimizu, A.; Kurachi, M.; Noda, M.; Yamaguchi, N.; Torri, H.; and Isaki, K. Influence of sex on age at onset of schizophrenia. Japanese Journal of Psychiatry and Neurology, 42: 35-40, 1988

Silverton, L.; and Mednick, S. Class drift and schizophrenia. Acta Psychiatrica Scandinavica, 70: 304-309, 1984

Singer, M.T.; and Wynne, L.C. Communication styles in parents of normals, neurotics, and schizophrenics. Psychiatry Research, 20: 25-38, 1966

Spitzer, R.L.; Endicott, J.; and Robins, E. Research Diagnostic Criteria (RDC): Rationale and reliability. Archives of General Psychiatry, 35: 773-782, 1978

Takei, N., and Murray, R.M. Gender difference of schizophrenia in seasonal admissions in Scotland. British Journal of Psychiatry, 162: 272-3, 1993

Takei, N.; O'Callaghan, E.; Sham, P.; Glover, G.; Tamura, A.; and Murray, R.M. Seasonality of admissions in the psychoses: effect of diagnosis, sex, and age at onset. British Journal of Psychiatry, 161: 506-511, 1992

Taylor, M.A. Are schizophrenia and affective disorder related? A selective literature review. American Journal of Psychiatry, 149: 22-32, 1992

Tien, A.Y. Distributions of hallucinations in the population. Social Psychiatry and Psychiatric Epidemiology, 26: 287-292, 1991

Tsuang, M.T.; and Winoker, G. Criteria for subtyping schizophrenia: Clinical differentiation of hebephrenic and paranoid schizophrenia. Archives of General Psychiatry, 31: 43-47, 1974

Tsuang, M.T.; Demsey, G.M.; and Rauscher, F. A study of "atypical schizophrenia": A comparison with schizophrenia and affective disorder by sex, age of admission, precipitant, outcome, and family history. Archives of General Psychiatry, 33: 1157-1160, 1976

Turner, R.J.; and Wagenfeld, M.O. Occupational mobility and schizophrenia: An assessment of the social causation and social selection hypothesis. American Sociological Review 32: 104-113, 1967

Tyrer, P.; Turner, R.; and Johnson, A.L. Integrated hospital and community psychiatric services and use of inpatients beds. British Medical Journal, 299: 298-300, 1989

Vaughan, C.; and Leff, J.P. The influence of family and social factors on the course of psychiatric illness. British Journal of Psychiatry, 129: 125-137, 1976

Walsh, C.; Asherson, P.; Castle, D.; Sham, P.; Williams, J.; Taylor, C.; Owen, M.; Gill, M.; McGuffin, P.; and Murray, R. Familial schizophrenia shows no gender difference in age of onset. Schizophrenia Research, 9: 127-128, 1993

Weinberger, D.R. Implications of normal brain development for the pathogenesis of schizophrenia. Archives of General Psychiatry, 44: 660-669, 1987

Weinberger, D.R.; Cannon-Spoor, E.; Potkin, S.G.; and Wyatt, R.J. Poor premorbid adjustment and CT scan abnormalities in chronic schizophrenia. American Journal of Psychiatry, 137: 1410-1413, 1980

Wessely, S.; Castle, D.; Douglas, A.; and Taylor, P. The criminal careers of incident cases of schizophrenia. Psychological Medicine, in press, 1994

Wilcox, J.A.; and Nasrallah, H.A. Childhood head trauma and psychosis. Psychiatry Research, 21: 303-307, 1987

Williamson, J.; Stokoe, I.H.; Gray, S.; Fisher, M.; and Smith, A. Old people at home: their unreported needs. Lancet, i: 1117-1120, 1964

Wing, J.K.; and Hailey, A.M. Evaluating a Cummunity Psychiatric Service: The Camberwell Register, 1964-1971. London: Oxford University Press, 1972

Wing, J.K; Cooper, J.E.; and Sartorius, N. The Measurement and Classification of Psychiatric Symptoms. London: Cambridge University Press, 1974.

Wolyniec, P.S.; Pulver, A.E.; McGrath, J.A.; and Tam, D. Schizophrenia: Gender and familial risk. Journal of Psychiatric Research, 26, 17-22, 1992

World Health Organisation. Mental Disorders: Glossary and Guide to their Classification in Accordance with the Ninth Revision of the International Classification of Diseases (ICD-9) Geneva: WHO, 1978

World Health Organisation. The ICD-10 Classification of Mental and Behavioural Disorders: Clinical Descriptions and Diagnostic Guidelines Geneva: WHO, 1993

Zigler, E.; and Levine, J. Premorbid adjustment and paranoid-nonparanoid status in schizophrenia: A further investigation. Journal of Abnormal Psychology, 82: 189-199, 1973

Zigler, E.; Levine, J.; and Zigler, B. Premorbid social competence and paranoid-nonparanoid status in female schizophrenic patients. Journal of Nervous and Mental Disease, 164: 333-339, 1977

APPENDIX 1
POPULATION EXTIMATES FOR CAMBERWELL CATCHMENT AREA, 1965-1984

1964: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	81523	89525	171048
0-14	19225	18685	37910
15-24	12479	13066	25545
25-34	10792	10812	21604
35-44	11674	11672	23346
45-54	11494	12286	23780
55-64	9064	10112	19176
65-74	4528	7573	12101
75+	2267	5320	7586

1965: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	80811	88817	169629
0-14	19158	18597	37755
15-24	12589	13228	25817
25-34	10591	10636	21227
35-44	11512	11356	22868
45-54	11072	12088	23160
55-64	9137	10111	19248
65-74	2233	7491	12011
75+	2267	5310	7543

1966: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	80100	88110	168210
0-14	19090	18510	37600
15-24	12700	13390	26090
25-34	10390	10460	20850
35-44	11350	11040	22390
45-54	10650	11890	22540
55-64	9210	10110	19320
65-74	4510	7410	11920
75+	2200	5300	7500

1967: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	78864	86698	165562
0-14	18858	18267	37125
15-24	12541	13156	25697
25-34	10087	10192	20279
35-44	10792	10604	21396
45-54	10486	11620	22106
55-64	9312	10153	19464
65-74	4622	7372	11994
75+	2166	5335	7501

1968: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	77628	85286	162914
0-14	18627	18024	36650
15-24	12383	12922	25305
25-34	9784	9923	19707
35-44	10234	10168	20402
45-54	10322	11350	21672
55-64	9413	10195	19608
65-74	4734	7334	12067
75+	2132	5371	7503

1969: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	76393	83874	160267
0-14	18395	17780	36176
15-24	12224	12688	24912
25-34	9481	9655	19136
35-44	9677	9731	19408
45-54	10157	11080	21237
55-64	9515	10238	19753
65-74	4845	7295	12141
75+	2098	5406	7504

1970: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	75157	82462	157619
0-14	18164	17537	35701
15-24	12066	12454	24520
25-34	9178	9386	18564
35-44	9119	9295	18414
45-54	9993	10810	20803
55-64	9616	10280	19897
65-74	4957	7257	12214
75+	2064	5442	7506

1971: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	73921	81050	154971
0-14	17932	17294	35226
15-24	11907	12220	24127
25-34	8875	9118	17993
35-44	8561	8859	17420
45-54	9829	10540	20369
55-64	9718	10323	20041
65-74	5069	7219	12288
75+	2030	5477	7507

1972: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	72596	79593	152191
0-14	17339	16690	34029
15-24	11840	12232	24072
25-34	8936	9156	18092
35-44	83534	86582	17012
45-54	9528	10201	19729
55-64	9472	10062	195346
65-74	5085	7162	12247
75+	2041	5433	7473

1973: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	69859	76718	146577
0-14	16335	15717	32052
15-24	11548	12058	23606
25-34	8808	8980	17788
35-44	7985	8302	16287
45-54	9062	9685	18747
55-64	9048	9631	186796
65-74	5042	7008	12050
75+	2027	5339	7366

1974: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	68623	75350	143974
0-14	15774	15144	30918
15-24	11490	12078	23568
25-34	8884	90342	17918
35-44	7789	81102	15898
45-54	8770	93576	18127
55-64	8813	93792	18192
65-74	5059	6954	12013
75+	2039	5297	7336

1975: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	67387	73982	141370
0-14	15213	14570	29784
15-24	11431	12098	23529
25-34	8960	9088	18049
35-44	7592	7917	15509
45-54	8478	9029	17507
55-64	8578	9127	17705
65-74	5077	6899	11976
75+	2051	5255	7306

1976: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	66152	72614	138767
0-14	14653	13997	28650
15-24	11372	12118	23490
25-34	9036	9142	18179
35-44	7396	7724	15120
45-54	8186	8701	16887
55-64	8343	8875	17217
65-74	5094	6845	11939
75+	2063	5213	7276

1977: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	64916	71247	136163
0-14	14092	13424	27516
15-24	11313	12138	23451
25-34	9112	9197	18309
35-44	7199	75312	14730
45-54	78934	8374	16268
55-64	8107	8622	16730
65-74	5111	6791	11903
75+	2074	5172	7247

1978: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	63680	69879	133560
0-14	13531	12850	26382
15-24	11254	12158	23412
25-34	9188	9251	18440
35-44	7003	7338	14341
45-54	76014	80466	15648
55-64	7872	83702	16243
65-74	5129	6736	11866
75+	2086	5130	7217

1979: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	62444	68511	130956
0-14	12970	12277	25248
15-24	11196	12178	23374
25-34	9264	9305	18570
35-44	6806	7146	13952
45-54	7309	7718	15028
55-64	7637	8118	15756
65-74	5146	6682	11829
75+	2098	5088	7187

1980: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	61208	67144	128353
0-14	12410	11703	24114
15-24	11137	12198	23335
25-34	9340	9360	18701
35-44	6610	6953	13562
45-54	7016	7391	14408
55-64	7401	7866	15268
65-74	5164	6627	11792
75+	2110	5047	7158

1981: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	59972	65776	125749
0-14	11849	11130	22980
15-24	11078	12218	23296
25-34	9416	9414	18831
35-44	6413	6760	13173
45-54	6724	7063	13788
55-64	7166	76142	14781
65-74	5181	6573	11755
75+	2122	5005	7128

1982: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	58736	64408	123146
0-14	11288	10557	21846
15-24	11019	12238	23257
25-34	9492	9468	18961
35-44	6217	6567	12784
45-54	6432	6735	12784
55-64	6432	67352	13168
65-74	6931	7362	14294
75+	2134	4963	7098

1983: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	57500	63041	120542
0-14	10728	9983	20712
15-24	10960	12258	23218
25-34	9568	9523	19092
35-44	6020	6374	12394
45-54	6139	6408	12548
55-64	6695	7110	13806
65-74	5216	6464	11681
75+	2146	4922	7069

1984: POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	56264	61673	117939
0-14	10167	9410	19578
15-24	10902	12278	23180
25-34	9644	9577	19222
35-44	5824	6182	12005
45-54	5847	6080	11928
55-64	6460	6858	13319
65-74	5233	6410	11644
75+	2158	4880	7039

TOTALS 1964-1984:
POPULATION ESTIMATES: CAMBERWELL CATCHMENT AREA

AGE	MALES	FEMALES	PERSONS
ALL AGES	1453533	1595776	3049309
0-14	325798	312146	637944
15-24	245429	261372	506801
25-34	198826	200677	399503
35-44	174126	178287	352413
45-54	182988	196452	379440
55-64	177508	190516	368024
65-74	104519	146621	251140
75+	44339	109705	154044

APPENDIX 2(A)

Camberwell Register
Schizophrenia Project

note: if data unknown, score 9

Register Number: ☐☐☐☐☐☐

Hospital Number: ☐☐☐☐☐☐

Age of patient at contact (yrs): ☐☐

dob (day month year): ☐☐☐☐☐☐

inpatient (no=0; yes=1) ☐

Occupation of father (nil=0; manual=1; white collar=2; professional=3)

Ethnicity (caucasion=0; afrocarrib=1; african=2; asian=3; other=4)

patient ☐

father ☐

mother ☐

Country of birth (uk&eire=0; w indies=1; africa=2; asia=3; other=4)

patient ☐

father ☐

mother ☐

Age of patient entry to UK (yrs) (if applicable) ☐☐

Criminality of parents (conviction only) (no=0; yes=1)

father ☐

mother ☐

Alcohol problem in parents (no=0; yes=1)

father ☐

mother ☐

Obstetric complications (code a separate scale) ☐

Developmental problems (code as separate scale)

developmental score ☐

Childhood neurotical traits (no=0; yes=1)

- enuresis ☐
- nailbiting ☐
- school refusal ☐

Child care (not applicable=0; poor=1; good=2) ☐
(rate poor if: malnutrition, neglect, or social service involvement)

Academic achiement (no exams=0; CSE=1; Olevel=2; Alevel=3, 3°=4) ☐

Criminality (no=0; yes=1) ☐
(include: juvenile offences, juvenile cautions, adult arrest, conviction)

Juvenile delinquency (no=0; yes=1) ☐
(include: drugs, arrest, expelled, truant, stealing, vandal, runaway, arson)

Premorbid employment (not on job market=0; unstable=3 or more in ☐
5 yrs=1; unemployed=6 or more months last 5 yrs=2; stable=3)

Premorbid sexual/marital adjustment

- married or living as (no=0; yes=1) ☐
- marital violence (physical only) (no=0; yes=1) ☐
- marital desertion (no=0; yes=1) ☐
- more than 10 sexual contacts per year (no=0; yes=1) ☐
- no relationships (no=0; yes=1) ☐
- first sex before 14 years (no=0; yes=1) ☐

Drug problem (no=0; recreational=1; problem=2)

- alcohol ☐
- cannabis ☐
- heroin ☐
- other ☐

Violence on admission (no=0; yes=1)

- police involvement ☐
- violent to self ☐
- violent to others ☐

Inpatient aggression (no=0; yes=1) ☐

Delusional behaviour (no=0; yes=1) ☐

Evidence of organicity (no=0; yes=1) ☐

EEG abnormal ☐

CT scan abnormal ☐

Homeless on discharge (no=0; yes=1) ☐

Outpatient contact (no=0; yes=1) ☐

APPENDIX 2(B)

Rating Scale for Developmental Problems

SPEECH ☐

0 - No problems reported by mother
1 - No talk other than mama or dada by age 3. Speech problems still exist at school entry. Either grammar or pronounciation faulty.
2 - As above but professional help sought or child referred to educational psychologist or speech therapist by school.

MOTOR ☐

0 - No problems reported by mother
1 - Could not walk unsupported before 2 years
2 - As above but professional advice sought

ENCOPRESIS ☐

0 - No problems reported by mother
1 - Soiling after age 4 at least once a week over a period of at least 6 weeks
2 - As above but profesional help sought and physical cause excluded

ENURESIS ☐

0 - No problems reported by mother
1 - Bed wetting or day time wetting continuously beyond the age of 5 at least once a week
2 - Professional help sought. Physical causes excluded

READING DIFFICULTIES ☐

0 - No problems learning to read or spell
1 - Reading or spelling difficulties reported by mother
2 - Remedial teaching for reading and spelling required but no special schooling

DEVELOPMENTAL SCORE ☐

0 - No problems reported by mother in any area
1 - Problems reported by mother in one or more areas but no professional advice sought
2 - Professional advice sought by mother or referral to EP or speech therapist by school for at least one of the above

APPENDIX 2(C)

Obstetric Complications Scale

Score: Definite = 2
Equivocal = 1
Absent = 0
Insufficient information = 9

Antepartum:

(Equivocal:
pre-eclampsia NOS) ☐

1. Rubella or syphilis ☐
2. Rhesus incompatability ☐
3. Pre-eclampsia: severe and/or leading to early induction or hospitalisation ☐
4. APH or threatended abortion ☐

Intrapartum:

(Equivocal: ☐
Labour >24 or "long/difficult/precipitate" NOS
Twin birth NOS
Cord knotted or round neck
"premature" or "postmature" NOS
Caesarian NOS
Forcepts or other instrumental delivery, NOS
<5 1/2 ib (2500g) or "small" NOS
Incubator/resuscitation/"blue" NOS
Gross physical anomaly)

5. Premature rupture of membranes, >24 hours ☐
6. Labour >36 hours or < 3 hours ☐
7. Twin birth, complicated ☐
8. Cord prolapse ☐
9. Gestational age <37 weeks or >42 weeks ☐
10. Caesarian, complicated or emergency ☐
11. Breech or abnormal presentation ☐
12. High or "difficult" forceps ☐
13. Birthweight <4 1/2 ibs (2000g) ☐
14. Incubator >4 weeks

This scale represents a consensus derived from six scales previously used, three from the obstetric and three from the psychiatric literature:

Hobel et al (1973) Am J Obstetr Gynae
Prechtel et al (1967) Br Med Journ
Littman & Parmalee (1978) Pediatrics
Woerner et al (1973) Acta Psychiat Scand
Zax et al (1977) Am J Orthopsychiat
Parnas et al (1982) Brit J Psychiatr

(Four of these are reviewed and compared in Molfese & Thomson (1985), Chld Dev).

All items on the derived scale are complications appearing in agreement in at least three of the six scales. Maternal non-pregnancy variables such as age, parity and history of previous abortion were not included.

A few notes on scoring:

i) "Equivocal" complications are counted as present if the listed conditions are met or if one of the definite complications is "probably" present. This latter condition requires conservative discretion on the part of the scorer.

ii) Complications are not additive. If more than one definite complication is present, the item is still scored as '2'. Likewise, if more than one equivocal complication is present, the item is still scored as '1'.

iii) It should be noted that some "complications" such as induction or jaundice should not be scored, since they are of high incidence and of doubtful significance.

APPENDIX 2(D)

Operational Criteria Checklist for Psycholtic Illness (OCCPI) (for OPCRIT version 2.5)

ID Number ☐☐☐☐

1.	Sex code (0,1)	☐ 5
2,3.	Age of onset	☐ 6,7
4.	Single (0,1)	☐ 8
5.	Unemployed (0,1)	☐ 9
6.	Duration of illness at least 2 weeks (0,1)	☐ 10
7.	Duration of illness at least 6 months (0,1)	☐ 11
8.	Duration of prodroml/acute/residual stages at least six months (0,1)	☐ 12
9.	Poor premorbid work adjustment (0,1)	☐ 13
10.	Poor premorbid social adjustment (0,1)	☐ 14
11.	Premorbid personality disorder (0,1)	☐ 15
12.	Alcohol/drug abuse within on year of onset (0,1)	☐ 16
13.	Family history of schizophrenia (0,1)	☐ 17
14.	Family history of other psychiatric disorder (0,1)	☐ 18
15.	Bizarre behaviour (0,1)	☐ 19
16.	Catatonia (0,1)	☐ 20
17.	Speech difficult to understand (0,1)	☐ 21
18.	Incoherent (0,1)	☐ 22
19.	Positive formal thought disorder	☐ 23
20.	Negative formal thought disorder (0,1)	☐ 24
21.	Affective symptoms predominate (0,1)	☐ 25

22. Restricted affect (0,1) ☐ 26
23. Blunted affect (0,1) ☐ 27
24. Inappropriate affect (0,1) ☐ 28
25. Rapport difficult (0,1) ☐ 29
26. Persecutory delusions (0,1) ☐ 30
27. Well organised delusions (0,1) ☐ 31
28. Grandiose delusions (0-2) ☐ 32
29. Delusions of influence (0,1) ☐ 33
30. Bizarre delusions (0,1) ☐ 34
31. Widespread delusions (0,1) ☐ 35
32. Delusions of passivity (0-2) ☐ 36
33. Primary delusional perception (0-2) ☐ 37
34. Other primary delusions (0,1) ☐ 38
35. Delusions and hallucinations lasting one week (0,1) ☐ 39
36. Persecutory/jealous delusions with hallucinations (0,1) ☐ 40
37. Thought insertion (0-2) ☐ 41
38. Thought withdrawal (0-2) ☐ 42
39. Thought broadcast (0-2) ☐ 43
40. Thought echo (0-2) ☐ 44
41. Third person auditory hallucinations (0-2) ☐ 45
42. Running commentary voices (0-2) ☐ 46
43. Abusive/accusatory/persecutory voices (0,1) ☐ 47
44. Other (non affective) auditory hallucinations (0,1) ☐ 48
45. Information not credible (0,1) ☐ 49
46. Lack of insight (0,1) ☐ 50
47. Deterioration from premorbid level of functioning (0,1) ☐ 51
48. Schizophrenic symptoms respond to neuroleptics (0,1) ☐ 52
49. Non-affective hallucination in any modality (0,1) ☐ 53

50. Elevated mood (0-2) ☐ 54
51. Irritable mood (0-2) ☐ 55
52. Schizophrenic symptoms at some time as affective symptoms (0,1) ☐ 56
53. Excessive activity (0-2) ☐ 57
54. Reckless activity (0-2) ☐ 58
55. Pressured speech (0-2) ☐ 59
56. Increased self esteem (0-2) ☐ 60
57. Thought racing (0-2) ☐ 61
58. Distractibility (0-2) ☐ 62
59. Reduced need for sleep (0-2) ☐ 63
60. Dysphoria (0-3) ☐ 64
61. Agitated activity (0-3) ☐ 65
62. Slowed activity (0-3) ☐ 66
63. Loss of energy/tiredness (0-3) ☐ 67
64. Loss of pleasure (0-3) ☐ 68
65. Poor concentration (0-3) ☐ 69
66. Excessive self reproach (0-3) ☐ 70
67. Suicidal ideation (0-3) ☐ 71
68. Initial insomnia (0-3) ☐ 72
69. Early morning waking (0-3) ☐ 73
70. Excessive sleep (0-3) ☐ 74
71. Poor appetite (0-3) ☐ 75
72. Weight loss (0-3) ☐ 76
73. Increased appetite (0-3) ☐ 77
74. Weight gain (0-3) ☐ 78

APPENDIX 3

Glossary for Operational Criteria Checklist for Psychotic Illness (OCCPI) (OPCRIT version 2.5)

Specification of items

Following the general approach adopted by the authors of the Present State Examination (PSE), we have produced a glossary to be used with the OPCRIT checklist that provides definitions of every item. This can be referred to in written form when completing a checklist. Alternatively, when entering the data directly onto computer using the OPCRIT program,s a "Help" facility can be called that displays the definition of each item on the screen. The specification of items, where possible, follows the descriptions provided by authors of the various criteria. Otherwise the definitions of signs and symptoms follows the description in standard textbooks and takes as a model the glossary of the PSE.

The definition and coding of each item follow:

1. Sex code: 0 indicates male; 1, female

2,3. Age at onset: This should be given to the nearest year and is defined as the earliest age at which medical advice was sought for psychiatric reasons or at which symptoms began to cause subjective distress or impair functioning (enter age in years, eg. 35).

4. Single: The subject has never married or lived as married (0 indicates married; 1, single).

5. Unemployed: The subject was not employed at onset as defined above. Women working full time in the home are scored as if employed. Students attending classes on full time course are scored as if employed (0, employed; 1, unemployed).

6. Duration of illness at least 2 weeks: Persistent symptoms or disability such that the patient did not return to premorbid level of functioning within 2 weeks (0, 1 [illness lasted 2 weeks]).

7. Duration of illness at least 6 months: Persistent symptoms or disability such that the patient did not return to premorbid level of functioning within 6 months (0, 1 [illness lasted 6 months]).

8. Duration of total prodromal/acute and residual stages at least 6 months: Total duration of illness is 6 months when prodromal and residual disabilities are included with the acute phase of illness. Prodromal/residual phase symptoms (any two of the following before or after the acute episode): social isolation/marked impairment in role/markedly peculiar behaviour/marked impairment in personal hygiene/blunted, flat, or inappropriate affect/digressive, vague, overelaborate speech/odd or bizarre ideation/unusual perceptual experiences (0,1 [illness lasted 6 months]).

9. Poor work adjustment: This refers to work history before onset of illness. It should be scored if the patient was unable to keep any job for more than 6 months, had a history of frequent changes of job, or was only able to sustain a job well below that expected by his or her educational level or training at the time of first psychiatric contact. Also score positively for a persistently very poor standard of housework (homemakers) and badly failing to keep up with studies (students) (0, absent; 1, poor work adjustment).

10. Poor premorbid social adjustment: Patient found difficulty entering or maintaining normal social relationships, showed persistent social isolation or withdrawal, or maintained solitary interests before onset of psychotic symptoms (0, absent; 1, poor social adjustment).

11. Premorbid personality disorder: Evidence of inadequate/schizoid/schizotypal/paranoid/cyclothymic/psychopathic/sociopathic personality disorder present since adolescence and before onset of psychotic symptoms (0, absent; 1, personality disorder present).

12. Alcohol/other drug abuse within 1 year of onset of psychotic symptoms: alcohol abuse where quantity is excessive (rater judgment) where alcohol-related complications occur, during the year before first psychiatric contact (rated strictly as exclusion criteria for some definitions of schizophrenia); other drug abuse where non prescribed drugs are repeatedly taken or prescribed drugs are used in excessive quantities and without medical supervision in the year before first psychiatric contact (0, absent; 1, family history present).

13. Family history of schizophrenia: Definite history of schizophrenia in a first or second-degree relative (0, absent; 1, family history present).

14. Family history of other psychiatric disorder: First or second-degree relative has another psychiatric disorder severe enough to warrant psychiatric referral (0, absent; 1, family history present).

15. Bizarre behaviour: Behaviour that is strange and incomprehensible to others; includes behaviour that could be interpreted as a response to auditory hallucinations or thought interference (0, absent; 1, present).

16. Catatonia: Patient exhibits persistent mannerisms, stereotypes, posturing, catalepsy, stupor, or excitement that is not explicable by affective change (0, absent; 1, present).

17. Speech difficult to understand: Speech that makes communication difficult because of lack of logical or understandable organisation; does not include dysarthria or speech impediment (0, absent; 1, present).

18. Incoherent: Normal grammatical sentence construction has broken down, includes "word salad" and should only be rated conservatively for extreme forms of formal thought disorder (0, absent; 1, present).

19. Positive formal thought disorder: Patient has fluent speech but tends to communicate poorly due to neologisms, bizarre use of words, derailments, or loosening of associations (0, absent; 1, present).

20. Negative formal thought disorder: Includes paucity of thought, frequent thought blocking, poverty of speech, or poverty of content of speech (0, absent; 1, present).

21. Affective symptoms predominate: Depressive of manic features form a prominent part of the illness, and mood disorder alone might explain much or all of the symptoms. Isolated examples of depressed or exalted mood during the course of the illness should not be rated positively for this item. Rate conservatively, as this is an exclusion item for several operational systems for schizophrenia, although it would be present in cases of schizoaffective disorder (0, absent; 1, present).

22. Restricted affect: Patient's emotional responses are restricted in range, and at interview there is an impression of bland indifference of "lack of contact" (0, absent; 1, present).

23. Blunted affect: Where the patient's emotional responses are persistently flat and show a complete failure to "resonate" to external change. The difference between restricted and blunted affect should be regarding as one of degree, with "blunted" only being rated in extreme cases (0, absent; 1, present).

24. Inappropriate affect: Patient's emotional responses are in appropriate to the circumstance, eg. laughter when discussing painful or sad occurrences, fatuous giggling without apparent reason (0, absent; 1, present).

25. Rapport difficult: Interviewer finds difficulty in establishing contact with the patient, who appears remote or cut off; does not include patients who are difficult to interview because of hostility or irritability (0, absent; 1, present).

26. Persecutory delusions: Includes all delusions with persecutory ideation (0, absent; 1, present)/

27. Well organised delusions: Illness is characterised by a series of well organised or well systematised delusions (0, absent; 1, present).

28. Grandiose delusions: Patient has grossly exaggerated sense of his or her own importance, has exceptional abilities, or believes that he or she is rich or famous, titled, or related to royalty. Also included are delusions of identification with God, angels, the Messiah, etc. (see also item 56). (Any duration, score 1; if symptom lasts at least 2 weeks, score 2.).

29. Delusions of influence: Events, objects, or other people in the patient's immediate surroundings have a special significance, often of a persecutory nature; includes ideas of reference from the television, radio, or newspapers, where the patients believes that these are providing instructions or prescribing certain behaviour (0, absent; 1, present).

30. Bizarre delusions: Strange, absurd, or fantastic delusions whose content may have a mystical, magical , or "science fiction" quality (0, absent; 1, present).

31. Widespread delusions: Delusions that intrude into most aspects of the patient's life and/or preoccupy the patient for most of his or her time (0, absent; 1, present).

32. Delusions of passivity: Include all "made" sensations, emotions, or actions. Score 1 for all experiences of influence where the patient knows that his or her own thoughts, feelings, impulses, volitional acts, or somatic sensations are controlled or imposed by an external agency. Score 2 when there are "experiences of alienation", ie. the patients is aware that thoughts, feelings, etc are not his or her own but are coming from an outside source (0, absent; 1, present).

33. Primary delusional perception: Score 1 where the patient perceives something in the outside world that triggers a special, significant, relatively non understandable belief of which he or she is certain and that is in some way loosely linked to the triggering perception. Score 2 when the special significance is attached to the perception itself and not merely linked to it (0, absent; 1, present).

34. Other primary delusions: Includes delusional mood and delusional ideas. Delusional mood is a strange mood in which the environment appears changed in a threatening way but the significance of the change cannot be understood by the patient, who is usually tense, anxious, or bewildered. This can lead to a delusional belief. A delusional idea appears abruptly in the patient's mind fully developed and unheralded by any related thoughts (0, absent; 1, present).

35. Delusions and hallucinations lasting for 1 week: Any type of delusion accompanied by hallucinations of any type lasting 1 week (0, absent; 1, present).

36. Persecutory or jealous content delusions accompanied by hallucinations of any type: this is self-explanatory, but note that abnormal beliefs are of delusional intensity and quality and are accompanied by true hallucinations (0, absent; 1, present).

37. Thought insertion: Score 1 when the patient recognises that thoughts are being put into his or her head that are not the patient's own. Score 2 when the patient experiences thoughts that are not his or her own and have been imposed by an outside agency.

38. Thought withdrawal: Score 1 when the patient experiences thoughts ceasing in his or her head and may experience "pure thought block". Score 2 when the patient experiences an external agency removing thoughts from his or her head.

39. Thought broadcast: Score 1 when the patient experiences thoughts diffusing out of his or her head. Score 2 when the patient experiences thoughts diffusing out of his or her head and they are shared with others, ie. the belief that others actually hear the thoughts.

40. Thought echo: Score 1 if the patient experiences thoughts repeated or echoed in his or her head. Score 2 if thoughts are repeated by a voice outside the patient's head.

41. Third person auditory hallucinations: Two or more voices discussing the patient in the third person. Score 1 if either "true" or "pseudo" hallucinations, ie. differentiation of the source of the voices is unimportant. Score 2 if "true" hallucinations can be established, ie. definitely perceived to arise outside patient's subjective space.

42. Running commentary voices: Patient hears voices describing his or her actions, sensations, or emotions as they occur. Score 1 if there are possible "pseudo" hallucinations, but score 2 if definite "true" hallucinations can be defined (see also definitions of item 41).

43. Abusive/accusatory/persecutory voices: Voices talking to the patient in an accusatory, abusive, or persecutory manner (0, absent; 1, present).

44. Other (non affective) auditory hallucinations: Any other kind of auditory hallucinations; includes pleasant or neutral voices and non verbal hallucinations (0, absent; 1, present).

45. Information not credible: Patient gives misleading answers to questions and provides a jumbled, incoherent or inconsistent account (0, absent; 1, present).

46. Lack of insight: Patient is unable to recognise that his or her experiences are abnormal or that they are the produce of an anomalous mental process, or recognises that the experiences are abnormal but gives a delusional explanation (1 indicates lack of insight; 0, insight present).

47. Deterioration from premorbid level of functioning: Patient does not regain premorbid social, occupational, or emotional functioning after an acute episode of illness (0, absent; 1, deterioration present).

48. Schizophrenic symptoms respond to neuroleptics: Rate globally over the total period. Score positively if illness appears to respond to any type of neuroleptics (depot or oral) or if relapse occurs when medication is stopped (0, symptoms do not respond; 1, symptoms respond).

49. Nonaffective hallucination: Hallucinations in any modality in which the content has not apparent relationship to elation or depression. Score positively only if they are present throughout the day for several days or intermittently for 1 week (0, absent; 1, present).

50. Elevated mood: Patient's predominant mood is one of elation lasting at least 1 week to score 1 week to score 1 or lasting at least 2 weeks to score 2. If elation lasted less than 1 week but the patient was hospitalised for affective disorder, score 1.

51. Irritable mood: Patient's mood is predominantly irritable and lasts at least 1 week to score 1 or at least 2 weeks to score 2. If the patient is hospitalised for affective disorder but less than 1 week of irritable mood, score 1.

52. Schizophrenic symptoms occur at the same time as affective symptoms: Score positively if dubiety is present whether episode is one of affective disorder or schizophrenia (0, absent; 1, present).

53. Excessive activity: Patient is markedly overactive. This includes motor, social, and sexual activity. Score 1 for hyperactivity lasting 1 week and 2 for a duration of 2 weeks.

54. Reckless activity: Patient is excessively involved in activities with high potential for painful consequences that are not recognised, eg. excessive spending, sexual indiscretions, reckless driving, etc. Duration of 1 week is scored 1, and duration of 2 weeks is scored 2.

55. Pressured speech: Patient is much more talkative than usual or feels under pressure to continue talking; includes manic type of formal thought disorder with clang associations, punning and rhyming, etc. Score 1 for duration of 1 week and 2 for duration of 2 weeks.

56. Increased self esteem: Patient believes that he or she is an exceptional person with special powers, plans, talents, or abilities. Rate positively here if over valued idea, but if delusional in quality also score item 28 (grandiose delusions). Score 1 if duration is 1 week and 2 if it lasts 2 weeks.

57. Thoughts racing: Patient experiences thoughts racing through his or her head or others observe flights of ideas and find difficulty in following what the patient is saying or in interrupting because of the rapidity and quantity of speech. Duration of 1 week scores 1, and duration of 2 weeks scores 2.

58. Distractibility: Patient experiences difficulty concentrating on what is going on around him or her because attention is too easily drawn to irrelevant or extraneous factors. Duration of 1 week scores 1 and 2 weeks scores 2.

59. Reduced for need for sleep: Patient sleeps less but there is no complaint of insomnia. Extra waking time is usually taken up with excessive activities. Duration of 1 week scores 1 and 2 weeks scores 2.

60. Dysphoria: Persistently low or depressed mood, irritable and sad mood, or pervasive loss of interest. Score 1 if present for at least 1 week, 2 if present for 2 weeks, and 3 if present for 1 month.

61. Agitated activity: Patient shows excessive repetitive activity, such as fidgeting restlessness, wringing of hands, or pacing up and down, all usually accompanied by expression of mental anguish. Score 1 if present for 1 week, 2 if present for 2 weeks, and 3 if present for 1 month.

62. Slowed activity: Patient complains that he or she feels slowed and unable to moved. Others may report a subjective feeling of retardation, or retardation may be noted by the examining clinician. Score 1 if present for 1 week, 2 if present for 2 weeks, and 3 if present for 1 month.

63. Loss of energy/tiredness: Subjective complaints of being excessively tired with no energy. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

64. Loss of pleasure: Pervasive inability to enjoy any activity. this includes marked loss of interest or loss of libido. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

65. Poor concentration: Subjective complaint of being unable to think clearly, make decisions, etc. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

66. Excessive self-reproach: Extreme feelings of guilt and unworthiness. This may be of delusional intensity ("worst person in the whole world"). Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

67. Suicidal ideation: Preoccupation with thoughts of death (no necessarily own); includes thinking of suicide, wishing to be dead, and attempts to kill self. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

68. Initial insomnia: Patient complains of being unable to get to sleep and lies awake for at least 1 hour. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

69. Early morning waking: Patient complains of persistently waking up at least 1 hour earlier than usual waking time. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

70. Excessive sleep: Patient complains of sleeping too much. Score 1 if present for 1 week, 2 for 2 weeks, and 3 for 1 month.

71. Poor appetite: Subjective complaint that the patient has a poor appetite (not necessarily observed to be eating less). Score 1 if present for 1 week, 2 for 2 weeks, and 3 for 1 month.

72. Weight loss: Weight loss of at least 0.9 kg per week or 4.5 kg per year when not dieting. Score 1 for duration one week, 2 for 2 weeks, and 3 for 1 month.

73. Increased appetite: Patient reported increased appetite and/or comfort eating. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.

74. Weight gain: Weight gain of at least 0.9 kg per week or 4.5 kg per year. Score 1 for duration of 1 week, 2 for 2 weeks, and 3 for 1 month.