Schizophrenia Bulletin vol. 31 no. 3 pp. 624–638, 2005
doi:10.1093/schbul/sbi025
Advance Access publication on June 8, 2005

Epidemiology of First-Episode Psychosis: Illustrating the Challenges Across Diagnostic Boundaries Through the Cavan-Monaghan Study at 8 Years

Patrizia Baldwin,[1] David Browne,[1] Paul J. Scully,[1] John F. Quinn,[1] Maria G. Morgan,[1] Anthony Kinsella,[2] John M. Owens,[1,3] Vincent Russell,[1,4] Eadbhard O'Callaghan,[5] and John L. Waddington[1,6]

[1]Stanley Research Unit, Cavan-Monaghan Mental Health Service, St. Davnet's Hospital, Monaghan, Ireland; [2]School of Mathematics, Dublin Institute of Technology, Dublin 8, Ireland; [3]Mental Health Commission, Dublin 4, Ireland; [4]Cavan-Monaghan Mental Health Service, Cavan General Hospital, Cavan, Ireland; [5]Stanley Research Unit, Cluain Mhuire Family Centre, Blackrock, Co. Dublin, Ireland; [6]Department of Clinical Pharmacology, Royal College of Surgeons in Ireland, St. Stephen's Green, Dublin 2, Ireland

The epidemiology of first-episode psychosis is poorly understood because of the paucity of systematic studies, yet it constitutes the fundamental basis for understanding the disorder and the foundations on which clinical, biological, therapeutic, and long-term outcome studies are built. A particular need is to clarify the diagnostic breadth of first-episode psychosis and, on this basis, to undertake systematic comparisons across representative populations of the psychoses, to include comparisons with first-episode mania. Considered here is the new generation of prospective studies that may be able to inform in some way on these issues. Attainment of the above goals requires prolonged accrual of "all" cases of nonaffective, affective, and any other psychotic illness, including first-episode mania, to derive the required representative populations. To illustrate some of the challenges, the structure of the Cavan-Monaghan prospective first episode study is described and its interim findings are outlined, as rural Ireland provides psychiatric care based on strict catchment areas and is characterized by substantive ethnic and socioeconomic homogeneity and stability. It is argued that there are 3 primary diagnostic nodes (schizophrenia spectrum psychosis, bipolar disorder, and major depressive disorder with psychotic features) around which there exist numerous additional, overlapping, and well-populated diagnostic categories that are distinct only in terms of their operational definition. Only through systematic, epidemiologically based studies that access this intrinsic diversity are we likely to understand fully the origins and pathobiology of first-episode psychosis.

Key words: schizophrenia/bipolar disorder/mania/major depressive disorder/incidence

Introduction

If aspects of the epidemiology of schizophrenia remain to be clarified because of the diversity of findings,[1–3] the epidemiology of first-episode psychosis is poorly understood because of the paucity of systematic studies. It remains a conceptual challenge that, to our knowledge, no study has specifically sought to address epidemiologically the boundaries of first-episode psychosis in terms of contemporary operational diagnoses, particularly in relation to primary psychotic disorders vis-à-vis psychotic mood disorders and other forms of psychotic illness. Additionally, at the heart of every first-episode study are its constituent patients, and this raises numerous methodological challenges that are fundamental to how each such study is to be interpreted. These include the following: How were cases ascertained, on what basis were they incepted diagnostically into the study, how stable are those inception diagnoses, what are their demographic and clinical characteristics, and how representative are they of the "totality" of such patients on a population basis? Critically, the epidemiology of any disorder is predicated on such data, both as the fundamental basis for understanding that disorder and as the foundations on which clinical, biological, therapeutic, and long-term outcome studies are built.

However, most first-episode studies to date have involved diverse patient populations, often derived from urban or mixed service intakes, tertiary referrals (often to academic centers), or "samples of convenience" in the face of diverse elements of service provision; this reflects the vagaries of day-to-day clinical practice in real-world settings. They have focused primarily on schizophrenia, often within a restricted age range. Yet what, if any, are the diagnostic boundaries of first-episode psychosis? For example, to what extent does inclusion of other psychotic diagnoses, or even "psychotic disorder not otherwise specified" (psychosis NOS),

[6]To whom correspondence should be addressed; tel: +353-1-402 2245, fax: +353-1-402 2453, jwadding@rcsi.ie.

confound or help our holistic understanding of the nature of psychotic illness, and how does mania fit into this schema? If patients are ascertained on a clinical service basis, what is the impact on the epidemiology of first-episode psychosis if, as is often the case, onset in arbitrarily defined "old age" is excluded? These issues and our own studies to address them are the subject of the present article.

Boundaries of First-Episode Psychosis?

At the center of any study of first-episode psychosis is the definition of *psychosis* to be adopted and how it is to be applied. The majority of studies have used the term *first-episode psychosis* as a pseudonym for schizophrenia and usually apply an internationally recognized operational definition, most commonly from RDC, ICD-9/10, or DSM-III-R/IV. Given the possibly acute, florid onset of first-episode psychosis and DSM-III-R/IV duration of illness criteria for schizophrenia, diagnosis is sometimes extended to schizophrenia spectrum psychosis so as to include schizophreniform disorder and schizoaffective disorder. However, the boundaries of schizophrenia spectrum psychosis are poorly understood. For example, other DSM-IV diagnoses such as delusional disorder and psychosis NOS are sometimes included but often not, and brief psychotic disorder is less commonly entertained. Diagnoses of schizophrenia with comorbid substance abuse and/or substance-induced psychotic disorder are very often exclusion criteria, unless they are a specific topic of investigation, as is psychotic disorder caused by a general medical condition.

However, perhaps the most overlooked issue relates to affective psychosis. Most studies of first-episode psychosis confine themselves to "nonaffective psychosis" (usually including schizoaffective disorder) and handle the matter by exclusion. The number of studies on first-episode psychosis in major depressive disorder is small; hence systematic information on its epidemiology and biology is minimal. However, there is an increasing number of studies on bipolar I disorder, and this raises a particular challenge: To what extent should a first manic episode be considered to indicate in itself a psychotic disorder, or does this only apply when, for example, the DSM-IV modifier of "severe with psychotic features" is also satisfied? As a specific example, do "grandiose delusions" reflect the intrinsically psychotic nature of bipolar disorder, or does their presence constitute a feature that distinguishes psychotic from nonpsychotic bipolar disorder?

The European tradition has addressed this issue through the older, generic terms *functional psychosis* and *manic-depressive psychosis* (e.g., [4]). Other schools, including the United States, more often place emphasis on the presence or absence of the modifier "severe with psychotic features."[5] Evidence suggests that, just as they manifest cognitive impairment,[6] the great majority of patients with bipolar I disorder manifest "psychosis" at some time over their illness.[7–8] Thus, when made, the distinction between psychotic and nonpsychotic bipolar I disorder may be arbitrary. In the context of first-episode psychosis, restricting studies of first-episode mania to those having a diagnosis of bipolar I disorder "severe with psychotic features" is likely to omit a number of relevant cases. It results in incomplete ascertainment of the totality of first-episode mania and hence seriously confounds the study of its epidemiology. Substance (primarily antidepressant)-induced mood disorder with manic features is recognized clinically, but in the context of first-episode mania it is rarely considered diagnostically and epidemiologically other than by exclusion.

Demographically, many studies exclude patients using arbitrary and diverse age cutoffs that relate primarily to patients experiencing the onset of psychosis at older ages. This can be implemented for many reasons, for example, as a consequence of case ascertainment via a clinical service that provides only for patients within a particular age range, to ensure that cases are "typical" of first-episode psychosis, to exclude any first psychotic episodes in old age out of concern that they constitute a separate "subgroup," and to ensure a more homogenous sample by minimizing presumed nonspecific effects of old age. Such cutoffs, however pragmatic and well intentioned, can materially confound the study of first-episode psychosis.

Utilitarian First-Episode Samples

Over the past 20 years an increasing and now substantial number of first episode studies have been conducted, the majority of which involve (i) ascertainment on a pragmatic basis as "samples of convenience"; (ii) relatively small numbers of cases; (iii) restriction to a specific diagnostic category, usually schizophrenia; and (iv) a single or limited number of assessments to address a specific question. Such "utilitarian" studies provide important information, as reviewed previously,[9–13] and many are considered in the specific *first episode* articles constituting this issue. However, by their nature, such studies have limited capacity to inform on the epidemiology of first-episode psychosis or on the epidemiological representativeness of the specific findings reported and are not considered further in this context.

Cohort/Database Studies

Similarly, birth cohorts, population-based cohorts, and retrospective/follow-up studies of national or large regional hospital databases can provide important epidemiological information, usually on schizophrenia[2] but increasingly in relation to bipolar disorder.[14] However, though they may have some advantage in the face of high residential mobility, such studies have their own

limitations in terms of dependence on those preexisting databases and are not considered further.

Contemporary Prospective Studies

Emphasis here is on the new generation of prospective studies that may be able to inform in some way on the epidemiology of first-episode psychosis and/or on the epidemiological representativeness of biological and clinical findings in first-episode psychosis. Those that include more than 50 subjects for purposes other than therapeutic trials are considered particularly in relation to the diversity in their modes of ascertainment, diagnostic inclusions, and demographic exclusions.[9, 15–41]

It is evident (Table 1) that the above studies are heterogeneous, with diversity particularly prominent in relation to ascertainment via inpatient versus outpatient facilities; ascertainment via public versus private facilities; age cutoff; diagnostic criteria; diagnostic scope, particularly inclusion of nonaffective versus affective psychosis; longitudinal determination of stability of inception diagnoses; and exclusion of substance abuse and learning disability. The vast majority of studies involve urban populations of considerable ethnic and socioeconomic diversity. Studies that include first-episode mania are substantially underrepresented and are diverse with respect to their inclusion of bipolar I disorder with versus without psychotic features. The great majority of these studies are neither designed nor powered on an epidemiological basis, do not incept representative populations, are depleted of cases who decline assessment, and thus do not allow incidence data to be derived. Conversely, the few that present incidence data do so primarily in terms of diagnostic composites rather than systematically for the individual diagnoses incepted; though diverse, reflecting such methodological heterogeneity, the values for schizophrenia or schizophrenia spectrum psychoses that they report are all within the wide range reported on recent meta-analysis (15.2/100,000 [90% CI 7.7, 43.0]).[3]

The potential of first episode studies would be facilitated via systematic epidemiological, biological, and clinical comparisons among homogenous populations of the psychoses, but how is this to be achieved? It requires prolonged accrual of "all" cases of nonaffective, affective, and any other psychotic illness on an epidemiologically complete basis, to derive representative populations,[1, 42] together with a prospective component to determine longitudinally the stability of inception diagnoses. The Suffolk County Mental Health Project constitutes the closest approximation to date, but its authors note that "while the Suffolk County Mental Health Project provides a broad coverage of most cases with first admission psychosis admitted to various facilities in the County, its sample does not necessarily represent *all* cases within this catchment area."[43(pp53)]

Given that rural Ireland offers substantive ethnic and socioeconomic homogeneity and stability, and that provision of psychiatric care is based on strict catchment areas, in 1995 we sought to initiate such a study. The structure of the Cavan-Monaghan prospective first episode study has been outlined previously in the context of preliminary data over its first 5 years.[44] It is complemented by its Dublin counterpart at St. John of God Hospital, which applies similar methods to inpatients and outpatients within an urban catchment area, population 165,000.[45–46] The following sections illustrate some of the challenges relating to the ascertainment and epidemiology of first-episode psychosis via interim data obtained from the Cavan-Monaghan study over its first 8 years.

The Cavan-Monaghan First Episode Study

Study Region and Health Care Provision

As described previously in detail,[44] this study is based in Cavan and Monaghan, 2 contiguous, northeastern border counties of the Republic of Ireland having a total population of 103,054 (52,756 males, 50,298 females). Its objective is to identify "all" instances of first-episode psychosis affecting any resident of the region covered by the Cavan-Monaghan Mental Health Service under a strict catchment area policy in accordance with Irish mental health legislation; patients presenting to any catchment area other than that of their residence should be referred as soon as is practicable back thereto.

Among the population of Cavan-Monaghan, 92% were born in the Republic of Ireland (74% in their county of residence, 18% elsewhere in Ireland); 7% were born in the United Kingdom, and 0.3% were born in the United States, the vast majority of whom had at least 1 Irish parent; 0.7% were born elsewhere; and 97% were currently resident at the same location as 1 year previously. These counties are entirely rural, the largest town having a population of 5,750, with a primarily agriculture-based economy; 81% of households are owner occupied, and 70% of private households have at least 1 car.[44] While this attests to the ethnic and socioeconomic homogeneity and low social mobility of the study region, with Cavan-Monaghan still having the lowest social mobility index in Ireland,[47] even rural Ireland is now beginning to experience some ethnic and socioeconomic diversification.

At the start of this study in 1995, Cavan-Monaghan Mental Health Service provided integrated, sector-based care through clinical teams led by 4 consultants in general adult psychiatry with 2 admission units. The service had pioneered in an Irish context the development of rehabilitation psychiatry, leading to the provision of substantial alternative residential supports in the community. In 1998, the service was radically reorganized: a full-time specialist rehabilitation service was established; a new

Table 1. Prospective Studies of First-Episode Psychosis

Study	Setting	Population	Cases	Age Cutoff	Diagnostic Criteria	Diagnostic Scope (incidence/100k/yr [95% CI])
ÆSOP[15]	Consecutive multiethnic presentations to psychiatric services in London, Nottingham, and Bristol, U.K.	Urban: 1,631,000	568	16–64	ICD-10	SZ, AP
Bordeaux[16]	Consecutive admissions to psychiatric hospital in Bordeaux, France	Urban: 250,000	65	<60	DSM-IV	SZ, SF, SA, BrPD, DD, AP, SIPD, PNOS
CEPP[17]	Consecutive admissions to Early Psychosis Program in Calgary, Canada	Urban: 930,000	278	–	DSM-IV	SZ, SF, SA, BrPD, DD, PNOS
Cantabria[18]	Consecutive presentations to mental health services in Cantabria, Spain	523,000	86	–	CATEGO	SZ
Cincinnati[19]	Consecutive hospital admissions in Cincinnati	Urban	109	15–45	DSM-III-R	BP-P$^+$, MDD-P$^+$; LD excluded
Cincinnati[20]	Consecutive hospital admissions in Cincinnati	Urban	55	15–45	DSM-III-R	BP
Ealing/Lambeth/ Southwark[21]	Consecutive multiethnic presentations to health services in London	Urban: 128,675	123	18–64	CATEGO	SZ, ''broad'' SZ (white, ''broad'' SZ: 30/100k)
Enfield/Haringey[22]	Consecutive multiethnic presentations to psychiatric services in London	Urban: 167,984	93	16–54	ICD-9	SZ, paranoid states, other nonorganic psychoses (white, SZ: 12/100k [6,19])
EPPIC[23]	Consecutive admissions to Early Psychosis Prevention and Intervention Centre in Melbourne, Australia	Urban: 800,000	565	16–30	DSM-III-R	SZ, SF, SA, BrPD, DD, BP, MDD-P$^+$, SIPD, PNOS; LD excluded
ETIP (TIPS)[24]	Consecutive referrals to psychiatric services in 4 health care sectors in Norway	670,000	301	18–65	DSM-IV	SZ, SF, SA, DD, AP, PNOS; LD excluded
Finnish/Spanish[25]	Consecutive presentations to inpatient or outpatient services of 3 city hospitals in Finland and Spain	Urban	86	16–44	DSM-III-R	SZ, SF, SA, BrPD, DD, PNOS; S, V excluded
Groningen[26]	Consecutive hospital admissions in Groningen, Sweden	Urban	191	18–55	DSM-IV	SZ, SF, SA, BrPD, DD, PNOS
The Hague[27]	Consecutive multiethnic presentations to health services in The Hague, the Netherlands	Urban: 258,493	181	15–54	DSM-IV	SZ, SF, SA, BrPD, DD, BP-P$^+$, MDD-P$^+$, PNOS (natives, S/SF/SA: 12/100k [8,16]; natives, all psychoses: 22 [17,27]); SIPD excluded
Hillside[28–29]	Consecutive hospital admissions in New York	Urban	118	>16	RDC	SZ, SA
Manchester[30]	Consecutive admissions to psychiatric units in Manchester, U.K.	Urban: 307,000	112	16–50	RDC	SZ, SF, SA, BrPD, BP (S/SF/SA/BrPD: 17/100k [10,22])
McLean-Harvard[31]	Hospital admissions in Boston	Urban	296	>16	DSM-IV	SZ, SF, SA, BrPD, DD, BP-P$^+$, MDD-P$^+$, PNOS; LD excluded

Table 1. Continued

Study	Setting	Population	Cases	Age Cutoff	Diagnostic Criteria	Diagnostic Scope (incidence/100k/yr [95% CI])
McLean-Harvard[32]	Hospital admissions in Boston	Urban	239	18–75	DSM-IV	BP; LD excluded
Nottingham[33]	Consecutive contacts with psychiatric services in Nottingham, U.K.	Urban: 397,000	166	16–64	ICD-10	SZ, SA, SF, DD, BP-P$^+$, MDD-P$^+$, SIPD, PNOS (SZ: 7/100k [5,10]; S/SF/SA: 13 [11,16]; all psychoses: 21 [18,24])
Pamplona[34]	Consecutive admissions to psychiatric unit in Pamplona, Spain	Urban	70	–	DSM-IV	SZ, SF, SA, BrPD, DD; SIPD, LD excluded
PEPP[35]	Consecutive admissions to prevention and Early Intervention Program for Psychoses in Western Ontario, Canada	Urban	130	16–50	DSM-IV	SZ, SF, SA, BrPD, DD, BP-P$^+$, SIPD, PNOS
SAP[36]	Admissions to inpatient or outpatient facilities in Turku, Finland	Urban	116	16–64	DSM-IV	SZ, BP, severe MDD
Suffolk County[37–38]	Admissions to 12 inpatient facilities in Suffolk County, New York	Urban/rural: 1,300,000	696	15–60	DSM-III-R/ DSM-IV	SZ, SF, SA, BrPD, DD, BP-P$^+$, MDD-P$^+$, SIPD, PNOS; LD excluded
Swedish Parachute[39]	Consecutive presentations to clinics in cities in Sweden	Urban: 1,500,000	253	18–45	DSM-IV	SZ, SF, SA, BrPD, DD, AP, PNOS; SIPD excluded
West London[40]	Presentations to mental health services in West London	Urban	136	16–50	DSM-IV	SZ, SF
WPIC[9, 41]	Hospital admissions in Pittsburgh	Urban	129	15–45	DSM-IV	SZ, SF, SA, DD, BP-P$^+$, MDD-P$^+$, PNOS; SIPD, LD excluded

Note: SZ = schizophrenia, SF = schizophreniform disorder, SA = schizoaffective disorder, BrPD = brief psychotic disorder, DD = delusional disorder, AP = affective psychosis, BP = bipolar disorder, BP-P$^+$ = bipolar disorder with psychotic features, MDD = major depressive disorder, MDD-P$^+$ = major depressive disorder with psychotic features, SIPD = substance-induced psychotic disorder, PNOS = psychotic disorder not otherwise specified, LD = learning disability, S = threat of suicide, V = threat of violence. Where ethnicity is a specific topic of study, incidence values are given for "white" or "native" groups to allow comparison with findings in the present study.

community mental health team was set up for Co. Monaghan; a new community mental health team was set up for Co. Cavan in 2000; and a specialist service in psychiatry for the elderly for Cavan-Monaghan was inaugurated in 2000. This model of care is community based, with close links to primary care and geriatric services.[48] In these specialist teams, domiciliary visiting and home base working are emphasized.[49] There is a high provision of psychiatric nurses in new specialist roles. There are multicenter outpatient clinics together with day hospital and day center services. Referrals to the service are predominantly from general practitioners, sometimes from Health Board agencies, and occasionally from the police. The combined effect of these various changes in service delivery, with a central emphasis on the provision of home base care for acute illness as an alternative to admission, has been that annual admission rates have declined substantially since 1995 and are now 2.5/1,000, the lowest rate nationally.[50]

Ascertainment of Cases

Under a protocol approved by the Research Ethics Committee of the North Eastern Health Board and the director of Cavan-Monaghan Mental Health Service, the fulcrum of identification is a clinical research fellow whose appointment is structured within Cavan-Monaghan Mental Health Service and includes 2 clinical sessions per week. Thus, the research fellow is also a registrar having an integral role in the service, to ensure that the study is complementary to service provision. The registrar/fellow remains in regular contact with all mental

health teams, who refer all putative cases with any first psychotic episode (to include any first manic episode) aged 16 or above, of whatever provisional diagnosis or none, and whether seen by the team in their own homes, at a community/outpatient clinic, or following admission to an acute unit.

The ethos is one where members of any mental health team are encouraged to refer retrospectively putative cases that they believe may have been missed, where initial presentation was within the time frame of the study. In a complementary manner, the registrar/fellow conducts periodic retrospective reviews of clinical documentation within Cavan-Monaghan Mental Health Service to identify any putative cases that may have been missed. Additionally, formal arrangements approved by their Research Ethics Committees allow the inception of cases admitted to either of the 2 private psychiatric hospitals in Dublin[44]; the procedures are that the fellow/registrar contacts each private hospital periodically to determine whether any cases have been admitted from the study area and seeks information for the anonymized data set via their treating consultant.

Assessment of Cases

There are no formal diagnostic criteria for entry into the study. The primary inclusion criterion is clinical evidence for a first lifetime episode of any psychotic illness (to include any first manic episode) occurring after the commencement of the study; any presentation with/treatment for that first psychotic episode by a family practitioner or other health professional before referral to Cavan-Monaghan Mental Health Service defines study entry. Thus, for example, previous presentation with/treatment for a depressive illness would not result in inception unless followed by a subsequent presentation for a first psychotic episode, with the date of that episode defining study entry. Conversely, the primary exclusion criteria are (i) any presentation with/treatment for psychotic illness prior to the commencement of the study and (ii) psychosis in the context of a previous, overriding diagnosis of gross neurodegenerative disease (e.g., psychosis in Alzheimer's disease or Huntington's disease or as an adverse effect of dopaminergic therapy for Parkinson's disease).

On notification of each case of putative first-episode psychosis, the registrar/fellow seeks to assess that individual as soon as practicable, either in his or her own home, at a community/outpatient clinic, or on an acute admission ward. Diagnosis is integral to rather than a specific requirement for entry into the study and is in accordance with DSM-IV criteria.[51] On obtaining informed consent to participation, with parental involvement also for those aged 16 or 17, patients are evaluated using the Structured Clinical Interview for DSM-III-R (SCID)[52] and later DSM-IV,[53] to facilitate a DSM-IV diagnosis at inception into the study; any uncertainties are resolved by consensus among members of the team. At 6 months after inception, the fellow/registrar reviews all clinical material to confirm or modify the initial DSM-IV diagnosis, with any uncertainties resolved by consensus among members of the team, or accords the preceding diagnosis in instances of suicide. Where individual cases decline assessment, the Research Ethics Committee has approved a protocol whereby the registrar/fellow has access to basic demographics and clinical records to facilitate a DSM-IV diagnosis in accordance with standard health service audit; these demographics and DSM-IV case note diagnoses are then entered into the anonymized data set by study number, with any uncertainties resolved by consensus among members of the team. Additionally, for persons giving informed consent, psychopathological, neuropsychological, neurological, developmental, and other assessments are made, to be described in detail elsewhere.

Incidence is expressed as the annual number of cases per 100,000 of the population aged $\geq$15 years (76,670 [39,301 males, 37,369 females] of the total population of 103,054), with 95% confidence intervals (CI) for incidence rates and incidence ratios between the genders; these analyses are performed using Stata Release 7 in the Department of Epidemiology, Royal College of Surgeons in Ireland. Age at first presentation, defined in terms of initial contact with any health professional in relation to the first psychotic episode, is expressed by mean (SD) and analyzed using analysis of variance followed by Student's *t*-test (2-tailed) with pooled or separate variance estimates as appropriate.

Interim Findings

Overall Incidence of Psychosis

Over the 8-year period May 1995–April 2003, there were 194 cases of any DSM-IV psychotic illness (117 male, 77 female; Table 2). The annual incidence of "all psychoses" was 31.6/100,000 aged >15, this being higher in males (37.2) than in females (25.7; risk ratio [RR] = 1.44 [95% CI 1.08, 1.93], $p < .02$; Table 3).

Incidence of Psychosis by Major and "Core" Diagnostic Group

For schizophrenia spectrum psychoses (i.e., schizophrenia, schizoaffective disorder, or schizophreniform disorder), annual incidence was 10.8/100,000 aged >15, this being higher in males (15.3) than in females (6.0; RR = 2.54 [95% CI 1.47, 4.36], $p < .001$). For schizophrenia, incidence was 7.0, this being higher in males (11.1) than in females (2.7; RR = 4.16 [95% CI 1.93, 8.97], $p < .001$). For schizoaffective disorder, incidence was 2.0, this being indistinguishable between males (2.5) and females (1.3; RR = 1.90 [95% CI 0.57, 6.32]). For schizophreniform

Table 2. Number of Cases and Age at First Presentation by Diagnosis at 6 Months

Diagnostic Group	Number of Cases and Age		
	Total	Males	Females
All Psychoses	194 35.9 (18.2) [16–84]	117 32.0 (15.9) [16–80]	77 41.8 (20.0)[b] [16–84]
Schizophrenia Spectrum Psychoses	66 31.3 (16.6) [16–84]	48 28.7 (13.5) [16–77]	18 38.4 (21.8)[a] [16–84]
Schizophrenia	43 29.4 (14.4) [16–77]	35 28.5 (14.6) [17–77]	8 33.6 (13.9) [16–53]
Schizophreniform	11 45.7 (24.0) [18–84]	5 35.6 (12.1) [25–56]	6 54.2 (29.1) [18–84]
Schizoaffective	12 25.1 (6.4) [16–42]	8 25.4 (7.8) [16–42]	4 24.5 (3.0) [20–26]
Affective Psychoses	71 40.7 (20.4) [16–81]	34 37.5 (20.0) [16–80]	37 43.6 (20.5) [17–81]
Bipolar disorder	32 34.8 (16.2) [19–80]	17 33.4 (15.5) [19–70]	15 36.3 (17.3) [20–80]
Major depressive disorder	39 45.6 (22.3) [16–81]	17 41.6 (23.5) [16–80]	22 48.6 (21.3) [17–81]
Other Psychoses	57 35.2 (16.0) [16–80]	35 31.2 (13.1) [16–65]	22 41.5 (18.3)[a] [17–80]

Note: Data are number of cases, mean age, SD in parentheses, and range in brackets.
Older age at first presentation in females: [a]$p < .05$; [b]$p < .001$.

disorder, incidence was 1.8, this being indistinguishable between males (1.6) and females (2.0; RR = 0.79 [95% CI 0.24, 2.59]; Table 3).

For "affective psychoses" (i.e., bipolar I disorder with or without the modifier "severe with psychotic features" or major depressive disorder with psychotic features), annual incidence was 11.6/100,000 aged >15, this being indistinguishable between males (10.8) and females (12.4; RR = 0.87 [95% CI 0.59, 1.39]). For bipolar I disorder, incidence was 5.2, this being indistinguishable between males (5.4) and females (5.0; RR = 1.08 [95% CI 0.54, 2.16]). For major depressive disorder with psychotic features, incidence was 6.4, this being indistinguishable between males (5.4) and females (7.4; RR = 0.73 [95% CI 0.39, 1.38]; Table 3).

For "other psychoses"—brief psychotic disorder, 10 (2 male, 8 female); delusional disorder, 9 (5 male, 4 female); simple deteriorative disorder, 1 male (see DSM-IV, "Criteria Sets and Axes Provided for Further Study," and *Discussion*, this article); psychotic disorder due to a general medical condition, 4 (2 male, 2 female); substance-induced psychotic disorder, 12 males; bipolar II disorder, 1 female; substance-induced mood disorder with manic features, 6 (4 male, 2 female); psychotic disorder not otherwise specified, 14 (9 male, 5 female)—annual incidence was 9.3/100,000 aged >15, this being indistinguishable between males (11.1) and females (7.4; RR = 1.51 [95% CI 0.89, 2.58]; Table 3). In addition to the above 12 male cases of substance-induced psychotic disorder, there were 36 cases (31 male, 5 female) of other diagnoses with comorbid substance abuse, mostly cannabis and alcohol but occasionally amphetamines, hallucinogens, "ecstasy," benzodiazepines, and polysubstance abuse; this occurred mostly in schizophrenia spectrum psychosis, bipolar I disorder, and psychosis NOS but occasionally in major depressive disorder with psychotic features, delusional disorder, and brief psychotic disorder. Thus, previous and/or current substance abuse was encountered in 48 (43 male, 5 female) of 194 cases (25%; 37% of males, 6% of females).

Table 3. Incidence of Psychosis by Diagnosis at 6 Months

Diagnostic Group	Incidence		
	Total	Males	Females
All Psychoses	31.6 (27.3, 36.4) [194]	37.2 (30.8, 44.6) [117]	25.7 (20.3, 32.2)[a] [77]
Schizophrenia Spectrum Psychoses	10.8 (8.3, 13.7) [66]	15.3 (11.3, 20.2) [48]	6.0 (3.6, 9.5)[b] [18]
Schizophrenia	7.0 (5.1, 9.4) [43]	11.1 (7.8, 15.5) [35]	2.7 (1.2, 5.3)[b] [8]
Schizophreniform	1.8 (0.9, 3.2) [11]	1.6 (0.5, 3.7) [5]	2.0 (0.7, 4.4) [6]
Schizoaffective	2.0 (1.0, 3.4) [12]	2.5 (1.1, 5.0) [8]	1.3 (0.4, 3.4) [4]
Affective Psychoses	11.6 (9.0, 14.6) [71]	10.8 (7.5, 15.1) [34]	12.4 (8.7, 17.1) [37]
Bipolar disorder	5.2 (3.6, 7.4) [32]	5.4 (3.2, 8.7) [17]	5.0 (2.8, 8.3) [15]
Major depressive disorder	6.4 (4.5, 8.7) [39]	5.4 (3.2, 8.7) [17]	7.4 (4.6, 11.1) [22]
Other Psychoses	9.3 (7.0, 12.0) [57]	11.1 (7.8, 15.5) [35]	7.4 (4.6, 11.1) [22]

Note: Data are incidence/100,000 population aged ≥15, 95% CI in parentheses, and number of cases in brackets.
Higher incidence in males: [a]$p<.02$; [b]$p<.001$.

Diagnostic Stability Over the First 6 Months

The substantial majority of initial diagnoses (171 of 194; 88% [85% of 117 males, 94% of 77 females]) were sustained at 6 months, with 23 (18 male, 5 female) transitions, as follows:

- Among 31 cases of schizophrenia (25 male, 6 female) and 7 cases of schizoaffective disorder (3 male, 4 female) at inception, all diagnoses (100%) were sustained at 6 months.
- Among 22 cases of schizophreniform disorder at inception (14 male, 8 female), 6 males (43%) and 2 females (25%) were given a diagnosis of schizophrenia, and 1 male was given a diagnosis of schizoaffective disorder at 6 months, primarily by satisfying the duration criterion of DSM-IV; 1 male was given a diagnosis of bipolar I disorder, and 1 male was given a diagnosis of major depressive disorder with psychotic features at 6 months.
- Among 12 cases of delusional disorder at inception, 3 of 8 males (38%) and none of 4 females were given a diagnosis of schizophrenia or schizoaffective disorder at 6 months; no other diagnoses were given at 6 months.
- Among 13 cases of brief psychotic disorder at inception (2 male, 11 female), none was given a diagnosis of schizophrenia or schizoaffective disorder at 6 months; 3 females (27%) were given an alternative diagnosis at 6 months, 2 of bipolar I disorder and 1 of major depressive disorder with psychotic features.
- Among 12 cases of substance-induced psychosis at inception (all male), 1 was given a diagnosis of schizoaffective disorder at 6 months.
- Among 16 cases of psychosis NOS at inception, 1 of 11 males and none of 5 females was given a diagnosis of schizophrenia or schizoaffective disorder at 6 months; 1 male was given a diagnosis of substance-induced psychosis.

- Among 30 cases of bipolar I disorder at inception, all diagnoses but 1 (97%) were sustained at 6 months; 1 male was given a diagnosis of schizoaffective disorder, while 1 male given an inception diagnosis of schizophreniform disorder and 2 females given an inception diagnosis of brief psychotic disorder were given a diagnosis of bipolar I disorder at 6 months.
- Among 6 cases of substance (antidepressant)-induced mood disorder with manic features at inception (4 male, 2 female), all diagnoses were sustained at 6 months.
- Among 39 cases of major depressive disorder with psychotic features at inception, all diagnoses but 2 (95%) were sustained at 6 months; 1 male was given a diagnosis of schizophrenia, and 1 was given a diagnosis of schizoaffective disorder, while 1 male given an inception diagnosis of schizophreniform disorder and 1 female given an inception diagnosis of brief psychotic disorder were given a diagnosis of major depressive disorder with psychotic features at 6 months.

There were 2 instances of suicide (1.0%; both male), 1 following a diagnosis of schizophrenia and 1 following a diagnosis of substance-induced psychosis.

Age at First Presentation by Major Diagnostic Group

Over all psychoses, mean age at first presentation was lower in males than in females; this held marginally for schizophrenia spectrum psychosis and psychosis NOS but not for any other individual diagnosis or diagnostic grouping (Table 2).

Discussion

A primary challenge is the nature of putative diagnostic ''boundaries'' to first-episode psychosis. Utilitarian approaches based on diagnostic homogeneity can satisfy a pragmatic need for a carefully delineated group of cases for biological and other studies that will inform on aspects of the psychotic diagnosis selected, usually schizophrenia, at and following a first episode; however, the group derived is likely to be unrepresentative epidemiologically of the diagnosis at issue, as well as being far removed from the ''totality'' of first-episode psychosis. An alternative approach is to seek to ascertain and assess cases on an epidemiological basis that will allow inter alia exploration of putative diagnostic ''boundaries'' and hence in itself inform on the nature of first-episode psychosis; the full potential of this approach is then realized by feeding cases identified into biological and other studies that will inform further on aspects of psychosis at and following a first episode across those diagnostic ''boundaries.''

As for essentially all such studies, the Cavan-Monaghan study is subject to the limitations of noncensus approaches but allows for methodological refinements to minimize their impact: Regarding public psychiatric care in Ireland, there is a strict catchment area policy in accordance with mental health legislation; regarding private psychiatric care in Ireland, which accounts for <2% of all general adult psychiatric admissions, we are able to ascertain relevant cases via the 2 hospitals in Dublin that account for 98% of private psychiatric admissions[44]; and as for essentially all such studies, we are unable to exclude leakage through presentation to psychiatric services in other countries. These factors allow some confidence that the vast majority of cases are ascertained. Furthermore, we are able to access diagnostic and demographic information on cases that decline formal assessment. Thus, this study is as epidemiologically complete as is currently conceivable. However, interim findings in this ongoing study require the accrual of additional cases to substantiate preliminary conclusions regarding diagnostic groups that to date involve relatively small numbers of cases. Also, as for all studies involving a single geographical region, it cannot be excluded that there exist in this area unknown, idiosyncratic factors that may limit generalizability to other regions and populations.

First-Episode Schizophrenia: The Epidemiology of Nonaffective Psychosis

In relation to a first episode of putative schizophrenia spectrum psychosis, schizophrenia and schizoaffective disorder appear to be essentially stable diagnoses over the 6 months following first presentation. First-episode schizophreniform disorder appears to identify a primarily male group among whom the majority of males and a minority of females evolve into schizophrenia or schizoaffective disorder, while a minority of males evolve into bipolar I disorder or major depressive disorder with psychotic features. First-episode delusional disorder appears also to identify a primarily male group, a minority of whom evolve into schizophrenia or schizoaffective disorder but not into other psychotic disorders. First-episode brief psychotic disorder appears to identify a primarily female group with transient symptoms, a minority of whom may be more likely to evolve into an affective psychosis.

First-episode psychosis NOS appears to identify a primarily male group where a particular diagnostic difficulty relates to distinguishing between schizophrenia with comorbid substance abuse and substance-induced psychosis. The overall rate of substance abuse (25%), primarily in males, is toward the lower end of the range encountered[54–58]; this may reflect, at least in part, the rural setting of the study.

There was also 1 case of first-episode schizophrenia-like deterioration in functioning with primarily negative symptoms but only vague, transient psychotic ideation. This 23-year-old male satisfied proposed criteria for

"simple deteriorative disorder" (see DSM-IV: "Criteria Sets and Axes Provided for Further Study"); we have recently encountered a second male case. The present findings elaborate to the first-episode setting an evolving contemporary literature on a rare, "rediscovered" entity that is best encapsulated as a form of schizophrenia.[59–61]

It is difficult to make overall comparisons with other studies that have used nonepidemiological or variant epidemiological approaches over differing follow-up periods, with application of age cutoffs and exclusion of some psychotic diagnoses and some prior or current comorbid diagnoses (e.g., [38, 62]). The Cavan-Monaghan study is epidemiologically based without any such exclusions other than psychosis in the context of a previous, overriding diagnosis of gross neurodegenerative disease.

First-Episode Schizophrenia: The Epidemiology of Age at Onset

In the face of enduring controversy as to how age at onset in schizophrenia should be defined, we use here the unambiguous term *age at first presentation*; in individual instances this may or may not be the same as "age at onset" depending on the definition thereof.[44, 63–64] Though controversy also endures as to the definition of how long psychosis may have run unchecked after "onset" before first presentation and treatment (duration of untreated psychosis [DUP]) and, importantly, the nature of its putative prognostic significance,[65–69] further discussion thereof is outside the scope of this article.

A mean age in the late 20s at first presentation in the present study might seem at variance with the presumption held by some that in schizophrenia presentation occurs more typically in the late teens/early 20s (see [44] and references therein). Also, the more widely held presumption that presentation occurs typically at a later age in females is evident here for all psychoses and is marginal for schizophrenia spectrum psychosis and psychosis NOS, but it is less evident for schizophrenia itself, in accordance with other findings.[44, 70–72] However, unlike the great majority of other studies, which typically impose an arbitrary upper age limit (see "Introduction"), the present study ascertains "all" cases of psychosis without loss of elderly cases through either exclusion or nonascertainment due to referral to external services for the psychiatry of old age. Indeed, the median age at first presentation for schizophrenia (23 [interquartile range 20, 35]) is considerably below the mean (29.4 [SD 14.4]), indicating a disorder primarily of early adulthood but with a nontrivial number of cases presenting over the life span through to old age. Thus, the present data are likely to reflect more accurately the epidemiology of first-episode schizophrenia (see [44]). Evidence indicates that operationally defined schizophrenia with onset in old age does not differ substantively from similarly defined schizophrenia with onset in the second or third decade.[73–75] Hence failure to ascertain and/or include such cases gives an incomplete perspective not only on the epidemiology but also on the biology of first-episode schizophrenia. Though the number of cases of schizoaffective disorder is as yet limited, it is notable that the median (25 [interquartile range 21, 27]) and mean (25.1 [SD 6.4]) ages at first presentation are identical, suggesting a disorder of early adulthood with a dearth of cases presenting over the life span through to old age.

First-Episode Schizophrenia: The Epidemiology of Sex Differences in Incidence

Our findings are complementary to, but have a different import from, the debate as to the overall incidence of schizophrenia, as subject to recent meta-analysis.[3] Rather, the present data specify the diversity of first-episode psychosis in relation to contemporary nosology and offer epidemiological quantification of their relative incidence in this region. On this basis, the most striking finding is the substantially higher risk for schizophrenia in males relative to females, with increasing stringency of definition (RR: all psychoses—1.4 < schizophrenia spectrum psychosis—2.5 < schizophrenia—4.2).

Two recent meta-analyses have each indicated an RR for schizophrenia in males of 1.4 across multiple diverse studies.[3, 76] As the present incidence value for schizophrenia in males (7/100,000) is similar to (i) previous incidence estimates across the genders in the United Kingdom (e.g., 7/100,000,[33, 77] 8/100,000)[78] and (ii) incidence estimates for "narrowly defined" schizophrenia in the World Health Organization 10-country study, including Dublin city, Ireland (males: 10/100,000, females: 8/100,000),[64] it must first be asked whether there might be some methodological basis for reduced case accrual among females. As discussed in detail elsewhere,[44] this is unlikely to be explained in terms of (i) female cases being more likely to remain "managed" or "tolerated" domestically in rural settings, (ii) female cases being more likely to present to private psychiatric hospitals, (iii) female cases being more likely to enter the judicial rather than the medical system, and (iv) females at risk for schizophrenia being more likely to migrate prior to onset.

On this basis, the reduced incidence of schizophrenia among females with increasing stringency of definition requires explanation in alternative terms. As elaborated elsewhere,[44] at least 3 factors may be relevant. First, there is previous evidence that increasing stringency of operational diagnostic criteria is associated with a particular reduction in women who receive a diagnosis of schizophrenia, though the extent of this effect did not attain the present level; one element in this effect may be the elimination of individuals with an affective component to their illness, which is more common in females. Second, there endures a controversy as to whether the

incidence of schizophrenia may have declined over recent decades, with some studies that have taken gender into account noting a greater decline in females. Third, studies indicate increased risk for schizophrenia among those having their birth/early upbringing in urban as opposed to rural environments, with a gradient that may be more pronounced for females.

Notably, all of the above factors, each of which alone could result in some reduction in incidence among females, apply to the present study. While such a confluence of effects might synergize to prominently deflate incidence of schizophrenia among females, putative synergism remains circumstantial and fails to resolve the specific nature of the underlying causal factor(s). Strikingly, the present fourfold male excess in rural Ireland echoes recent reports from rural areas of a twofold excess in Palau, Micronesia,[79] a sixfold excess in Kosrae, Micronesia,[80] and a sevenfold excess in Ethiopia.[81] Thus, ''protective'' factors may be operating among females in rural environments, the basis of which could repay further systematic study.

The Diversity of First-Episode Psychosis

A second major diagnostic grouping is as expected in terms of bipolar I disorder, that is, a first manic episode with or without prior history of a major depressive episode. Bipolar I disorder is an essentially stable diagnosis over 6 months following a first manic episode, as are first-episode schizophrenia and schizoaffective disorder. Furthermore, incidence of bipolar I disorder is indistinguishable from that of schizophrenia, with age at first presentation only slightly older and with little sex difference therein; as for schizophrenia, the median age at first presentation for bipolar I disorder (27 [interquartile range 22, 49]) is considerably below the mean (34.8 [SD 16.2]), indicating a disorder primarily of early adulthood but with a nontrivial number of cases presenting over the life span through to old age. However, one difference from first-episode schizophrenia appears substantive: there is no sex difference in risk for first-episode bipolar I disorder. Interestingly, the 6 DSM-IV diagnoses of substance-induced mood disorder with manic features all related to the use of antidepressants. These findings address the enduring challenge in bipolar disorder[82–83] of the action of antidepressants to induce mania by quantifying the contribution of this DSM-IV definition among a population experiencing their first manic episode.

However, a third major diagnostic grouping was unexpected. The incidence of major depressive disorder with psychotic features is considerably higher than anticipated, being indistinguishable from the incidence of schizophrenia and bipolar I disorder. First-episode psychosis in major depressive disorder is an essentially stable diagnosis over 6 months, as with first-episode schizophrenia, schizoaffective disorder, and bipolar disorder. Though the mean age at first presentation is somewhat higher than that for schizophrenia, schizoaffective disorder, and bipolar I disorder, with little sex difference therein, first-episode psychosis in major depressive disorder is in no way overrepresented along the elderly; in marked contrast to schizophrenia and bipolar I disorder, it is evident across the entire age range from the teens through to old age, with median (45 [interquartile range 21, 67]) and mean (45.6 [SD 22.3]) ages identical. As for bipolar I disorder, another difference from first-episode schizophrenia appears substantive: there is again no sex difference in risk for a first episode of psychosis in major depressive disorder. It would be important to clarify the extent to which the psychopathology of first-episode psychosis in major depressive disorder might differ qualitatively from that in schizophrenia.

Synthesis

The Cavan-Monaghan first episode study has the specific objective of accruing a large, epidemiologically complete population of ''all'' cases of the psychoses. Rural Ireland presents one of the few remaining opportunities in the developed world to undertake systematic epidemiological, clinical, and biological comparisons in first-episode psychotic illness across conventional diagnostic boundaries, with minimal impact from confounding factors such as urbanicity and ethnic, socioeconomic, and geographical diversity and instability.

Identification of the bases of increased risk for schizophrenia associated with urban birth/upbringing[84] and ethnic migration[85] is important; these may involve biological or psychosocial factors, or interactions between them, that are not present or else are present to a reduced extent in rural areas. Thus, rural investigations on ethnically homogenous and stable populations, such as the Cavan-Monaghan study, define the baseline epidemiology of first-episode psychosis and thus specify the substrate on which factors associated with urbanicity and ethnic migration act in other geographical regions and societies. The study is complemented by a similar, epidemiologically based study of ''all'' prevalent cases of schizophrenia within the same region,[86–87] with long-term follow-up. Thus, in an integrated manner, incident cases feed into the prevalent population. This allows for alternative approaches to issues such as DUP[88–89] and factors associated with premature mortality.[90–91] Additionally, these epidemiologically based patient populations contribute samples for molecular genetic studies.[92–94]

A substantive interim finding in the Cavan-Monaghan first episode study at 8 years is that psychosis can present in a multiplicity of forms vis-à-vis conventional operational (here DSM-IV) criteria. While ''core'' diagnoses such as schizophrenia and bipolar disorder constitute nodes about which large numbers of cases accumulate,

they in no way represent exclusive diagnostic entities other than in the circular sense of having distinct operational definitions; rather, around these nodes there exist numerous additional, overlapping, and well-populated diagnostic categories that are again distinct only in terms of their operational definition. An unexpected finding on seeking to ascertain "all" instances of first-episode psychosis is that there is another "core" diagnostic node in terms of the large number of cases of first-episode psychosis in major depressive disorder; yet there have been very few studies of this entity.[19, 31, 36] Each of these 3 "core" diagnostic nodes evidences its own epidemiological "signature."

Furthermore, diagnostic reevaluation between inception and 6-month follow-up indicates that the substantial majority of diverse inception diagnoses outside of these 3 "core" diagnostic nodes do not converge into any "core" diagnostic node. In particular, major depression with a first episode of psychotic features is a substantive and stable diagnosis that fails to converge into, for example, a schizophrenia spectrum psychosis such as schizoaffective disorder or into bipolar disorder. Similarly, there is no general evidence that a first episode of psychosis NOS converges into any "core" diagnostic node as several months of illness accrue and the extent of clinical information increases.

It is often held that there is diagnostic uncertainty around the period of initial presentation that reflects the "fluidity" of acute psychosis and will "settle" subsequently to reveal a more stable picture, usually schizophrenia or bipolar disorder. Rather, though the present follow-up is as yet limited to 6 months and may reveal a different picture over longer periods,[95] our data on the epidemiology of first-episode psychosis indicate intrinsic and stable diversity around at least *3* major diagnostic nodes that include major depressive disorder with psychotic features as well as schizophrenia and bipolar disorder. A more heuristic interpretation might be that operational allocation of a given case to one rather than another diagnostic category can be influenced by subtle nuances along dimensions of psychopathology or by vagaries of the diagnostic algorithm, rather than any intrinsic unity to that category.[96] Contemporary emphasis on first-episode schizophrenia, while superficially attractive, is likely to prove limiting. Only through systematic, epidemiologically based studies that access its essential diversity are we likely to understand fully the origins, pathobiology, and optimal treatment of first-episode psychosis.

Acknowledgments

We thank Drs. Teresa Carey, Rachael Cullivan, Patrick Kelly, Feargal Leonard, and Savio Sardinha, together with other members of the Cavan-Monaghan Mental Health Service, for their important contributions. We thank also Mr. Ronan Conroy, Department of Epidemiology, Royal College of Surgeons in Ireland, for assistance with incidence analyses. The Cavan-Monaghan first episode study is supported by the Stanley Medical Research Institute.

References

1. Bromet EJ, Fennig S. Epidemiology and natural history of schizophrenia. *Biol Psychiat* 1999;46:871–881.
2. Jablensky A. Schizophrenia: the epidemiological horizon. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia*. Oxford: Blackwell Science; 2003;203–231.
3. McGrath JJ. Myths and plain truths about schizophrenia epidemiology—the NAPE lecture 2005. *Acta Psychiat Scand* 2004;111:4–11.
4. Johnstone EC, Crow TJ, Frith CD, Owens DG. The Northwick Park "functional" psychosis study: diagnosis and treatment response. *Lancet* 1988;2:119–125.
5. Ketter TA, Wang PW, Becker OV, Nowakowska C, Yang YS. Psychotic bipolar disorders: dimensionally similar to or categorically different from schizophrenia? *J Psychiat Res* 2004;38:47–61.
6. Quraishi S, Frangou S. Neuropsychology of bipolar disorder: a review. *J Affect Disorders* 2002;72:209–226.
7. Benazzi F. A comparison of the age of onset of bipolar I and bipolar II outpatients. *J Affect Disorders* 1999;54:249–253.
8. Benabarre A, Vieta E, Colom F, Martínez-Arán A, Gastó C. Bipolar disorder, schizoaffective disorder and schizophrenia: epidemiologic, clinical and prognostic differences. *Eur Psychiat* 2001;16:167–172.
9. Keshavan MS, Schooler NR. First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bull* 1992;18:491–513.
10. Ram R, Bromet EJ, Eaton WE, et al. The natural course of schizophrenia: a review of first-admission studies. *Schizophrenia Bull* 1992;18:185–207.
11. Chatterjee A, Lieberman JA. Studies of biological variables in first-episode schizophrenia: a comprehensive review. In: McGorry PD, Jackson HJ, eds. *The Recognition and Management of Early Psychosis*. Cambridge: Cambridge University Press; 1999;115–152.
12. Cahn W, Pol HE, Bongers M, et al. Brain morphology in antipsychotic-naïve schizophrenia: a study of multiple brain structures. *Brit J Psychiat* 2002;suppl 43:S66–S72.
13. Torrey EF. Studies of individuals with schizophrenia never treated with antipsychotic medications: a review. *Schizophr Res* 2002;58:101–115.
14. Mortensen PB, Pedersen CB, Melbye M, Mors O, Ewald H. Individual and familial risk factors for bipolar affective disorders in Denmark. *Arch Gen Psychiat* 2003;60:1209–1215.
15. Morgan C, Mallett R, Hutchinson G, et al. Pathways to care and ethnicity. I: sample characteristics and compulsory admission. *Brit J Psychiat* 2005;186:281–289.
16. Verdoux H, Liraud F, Bergey C, Assens F, Abalan F, van Os J. Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first-admitted patients. *Schizophr Res* 2001;49:231–241.
17. Addington J, Mastrigt V, Addington D. Duration of untreated psychosis: impact on 2-year outcome. *Psychol Med* 2004;34:277–284.

18. Vázquez-Barquero JL, Cuesta MJ, Castanedo SH, Lastra I, Herrán A, Dunn G. Cantabria first-episode schizophrenia study: three-year follow up. *Brit J Psychiat* 1999;174:141–149.
19. Strakowski SM, Keck PE, McElroy SL, et al. Twelve-month outcome after a first hospitalization for affective psychosis. *Arch Gen Psychiat* 1998;55:49–55.
20. Strakowski SM, Williams JR, Fleck DE, Delbello MP. Eight-month functional outcome from mania following a first psychiatric hospitalization. *J Psychiat Res* 2000;34: 193–200.
21. Bhugra D, Leff J, Mallett R, Der G, Corridan B, Rudge S. Incidence and outcome of schizophrenia in whites, African-Caribbeans and Asians in London. *Psychol Med* 1997;27: 791–798.
22. King M, Coker E, Leavey G, Hoare A, Johnson-Sabine E. Incidence of psychotic illness in London: comparison of ethnic groups. *Brit Med J* 1994;309:1115–1119.
23. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? *Psychol Med* 2003;33:97–110.
24. Melle I, Larsen TK, Haahr U, et al. Reducing the duration of untreated first-episode psychosis. *Arch Gen Psychiat* 2004;61:143–150.
25. Kalla O, Aaltonen J, Wahlström J, Lehtinen V, Cabeza IG, de Chávez MD. Duration of untreated psychosis and its correlates in first-episode psychosis in Finland and Spain. *Acta Psychiat Scand* 2002;106:265–275.
26. Boks MPM, Liddle PF, Burgerhof JGM, Knegtering R, van den Bjosch R-J. Neurological soft signs discriminating mood disorders from first episode schizophrenia. *Acta Psychiat Scand* 2004;110:29–35.
27. Selten J-P, Veen N, Feller W, et al. Incidence of psychotic disorders in immigrant groups to the Netherlands. *Brit J Psychiat* 2001;178:367–372.
28. Lieberman JA, Alvir JM, Woerner M, et al. Prospective study of psychobiology in first-episode schizophrenia at Hillside Hospital. *Schizophrenia Bull* 1992;18:351–371.
29. Robinson DG, Woerner MG, Alvir JMJ, et al. Predictors of treatment response from a first episode of schizophrenia or schizoaffective disorder. *Am J Psychiat* 1999;156:544–549.
30. Stirling J, White C, Lewis S, et al. Neurocognitive function and outcome in first-episode schizophrenia: a 10-year follow-up of an epidemiological cohort. *Schizophr Res* 2003;65:75–86.
31. Tohen M, Strakowski SM, Zarate C, et al. The McLean-Harvard first-episode project: 6-month symptomatic and functional outcome in affective and nonaffective psychosis. *Biol Psychiat* 2000;48:467–476.
32. Tohen M, Zarate CA, Hennen J, et al. The McLean-Harvard first-episode mania study: prediction of recovery and first recurrence. *Am J Psychiat* 2003;160:2099–2107.
33. Brewin J, Cantwell R, Dalkin T, et al. Incidence of schizophrenia in Nottingham. *Brit J Psychiat* 1997;171:140–144.
34. Peralta V, Cuesta MJ, Martinez-Larrea A, Serrano JF. Patterns of symptoms in neuroleptic-naïve patients with schizophrenia and related psychotic disorders before and after treatment. *Psychiat Res* 2001;105:97–105.
35. Malla AK, Norman RMG, Manchanda R, et al. One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophr Res* 2002;54:231–242.
36. Salokangas RK, Cannon T, Van Erp T, et al. Structural magnetic resonance imaging in patients with first-episode schizophrenia, psychotic and severe non-psychotic depression and healthy controls: Results of the schizophrenia and affective psychoses (SAP) project. *Brit J Psychiat* 2002;suppl 43:S58–S65.
37. Bromet EJ, Schwartz JE, Fennig S, et al. The epidemiology of psychosis: the Suffolk County Mental Health Project. *Schizophrenia Bull* 1992;18:243–255.
38. Schwartz JE, Fennig S, Taneberg-Karant M, et al. Congruence of diagnoses 2 years after a first-admission diagnosis of psychosis. *Arch Gen Psychiat* 2000;57:593–600.
39. Culberg J, Levander S, Holmqvist R, Mattsson M, Wieselgren IM. One-year outcome in first episode psychosis patients in the Swedish Parachute Project. *Acta Psychiat Scand* 2002;106:276–285.
40. Joyce E, Hutton S, Mutsatsa S, et al. Executive dysfunction in first-episode schizophrenia and relationship to duration of untreated psychosis: the West London Study. *Brit J Psychiat* 2002;suppl 43:S38–S44.
41. Keshavan MS, Sanders RD, Sweeney JA, et al. Diagnostic specificity and neuroanatomical validity of neurological abnormalities in first-episode psychoses. *Am J Psychiat* 2003;160:1298–1304.
42. Kirch DG, Keith SJ, Matthews SM. Research on first-episode psychosis: report on a National Institute of Mental Health workshop. *Schizophrenia Bull* 1992;18:179–182.
43. Naz B, Bromet EJ, Mojtabai R. Distinguishing between first-admission schizophreniform disorder and schizophrenia. *Schizophr Res* 2003;62:51–58.
44. Scully PJ, Quinn JF, Morgan MG, et al. First-episode schizophrenia, bipolar disorder and other psychoses in a rural Irish catchment area: incidence and gender in the Cavan-Monaghan study at 5 years. *Brit J Psychiat* 2002;suppl 43:S3–S9.
45. Browne S, Clarke M, Gervin G, et al. Determinants of quality of life at first presentation with schizophrenia. *Brit J Psychiat* 2000;176:173–176.
46. Whitty P, Clarke M, Browne S, et al. Prospective evaluation of neurological soft signs in first-episode schizophrenia in relation to psychopathology: state versus trait phenomena. *Psychol Med* 2003;33:1479–1484.
47. Houghton F, Kelleher K. The exposure fallacy: migration, mobility and ecological analysis of health status in Ireland. *Irish Geography* 2003;36:47–58.
48. Russell V, McCauley M, McMahon J, Casey S, McCullagh H, Begley J. Liaison psychiatry in rural general practice. *Irish J Psychol Med* 2003;20:65–68.
49. McCauley M, Rooney S, Clarke C, Carey T, Owens J. Home-based treatment in Monaghan: the first two years. *Irish J Psychol Med* 2003;20:11–14.
50. Daly A, Walsh D, Moran R, O'Doherty YK. *Activities of Irish Psychiatric Services 2003*. Dublin: Health Research Board; 2004.
51. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, 4th ed. Washington, DC: American Psychiatric Association; 1994.
52. Spitzer RL, Williams JB, Gibbon J. *Structured Clinical Interview for DSM-III-R—Patient Version*. New York: New York State Psychiatric Institute; 1987.
53. First MB, Spitzer RL, Gibbon M *Structured Clinical Interview for DSM-IV Axis I Disorder—Patient Edition*. New York: New York State Psychiatric Institute; 1998.
54. Rabinowitz J, Bromet EJ, Lavelle J, Carlson G, Kovasznay B, Schwartz JE. Prevalence and severity of substance use disorders and onset of psychosis in first-admission psychotic patients. *Psychol Med* 1998;28:1411–1419.

55. Cantwell R, Brewin J, Glazebrook C, et al. Prevalence of substance misuse in first-episode psychosis. *Brit J Psychiat* 2000;174:150–153.
56. Cantor-Graae E, Nordström LG, McNeil TF. Substance abuse in schizophrenia: a review of the literature and a study of correlates in Sweden. *Schizophr Res* 2001;48:69–82.
57. Sevy S, Robinson DG, Solloway S, et al. Correlates of substance misuse in patients with first-episode schizophrenia and schizoaffective disorder. *Acta Psychiat Scand* 2001;104: 367–374.
58. Bühler B, Hambrecht M, Löffler W, an her Heiden W, Häfner H. Precipitation and determination of the onset and course of schizophrenia by substance abuse—a retrospective and prospective study of 232 population-based first illness episodes. *Schizophr Res* 2002;54:243–251.
59. Kendler KS, McGuire M, Gruenberg AM, Walsh D. An epidemiologic, clinical and family study of simple schizophrenia in County Roscommon, Ireland. *Am J Psychiat* 1994;151:27–34.
60. Galderisi S, Bucci P, Mucci A, D'Amato AC, Conforti R, Maj M. Simple schizophrenia": a controlled MRI and clinical/neuropsychological study. *Psychiat Res—Neuroim* 1999;91:175–184.
61. Serra-Mestres J, Gregory CA, Tandon S, Stansfield AJ, Kemp PM, McKenna PJ. Simple schizophrenia revisited: a clinical, neuropsychological, and neuroimaging analysis of nine cases. *Schizophrenia Bull* 2000;26:479–493.
62. Marneros A, Pillmann F, Haring A, Balzuweit S, Blöink R. What is schizophrenic in acute and transient psychotic disorder?. *Schizophrenia Bull* 2003;29:311–323.
63. Beiser M, Erickson D, Fleming JAE, Iacono WG. Establishing the onset of psychotic illness. *Am J Psychiat* 1993; 150:1349–1354.
64. Jablensky A. Schizophrenia: the epidemiological horizon. In: Hirsch SR, Weinberger DR, eds. *Schizophrenia*. Oxford: Blackwell Science; 1995;206–252.
65. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: marker or determinant of course? *Biol Psychiat* 1999;46:899–907.
66. Norman RMG, Malla AK. Duration of untreated psychosis: a critical examination of the concept and its importance. *Psychol Med* 2001;31:381–400.
67. McGorry PD. Early psychosis reform: too fast or too slow? *Acta Psychiat Scand* 2002;106:249–251.
68. Meagher D, Quinn J, Murphy P, Kinsella A, Mullaney J, Waddington JL. Relationship of the factor structure of psychopathology in schizophrenia to the timing of initial intervention with antipsychotics. *Schizophr Res* 2001;50:95–103.
69. Meagher DJ, Quinn JF, Bourke S, et al. Longitudinal assessment of psychopathological domains over late-stage schizophrenia in relation to duration of initially untreated psychosis: 3-year prospective study in a long-term inpatient population. *Psychiat Res* 2004;126:217–227.
70. Folnegovic Z, Folnegovic-Smalc V. Schizophrenia in Croatia: age of onset differences between males and females. *Schizophr Res* 1994;14:83–91.
71. Jablensky A, Cole SW. Is the earlier age at onset of schizophrenia in males a confounded finding? results from a cross-cultural investigation. *Brit J Psychiat* 1997;170:234–240.
72. Salokangas RKR, Honkonen T, Saarinen S. Women have later onset than men in schizophrenia—but only in its paranoid form: results of the DSP project. *Eur Psychiat* 2003;18:274–281.
73. Riecher-Rössler A, Löffler W, Munk-Jørgensen P. What do we really know about late-onset schizophrenia? *Eur Arch Psy Clin N* 1997;247:195–208.
74. Brodaty H, Sachdev P, Rose N, Rylands K, Prenter L. Schizophrenia with onset after age 50 years. 1: phenomenology and risk factors. *Brit J Psychiat* 1999;175:410–415.
75. Sachdev P, Brodaty H, Rose N, Cathcart S. Schizophrenia with onset after age 50 years. 2: neurological, neuropsychological and MRI investigation. *Brit J Psychiat* 1999; 175:416–421.
76. Aleman A, Kahn RS, Selton JP. Sex differences in the risk of schizophrenia. *Arch Gen Psychiat* 2003;60:565–571.
77. Drake RJ, Haley CJ, Akhtar S, et al. Causes and consequences of duration of untreated psychosis in schizophrenia. *Brit J Psychiat* 2000;177:511–515.
78. Der G, Gupta S, Murray RM. Is schizophrenia disappearing? *Lancet* 1990;335:513–516.
79. Myles-Worsley M, Coon H, Tiobech J, et al. Genetic epidemiological study of schizophrenia in Palau, Micronesia. *Am J Med Genet (Neuropsychiat Genet)* 1999;88:4–10.
80. Waldo MC. Schizophrenia in Kosrae, Micronesia: prevalence, gender ratios clinical symptomatology. *Schizophr Res* 1999;35:175–181.
81. Kebede D, Alem A, Shibre T, Negash A, Deyassa N, Beyero T. The sociodemographic correlates of schizophrenia in Butajira, rural Ethiopia. *Schizophr Res* 2004;69:133–141.
82. Bellmaker RH. Bipolar disorder. *N Engl J Med* 2004; 351:476–486.
83. Müller-Oerlinghausen B, Berghöfer A, Bauer M. Bipolar disorder. *Lancet* 2002;359:241–247.
84. van Os J. Does the urban environment cause psychosis? *Brit J Psychiat* 2004;184:287–288.
85. Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am J Psychiat* 2005;162:12–24.
86. Youssef HA, Scully PJ, Kinsella A, et al. Geographical variation in rate of schizophrenia in rural Ireland by place at birth vs place at onset of psychosis. *Schizophr Res* 1999;37:233–243.
87. Scully PJ, Owens JM, Kinsella A, Waddington JL. Schizophrenia, schizoaffective and bipolar disorder within an epidemiologically complete, homogeneous population in rural Ireland: small area variation in rate. *Schizophr Res* 2004;67:143–155.
88. Scully PJ, Coakley G, Kinsella A, Waddington JL. Psychopathology, executive (frontal) and general cognitive impairment in relation to duration of initially untreated versus subsequently treated psychosis in chronic schizophrenia. *Psychol Med* 1997;27:1303–1310.
89. Quinn J, Moran M, Lane A, Kinsella A, Waddington JL. Long-term adaptive life functioning in relation to initiation of treatment with antipsychotics over the lifetime trajectory of schizophrenia. *Biol Psychiat* 2000;48:163–166.
90. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia: Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Brit J Psychiat* 1998;173:325–329.
91. Morgan MG, Scully PJ, Youssef HA, Kinsella A, Owens JM, Waddington JL. Prospective analysis of premature mortality in schizophrenia in relation to health service engagement: a 7.5-year study within an epidemiologically complete, homogeneous population in rural Ireland. *Psychiat Res* 2003;117:127–135.

92. Corvin AP, Morris DW, McGhee K, et al. Confirmation and refinement of an ''at-risk'' haplotype for schizophrenia suggests the EST cluster, HS.97362, as a potential susceptibility gene at the Neuregulin-1 locus. *Mol Psychiatr* 2004;9:208–213.
93. Morris DW, Rodgers A, McGhee KA, et al. Confirming RGS4 as a susceptibility gene for schizophrenia. *Am J Med Genet (Neuropsychiat Genet)* 2004;125B:50–53.
94. Williams NM, Preece A, Morris DW, et al. Identification in two independent samples of a novel schizophrenia risk haplotype of the dystrobrevin binding protein gene (DTNBPI). *Arch Gen Psychiat* 2004;61:336–344.
95. Bromet EJ, Naz B, Fochtmann LJ, Carlson GA, Tanenberg-Karant M. Long-Term Diagnostic Stability and Outcome in Recent First-Episode Cohort Studies of Schizophrenia. *Schizophrenia Bull* 2005; doi: 10.1093/schbul/sbi030.
96. Baldwin PA, Hennessy RJ, Morgan MG, Quinn JF, Scully PJ, Waddington JL. Controversies in schizophrenia research: the ''continuum'' challenge, heterogeneity vs homogeneity and lifetime developmental- ''neuroprogressive'' trajectory. In: Gattaz W, Häfner H, eds. *Search for the Causes of Schizophrenia*. Darmstadt, Germany: Steinkopff; 2004;394–409.