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Systematic epidemiological and clinical comparisons across all 12 DSM-IV psychotic diagnoses in the Cavan–Monaghan First Episode Psychosis Study (CAMFEPS)

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Abstract

Background. Research on psychotic illness is loosening emphasis on diagnostic stringency in favour of including a more dimensionally based conceptualization of psychopathology and pathobiology. However, to clarify these notions requires investigation of the full scope of psychotic diagnoses.

Methods. The Cavan–Monaghan First Episode Psychosis Study ascertained cases of first episode psychosis across all 12 DSM-IV psychotic diagnoses via all routes to care: public, private or forensic; home-based, outpatient or inpatient. There was no arbitrary upper age cut-off and minimal impact of factors associated with variations in social milieu, ethnicity or urbanicity. Cases were evaluated epidemiologically and assessed for psychopathology, neuropsychology, neurology, antecedent factors, insight and quality of life.

Results. Among 432 cases, the annual incidence of any DSM-IV psychotic diagnosis was 34.1/100 000 of population and encompassed functional psychotic diagnoses, substance-induced psychopathology and psychopathology due to general medical conditions, through to psychotic illness that defied contemporary diagnostic algorithms. These 12 DSM-IV diagnostic categories, including psychotic disorder not otherwise specified, showed clinical profiles that were consistently more similar than distinct.

Conclusions. There are considerable similarities and overlaps across a broad range of diagnostic categories in the absence of robust discontinuities between them. Thus, psychotic illness may be of such continuity that it cannot be fully captured by operational diagnostic algorithms that, at least in part, assume discontinuities. This may reflect the impact of diverse factors each of which acts on one or more overlapping components of a common, dysfunctional neuronal network implicated in the pathobiology of psychotic illness.

Introduction

Though rooted in the traditional medical model of categorical diagnosis (DSM-IV/DSM-5, ICD-10/ICD-11), research on psychotic illness is loosening emphasis on diagnostic stringency in favour of including a more dimensionally based conceptualization of psychopathology and pathobiology (Barch et al., 2013; Guloksuz & van Os, 2018; van Os & Kapur, 2009). This revisionary process, long evident in the classical conundrum of the close relationship between schizophrenia and schizoaffective disorder, now extends to increasing evidence for a close relationship between schizophrenia and bipolar disorder (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Craddock & Owen, 2010) and, more recently, between schizophrenia and the under-studied diagnosis of major depressive disorder with psychotic features (Waddington & Buckley, 2013; Waddington, Kingston, Nkire, & Russell, 2019).

However, to appropriately address these notions requires investigation of the full scope of the psychosis spectrum, which in DSM-IV extends beyond these four diagnostic categories to include also: schizophreniform disorder; delusional disorder; brief psychotic disorder; substance-induced psychotic disorder; psychotic disorder due to a general medical condition; substance-induced mood disorder, with manic features; mood disorder due to a general medical condition, with manic features; and psychotic disorder not otherwise specified.

Additionally, subjects having these diagnoses should be from the same epidemiologically representative population via accrual of 'all' cases, ideally of incident, first episode psychosis (FEP), within a given region. It would be further advantageous if the socioeconomic milieu of that region were sufficiently uniform to minimize the impact of potentially confounding local factors, including the well-recognized effects of ethnicity and urbanicity (Castillejos, Martin-Perez, & Moreno-Kustner, 2018; Jongsma et al., 2018; Kirkbride et al., 2012).

The Cavan–Monaghan First Episode Psychosis Study (CAMFEPS) has a design that seeks to approach the above ideals and we have previously outlined preliminary findings in schizophrenia, bipolar disorder and major depressive disorder with psychotic features for selected measures over earlier years of CAMFEPS (Baldwin et al., 2005; Owoeye et al., 2013), pending accumulation of larger numbers of subjects having each of the other nine DSM-IV psychotic diagnoses. We here describe in the complete CAMFEPS dataset the epidemiology and clinical assessment of psychopathology, neuropsychology, neurology, antecedent factors, insight and quality of life for the totality of psychotic illness; duration of untreated illness and duration of untreated psychosis were also evaluated and will be the subject of a separate report. Given the increasing recognition of porous boundaries between at least some of these diagnoses, the objective was to systematically resolve similarities and differences that have not previously been examined across all 12 FEP diagnoses.

Methods

Study setting and ethical approvals

Initiated in 1995 and operating until 2010, CAMFEPS is a prospective study that seeks to identify 'all' incident cases presenting with a first episode of psychosis, without *a priori* diagnostic restriction, in two rural counties in Ireland, Cavan and Monaghan, as described previously in detail (Baldwin et al., 2005). Study protocols were approved by the Research Ethics Committees of the North Eastern Health Board (and, following restructuring, of the Health Service Executive Dublin North East Area), St. Patrick's Hospital, Dublin, St. John of God Hospital, Co. Dublin and the Central Mental Hospital, Dublin; these approvals included subjects giving written informed consent to assessment after these had been fully explained, and, for subjects from whom informed consent to assessment was not obtained, acquiring basic demographics and diagnostic information from case notes/treating teams for entry into an anonymised dataset (Baldwin et al., 2005). Cases were incepted from the age of 16 throughout the adult lifespan, in the absence of any arbitrary upper age cut-off. For those aged 16 or 17, informed consent was also sought from a parent or guardian. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

Cavan and Monaghan are two contiguous, rural counties having a total population of 109 139 (55 821 males and 53 318 females) at the 2002 census, the mid-point across the years of operation of CAMFEPS. These counties share relative ethnic and socioeconomic homogeneity, the vast majority of the population being white Irish, with minimal immigration and absence of any urban centres (see Omer et al., 2014, 2016). CAMFEPS and its associated Clinical Research Fellow/Registrar are embedded within Cavan–Monaghan Mental Health Service, which operates a community-based service with a focus on home treatment, general practice liaison and services based in small local clinics; central to the delivery of health services in this model is the use of home-based treatment as an alternative to hospital admission. In accordance with national policy, all cases from this catchment area who present to services in other parts of the country are returned to Cavan–Monaghan Mental Health Service as soon as is practicable. To maximize epidemiological completeness of case ascertainment, arrangements with St. Patrick's Hospital and St. John of God Hospital, the two main private psychiatric hospitals in Ireland, and the Central Mental Hospital, Dublin, ensured that cases were incepted through all routes to care, i.e. public, private and forensic, whether receiving home-based treatment or as outpatients or inpatients. The primary criterion for entry into the study is a first lifetime episode of any DSM-IV psychotic illness, to include a first manic episode (Baldwin et al., 2005).

Assessment

At entry into the study, cases giving informed consent to assessment were first evaluated using the Structured Clinical Interview for DSM-IV Axis I Disorders (First, Spitzer, Gibbon, & Williams, 2002). At 6 months thereafter, all clinical information, to include case notes and discussions with treating teams, was reviewed to confirm or update the initial DSM-IV diagnosis as more stable and representative (Baldwin et al., 2005); for individuals who died between study entry and 6 months, the most proximal diagnosis was carried forward. For individuals from whom informed consent to assessment was not obtained, the Research Ethics Committees approved a protocol for recording age and sex and accessing case notes and treating teams for DSM-IV diagnosis. For individuals giving informed consent to assessment, the following instruments were applied as soon as was practicable over the first few weeks following the initial presentation:

Psychopathology was assessed using the Positive and Negative Syndrome Scale (PANSS; Kay, Fiszbein, & Opler, 1987), to allow resolution of scores for positive, negative and general symptoms.

Neuropsychology was first assessed using the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975); the MMSE was not used as an incisive cognitive assessment but, rather, to evaluate general cognition in a population that extends naturalistically through to the tenth decade and includes cases of psychotic disorder due to a general medical condition and mood disorder due to a general medical condition, with manic features. For these same reasons, executive/frontal lobe function was evaluated using the Executive Interview (EXIT; Royall, Mahurin, & Gray, 1992; Scully, Coakley, Kinsella, & Waddington, 1997) to allow the inclusion of cases unable to perform more incisive instruments.

Neurology was assessed using the Neurological Evaluation Scale (NES; Buchanan & Heinrichs, 1989) to evaluate neurological soft signs (NSS). The Simpson–Angus Scale (SAS; Simpson & Angus, 1970) was used to evaluate extrapyramidal movement disorder and the Abnormal Involuntary Movement Scale (AIMS; Guy, 1976) to evaluate involuntary movement disorder.

Premorbid adjustment was assessed using the Premorbid Adjustment Scale (PAS; Cannon-Spoor, Potkin, & Wyatt, 1982). Premorbid intellectual functioning was assessed using the National Adult Reading Test (NART; Nelson, 1982).

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Insight was assessed using the Scale to Assess Unawareness of Mental Disorder (SUMD; Amador et al., 1993).

Quality of life was assessed using the Quality of Life Scale (QLS; Heinrichs, Hanlon, & Carpenter, 1984).

Data analysis

Incidence is expressed as the annual number of cases per 100 000 of the population aged ⩾15 years, with 95% confidence intervals (CI) for incidence rates and rate ratios (RR) between the sexes. These analyses were performed using Stata Release 14. Demographic and assessment data are expressed as means with standard deviations (S.D.) and medians with interquartile ranges. For schizophrenia (SZ), schizophreniform disorder (SF), brief psychotic disorder (BrP), schizoaffective disorder (SA), bipolar I disorder (BD), major depressive disorder, with psychotic features (MDDP), delusional disorder (DD), substance-induced psychotic disorder (SIP) and psychotic disorder not otherwise specified (PNOS), data for each demographic and clinical variable were analysed using analysis of variance (ANOVA) followed by Student's *t* tests that compared each diagnosis to SZ as reference, with the usual *p* value for significance ($p < 0.05$) subjected to Bonferroni correction ($p < 0.00625$). For substance-induced mood disorder, with manic features (SIM), psychotic disorder due to a general medical condition (PGMC) and mood disorder due to a general medical condition, with manic features (MGMC), the number of cases precluded formal analysis and data are presented descriptively. As a minority of cases did not give informed consent to assessment or were otherwise unable to complete assessment, the demographics of those completing and not completing PANSS measures were compared as a representative assessment; while there was no difference in sex distribution, mean age for those not completing was older than for those completing the PANSS [45.2 (S.D. 22.0) *v.* 33.2 (S.D. 14.9), $p < 0.01$]. Therefore, given this and some other differences in age between study groups (see Results section), ANOVAs were repeated using analysis of covariance for age. These analyses were performed using SPSS version 22.

Results

Epidemiology

Over the 15-year period between May 1995 and April 2010, 432 cases were ascertained and incepted into CAMFEPS: 249 males (58%) and 183 females (42%); mean age at inception was younger in males than in females (Table 1). The vast majority of cases were ascertained via local community mental health teams [$n = 424$ (98.2%)], with referrals from the two private psychiatric hospitals [6 (1.4%)] and forensic referrals from the Central Mental Hospital [2 (0.4%)] accounting for just 2% of incepted cases. Four cases [1% (3 males, 1 female)] died between inception and diagnostic re-evaluation at 6 months (2 males by suicide, 1 male and 1 female from natural causes), hence the diagnosis most proximal to demise was carried forward. Annual incidence of any psychotic disorder was 34.1/100 000 of population aged ⩾15 years, with risk for psychosis higher in males than in females (Table 2).

The number of cases by diagnosis was as follows: 81 SZ; 20 SF; 23 BrP; 25 SA; 88 BD; 92 MDDP; 25 DD; 25 SIP; eight SIM; 13 PGMC; four MGMC; 25 PNOS. There was one case of bipolar II disorder; while CAMFEPS did not incept cases of bipolar II disorder (BDII), one case of MDDP at inception subsequently

Table 1. Age at first presentation by diagnostic category at 6 months

Diagnosis	Total	Male	Female
All psychoses	432	249	183
	38.3 (19.2)	35.6 (18.3)	41.9 (19.8)[b]
	32{29}	29{24}	37{28}
	[16–92]	[16–87]	[16–92]
SZ	81	62	19
	30.4 (14.2)	28.3 (12.9)	37.4 (16.3)[a]
	25{17}	23{12}	35{27}
	[16–79]	[16–77]	[16–79]
SF	20	11	9
	41.6 (24.0)	40.0 (21.4)	43.6 (28.1)
	30.5{43}	32{31}	26{57}
	[18–87]	[21–87]	[18–84]
BrP	23	7	16
	34.7 (12.3)	34.9 (17.6)	34.6 (9.9)
	34{16}	27{30}	34.5{11}
	[17–67]	[20–67]	[17–49]
SA	25	17	8
	29.0 (10.1)	30.4 (11.4)	26.0 (6.3)
	26{14}	27{20}	26{8}
	[16–57]	[19–57]	[16–37]
BD	88	45	43
	32.9 (13.8)	32.0 (13.8)	33.8 (13.9)
	28{21}	24{22}	29{25}
	[16–80]	[18–70]	[16–80]
BDII	1	0	1
	46	–	46
	–	–	–
	–	–	–
MDDP	92	43	49
	49.3 (22.3)*	49.0 (22.8)	49.5 (22.1)
	55{42}	57{46}	52{43}
	[16–87]	[16–87]	[17–83]
DD	25	11	14
	45.5 (18.5)*	43.0 (18.4)	47.5 (19.0)
	39{22}	38{21}	45{26}
	[17–92]	[24–78]	[17–92]
SIP	25	22	3
	31.4 (14.4)	30.4 (13.2)	38.7 (23.7)
	25{16}	23.5{16}	32{-}
	[17–65]	[17–65]	[19–65]
SIM	8	6	2
	43.3 (20.9)	42.2 (23.4)	46.5 (–)
	41.5{33}	39.5{39}	46.5{–}

(*Continued*)

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Table 1. (*Continued.*)

Diagnosis	Total	Male	Female
	[16–79]	[16–79]	[34–59]
PGMC	13	7	6
	53.9 (13.9)	50.7 (13.9)	57.5 (14.1)
	46{25}	44{26}	54.5{28}
	[40–76]	[40–75]	[44–76]
MGMC	4	2	2
	65.8 (9.3)	59.0 (–)	72.5 (–)
	66.5{18}	59{–}	72.5{–}
	[54–76]	[54–64]	[69–76]
PNOS	25	15	10
	37.5 (24.3)	30.9 (20.5)	47.3 (27.2)
	24{37}	22{5}	39{55}
	[16–84]	[16–81]	[21–84]
SDD	2	1	1
	32.5 (–)	23	42
	32.5{–}	–	–
	[23–42]	–	–

SZ, schizophrenia; SF, schizophreniform disorder; BrP, brief psychotic disorder; SA, schizoaffective disorder; BD, bipolar I disorder; BD II, bipolar II disorder; MDDP, major depressive disorder with psychotic features; DD, delusional disorder; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder with manic features; PGMC, psychotic disorder due to general medical condition; MGMC, mood disorder due to a general medical condition with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder.
Data are number of cases, mean age (s.d.), median {interquartile range}, [range]; *$p < 0.00625$ *v.* schizophrenia as reference; [a]$p < 0.02$, [b]$p < 0.001$ *v.* males.

showed a hypomanic episode, leading to a diagnosis at 6 months of BDII, depressed with psychotic features. There were two cases of simple deteriorative disorder (SDD) (see DSM-IV Appendix B Criteria Sets and Axes Provided for Further Study) characterized by all the hallmarks of schizophrenia in terms of severity of negative symptoms and functional decline but without sufficiently prominent positive symptoms to satisfy criteria for SZ, which overlaps with attenuated psychosis syndrome (APS; see DSM-5 Section III Conditions for Further Study); these cases were included for exploratory purposes.

Table 1 shows mean and median ages at inception by sex for each diagnosis at 6 months: age was older in females than in males for SZ; setting SZ as the reference diagnosis, age was older for MDDP and DD.

Table 2 shows incidence by sex for each diagnosis at 6 months: incidence was highest for SZ, BD and MDDP; lower for SF, BrP, SA, DD, SIP and PNOS; and lowest for SIM, PGMC, MGMC and SDD; risk was higher in males than in females for SZ and SIP.

Psychopathology

Here and for all other clinical assessments, SZ was set as the reference diagnosis. As shown in Table 3, PANSS-total score did not differ significantly between SZ and SA, MDDP, DD, SIP or PNOS and was

Table 2. Incidence by diagnostic category at 6 months

Diagnosis	Total	Male	Female	RR
All psychoses	34.1	38.4	29.6	1.30**
	(30.9–37.5)	(33.8–43.5)	(25.5–34.2)	(1.07–1.57)
	[432]	[249]	[183]	
SZ	6.4	9.6	3.1	3.11***
	(5.1–8.0)	(7.3–12.3)	(1.9–4.8)	(1.86–5.21)
	[81]	[62]	[19]	
SF	1.6	1.7	1.5	1.17
	(0.9–2.4)	(0.8–3.4)	(0.7–2.8)	(0.48–2.81)
	[20]	[11]	[9]	
BrP	1.8	1.1	2.6	0.42
	(1.2–2.7)	(0.4–2.2)	(1.5–4.2)	(0.17–1.01)
	[23]	[7]	[16]	
SA	2.0	2.6	1.3	2.03
	(1.3–2.9)	(1.5–4.2)	(0.6–2.6)	(0.88–4.70)
	[25]	[17]	[8]	
BD	6.9	6.9	7.0	1.00
	(5.6–8.6)	(5.1–9.3)	(5.0–9.4)	(0.66–1.52)
	[88]	[45]	[43]	
BDII	0.1	–	0.1	–
	–	–	–	–
	[1]	[0]	[1]	
MDDP	7.3	6.6	7.9	0.88
	(5.9–8.9)	(4.8–8.9)	(5.9–10.5)	(0.56–1.26)
	[92]	[43]	[49]	
DD	2.0	1.7	2.3	0.75
	(1.3–2.9)	(0.8–3.0)	(1.2–3.8)	(0.34–1.65)
	[25]	[11]	[14]	
SIP	2.0	3.4	0.5	7.00***
	(1.3–2.9)	(2.1–5.1)	(0.1–1.4)	(2.09–23.38)
	[25]	[22]	[3]	
SIM	0.6	0.9	0.3	2.86
	(0.3–1.2)	(0.3–2.0)	(0.0–1.2)	(0.58–14.18)
	[8]	[6]	[2]	
PGMC	1.0	1.1	1.0	1.11
	(0.5–1.8)	(0.4–2.2)	(0.4–2.1)	(0.37–3.31)
	[13]	[7]	[6]	
MGMC	0.3	0.3	0.3	0.95
	(0.0–1.0)	(0.0–1.1)	(0.0–1.2)	(0.13–6.77)
	[4]	[2]	[2]	
PNOS	2.0	2.3	1.6	1.43
	(1.3–2.9)	(1.3–3.8)	(0.8–3.0)	(0.64–3.19)
	[25]	[15]	[10]	

(*Continued*)

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Table 2. (*Continued.*)

Diagnosis	Total	Male	Female	RR
SDD	0.2	0.2	0.2	0.95
	(0.0–0.6)	(0.0–0.9)	(0.0–0.9)	(0.06–15.25)
	[2]	[1]	[1]	

SZ, schizophrenia; SF, schizophreniform disorder; BrP, brief psychotic disorder; SA, schizoaffective disorder; BD, bipolar I disorder; BD II, bipolar II disorder; MDDP, major depressive disorder with psychotic features; DD, delusional disorder; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder with manic features; PGMC, psychotic disorder due to general medical condition; MGMC, mood disorder due to a general medical condition with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder.
Data are incidence/100 000 population aged ⩾15 (95% confidence interval) [number of cases]. RR, relative risk in males *v.* females (95% confidence interval);
$^{**}p < 0.01$, $^{***}p < 0.001$.

lower for SF, BrP and BD. PANSS-positive subscale score did not differ significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP or PNOS. PANSS-negative subscale score did not differ significantly between SZ and DD or MDDP and was lower for SF, BrP, SA, BD, SIP and PNOS. PANSS-general subscale score did not differ significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP or PNOS. There were no differences between the sexes, and on repeating these analyses with age as a covariate, the results were unaltered, with all PANSS measures unrelated to age.

Neuropsychology

As shown in Table 4, neither MMSE nor EXIT score differed significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP and PNOS; across diagnoses, MMSE score was lower in males [27.4 (S.D. 3.1)] than in females [28.2 (S.D. 1.8), $p < 0.02$]. On repeating these analyses with age as a covariate, the results were unaltered; MMSE score decreased and EXIT score increased with age (each $p < 0.02$).

Neurology

As shown in Table 4, NES scores did not differ significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP or PNOS. There were no differences between the sexes, and on repeating these analyses with age as a covariate, the results were unaltered; NES score increased with age ($p < 0.001$). SAS and AIMS scores were very low [SAS: mean 3.0 (S.D. 3.6); AIMS: mean 0.9 (S.D. 2.2)] and did not differ between SZ and any other diagnosis (data not shown); across diagnoses SAS score was lower in females [2.3 (S.D. 2.9)] than in males [3.5 (S.D. 3.9), $p < 0.01$]. On repeating these analyses with age as a covariate, the results were unaltered; SAS score increased with age ($p < 0.02$).

Premorbid features

As shown in Table 5, neither PAS nor NART score differed significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP or PNOS; across diagnoses, PAS score was lower in females [23.6 (S.D. 7.9)] than in males [28.4 (S.D. 9.4), $p < 0.02$]. On repeating these analyses with age as a covariate, the results were unaltered; both PAS and NART scores were unrelated to age.

Insight

As shown in Table 5, SUMD score did not differ significantly between SZ and SF, BrP, SA, BD, MDDP, DD, SIP or PNOS; there were no differences between the sexes. On repeating these analyses with age as a covariate, the results were unaltered; SUMD score was unrelated to age.

Table 3. PANSS symptom scores by diagnostic category at 6 months

Diagnosis	PANSS-t	PANSS-p	PANSS-n	PANSS-g
All psychoses	64.2 (21.6)	16.0 (6.9)	15.3 (8.1)	32.8 (11.7)
	[250]			
SZ	74.5 (17.2)	17.1 (5.8)	22.2 (7.2)	35.3 (9.7)
	[56]			
SF	48.8 (12.5)*	13.3 (6.3)	10.9 (4.2)*	24.6 (5.6)
	[10]			
BrP	42.1 (16.6)*	9.1 (3.5)	10.0 (5.9)*	23.0 (8.6)
	[12]			
SA	67.3 (21.6)	16.9 (7.6)	16.3 (7.5)*	34.1 (10.8)
	[21]			
BD	59.6 (20.5)*	17.7 (8.0)	10.0 (5.6)*	31.9 (11.2)
	[58]			
BDII	113	16	33	64
	[1]			
MDDP	69.1 (22.7)	15.0 (5.8)	17.4 (8.2)	36.0 (13.5)
	[47]			
DD	60.8 (20.9)	15.5 (6.2)	13.8 (3.8)	31.5 (13.4)
	[6]			
SIP	59.1 (19.7)	16.6 (8.4)	11.0 (3.2)*	31.5 (10.2)
	[16]			
SIM	46.4 (7.5)	10.2 (3.8)	12.8 (4.9)	23.4 (4.8)
	[5]			
PGMC	72.5 (34.2) [4]	19.0 (5.5)	16.3 (10.4)	37.3 (18.4)
MGMC	78 [1]	27	9	42
PNOS	56.1 (20.3) [12]	14.0 (5.4)	12.7 (6.4)*	29.4 (12.5)
SDD	68 [1]	11	27	30

PANSS, Positive and Negative Syndrome Scale; PANSS-t, total symptom subscale; PANSS-p, positive symptom subscale; PANSS-n, negative symptom subscale; PANSS-g, general symptom subscale; SZ, schizophrenia; SF, schizophreniform disorder; BrP, brief psychotic disorder; SA, schizoaffective disorder; BD, bipolar I disorder; BD II, bipolar II disorder; MDDP, major depressive disorder with psychotic features; DD, delusional disorder; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder with manic features; PGMC, psychotic disorder due to general medical condition; MGMC, mood disorder due to a general medical condition with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder.
Data are mean scores (S.D.) [number of cases]; *$p < 0.00625$ *v.* schizophrenia as reference.

Quality of life

As shown in Table 5, QLS score did not differ significantly between SZ and SA, MDDP, DD or SIP and was higher for SF, BrP, BD and PNOS; there was no difference between the sexes. On repeating these analyses with age as a covariate, the results were unaltered; QLS score was unrelated to age.

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Table 4. MMSE, EXIT and NES scores by diagnostic category at 6 months

Diagnosis	MMSE	EXIT	NES
All psychoses	27.7 (2.7)	8.0 (5.1)	13.7 (8.9)
	[231]	[220]	[211]
SZ	28.1 (2.2)	8.6 (4.8)	14.7 (7.9)
	[53]	[48]	[50]
SF	28.1 (1.4)	7.0 (5.2)	12.8 (5.1)
	[8]	[8]	[9]
BrP	28.6 (1.6)	5.9 (4.4)	9.2 (7.3)
	[11]	[12]	[10]
SA	28.1 (1.5)	6.6 (4.3)	13.8 (8.2)
	[19]	[19]	[18]
BD	28.1 (2.0)	7.2 (5.7)	11.6 (8.7)
	[52]	[52]	[47]
BDII	30	2	13
	[1]	[1]	[1]
MDDP	27.7 (2.5)	8.9 (4.2)	16.3 (9.3)
	[46]	[43]	[40]
DD	24.8 (8.4)	7.0 (5.2)	10.0 (6.4)
	[6]	[6]	[4]
SIP	27.3 (1.8)	8.1 (4.6)	13.7 (11.2)
	[16]	[13]	[15]
SIM	26.0 (4.2)	13.5 (5.1)	13.7 (13.4)
	[4]	[4]	[3]
PGMC	25.3 (4.1) [4]	13.3 (10.9) [4]	17.5 (14.1) [4]
MGMC	21 [1]	15 [1]	39 [1]
PNOS	26.4 (5.1)	8.0 (5.2)	9.5 (7.9)
	[9]	[8]	[8]
SDD	29 [1]	9 [1]	19 [1]

MMSE, Mini-Mental State Examination; EXIT, Executive Interview; NES, Neurological Evaluation Scale. SZ, schizophrenia; SF, schizophreniform disorder; BrP, brief psychotic disorder; SA, schizoaffective disorder; BD, bipolar I disorder; BD II, bipolar II disorder; MDDP, major depressive disorder with psychotic features; DD, delusional disorder; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder with manic features; PGMC, psychotic disorder due to general medical condition; MGMC, mood disorder due to a general medical condition with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder.
Data are mean scores (s.d.) [number of cases].

Table 5. PAS, NART, SUMD and QLS scores by diagnostic category at 6 months

Diagnosis	PAS	NART	SUMD	QLS
All psychoses	26.5 (9.1)	23.5 (11.1)	8.0 (4.9)	80.0 (26.4)
	[192]	[211]	[191]	[214]
SZ	27.3 (8.8)	23.1 (11.8)	8.7 (5.0)	63.1 (20.8)
	[44]	[49]	[43]	[47]
SF	27.5 (5.8)	19.5 (6.9)	4.7 (2.8)	96.1 (22.2)*
	[8]	[8]	[7]	[10]
BrP	24.0 (7.7)	19.6 (9.4)	6.2 (4.2)	104.2 (22.7)*
	[10]	[11]	[8]	[11]
SA	25.8 (7.1)	28.4 (12.7)	8.1 (4.9)	73.8 (21.7)
	[18]	[18]	[18]	[19]
BD	22.8 (8.0)	27.0 (9.1)	8.5 (4.9)	95.1 (24.2)*
	[42]	[48]	[44]	[50]
BDII	28	43	12	50
	[1]	[1]	[1]	[1]
MDDP	28.7 (10.7)	23.2 (9.7)	8.2 (5.0)	73.6 (25.5)
	[32]	[40]	[36]	[38]
DD	30.3 (6.2)	20.5 (13.7)	12.7 (2.5)	72.5 (24.5)
	[4]	[4]	[4]	[4]
SIP	26.5 (10.2)	18.2 (10.8)	6.6 (4.9)	82.6 (24.1)
	[14]	[13]	[13]	[14]
SIM	34.3 (10.7)	14.7 (14.2)	5.6 (2.9)	78.8 (18.5)
	[3]	[3]	[4]	[4]
PGMC	21.8 (3.3) [4]	19.8 (18.5) [4]	6.9 (1.9) [4]	52.8 (13.3) [4]
MGMC	19 [1]	13 [1]	9.8 [1]	80 [1]
PNOS	32.4 (12.0)	20.4 (13.6)	7.8 (7.8)	89.2 (22.8)*
	[10]	[10]	[7]	[11]
SDD	22 [1]	24 [1]	9.0 [2]	– [0]

PAS, Premorbid Adjustment Scale; NART, National Adult Reading Test; SUMD, Scale to Assess Unawareness of Mental Disorder; QLS, Quality of Life Scale. SZ, schizophrenia; SF, schizophreniform disorder; BrP, brief psychotic disorder; SA, schizoaffective disorder; BD, bipolar I disorder; BD II, bipolar II disorder; MDDP, major depressive disorder with psychotic features; DD, delusional disorder; SIP, substance-induced psychotic disorder; SIM, substance-induced mood disorder with manic features; PGMC, psychotic disorder due to general medical condition; MGMC, mood disorder due to a general medical condition with manic features; PNOS, psychotic disorder not otherwise specified; SDD, simple deteriorative disorder.
Data are mean scores (s.d.) [number of cases]; *$p < 0.00625$ *v.* schizophrenia as reference.

Discussion

Overview

To our knowledge, no previous study has systematically collected and compared data on all 12 DSM-IV FEP diagnoses, via all routes to care, among a rural region of relative uniformity in socioeconomic milieu in as close an approximation to epidemiological completeness as might reasonably be attained. CAMFEPS describes the total incident scope of FEP (34.1/100 000 per annum) in a 'real-world' health service setting, from the full breadth of functional illness, through substance-induced psychopathology, both substances of abuse and adverse effects of prescribed medications, and psychopathology due to general medical conditions, through to psychotic illness that defies contemporary diagnostic algorithms.

Epidemiology

The overall incidence of any DSM-IV psychotic diagnosis was 1.30-fold more common in men than in women. This elaborates meta-analytic findings that heterogeneously defined and ascertained psychotic disorder is 1.54-fold more common in men and broadly defined SZ is 1.15-fold (Van der Werf et al., 2014) to 1.42-fold (Aleman, Kahn, & Selten, 2003) more common in men. In CAMFEPS, the incidence of conservatively defined SZ was 3.1-fold more common in men than in women. This would

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elaborate how increasing stringency for specifying this diagnostic category from the breadth of psychotic illness is associated with increasing male preponderance and increasing difficulty in identifying female cases for research studies thereon (Iacono & Beiser, 1992; Lewine, Burbach, & Meltzer, 1984; Longenecker et al., 2010). The risk ratio between men and women for SA was intermediate between SZ and that for SF, BrP, BD, MDDP and DD, each of which occurred similarly in both sexes. Thus, increasing stringency for the diagnostic categories of SA and SZ may result in the progressive concentration of processes associated with male sex (Waddington, Hennessy, O'Tuathaigh, Owoeye, & Russell, 2012).

A notable finding was the number of cases of MDDP, which was similar to that for SZ and BD; this may exemplify the completeness of case ascertainment in the absence of any arbitrary upper age cut-off, recent meta-analysis indicating that psychotic depression appears more common and over-represented in older age relative to SZ (Jääskeläinen et al., 2018; Stafford, Howard, & Kirkbride, 2018). These three most populous diagnoses, SZ, BD and MDDP, each appeared to evidence a distinct epidemiological 'signature': incidence of SZ was threefold more common, and cases first presented at an earlier age, in men than in women; incidence of BD was similar among men and women, with both sexes first presenting at a mean age similar to that for SZ; incidence of MDDP was also similar among men and women, but both sexes first presented at a mean age 15–20 years later than for SZ and BD. However, such 'signatures' should not be misinterpreted as validating these diagnostic categories. These are quantitative variations rather than qualitative distinctions, such that each of the diagnoses of SZ, SF, BrP, SA, BD, MDDP and DD were evident in both sexes from the late teens through to the eighth or ninth and, in a few instances, even the tenth decade.

As expected, SIP was primarily a disorder of younger males in association with a wide range of substances of abuse (Brunette et al., 2018). While the number of cases of SIM was smaller, these tended to be older in the additional context of prescribed medications (Peet & Peters, 1995). As expected, PGMC (Joyce, 2018) and MGMC (Sami, Khan, & Nilforooshan, 2015) were less common and occurred across later adulthood in the context of heterogeneous medical conditions that impact on brain function.

Though cases of PNOS defied DSM-IV criteria, their epidemiology was similar to that of the functional psychotic diagnoses; as for SZ, SA, SF, BrP, BD, MDDP and DD, cases of PNOS emerged essentially throughout the lifespan in both sexes from the late teens through to the ninth decade.

Domains of clinical assessment

The extent of the defining characteristic of psychosis, i.e. positive psychotic symptoms, together with general symptoms, was similar for SZ, SF, BrP, SA, BD, MDDP, DD and PNOS; that scores were lowest for BrP may reflect, at least in part, its defining characteristic of rapid diminution in psychopathology following initial presentation. A recent study has indicated that a generalized psychosis factor, characterized primarily by positive and disorganization symptoms, is shared across SZ, SA and BD (Anderson et al., 2018). The present findings suggest that the extent of positive psychotic symptoms in FEP is similar across the full complement of DSM-IV functional psychotic diagnoses and PNOS.

Negative symptoms were more graded, being highest for SZ, DD and MDDP and lower for SF, BrP, BD, DD and PNOS. This elaborates previous studies across a more limited range of diagnostic categories (Lyne et al., 2012; van Os & Kapur, 2009) and emphasizes overlap among, rather than rarity between, scores across the breadth of DSM-IV psychotic diagnoses. It might be argued that extent of depressive symptoms, particularly in MDDP, could confound assessment of negative symptoms; however, features such as anhedonia are considered to be a 'core' feature of both SZ and major depressive disorder, whether with or without psychotic features (see DSM-IV), having a neurobiology that appears to transcend diagnostic categories (Der-Avakian & Markou, 2012; Lambert et al., 2018; Waddington et al., 2019; Zhang et al., 2012).

Each of general and executive cognitive dysfunction, the extent of NSS, impaired premorbid social adjustment and lower premorbid intellectual function were similar for SZ, SF, BrP, SA, BD, MDDP, DD and PNOS. These findings elaborate recent systematic reviews and meta-analytic findings in SZ and BD (Bora & Pantelis, 2015; Bora, Akgül, Ceylan, & Özerdem, 2018; Parellada, Gomez-Vallejo, Burdeus, & Arango, 2017; Trotta, Murray, & MacCabe, 2015) to the full complement of DSM-IV functional psychotic diagnoses and PNOS.

Reduced insight was also similar for SZ, SF, BrP, SA, BD, MDDP, DD and PNOS. These findings elaborate the most recent study (Novick et al., 2015) and systematic review (García et al., 2016) in SZ and BD to the full complement of DSM-IV functional psychotic diagnoses and PNOS. Impairment in quality of life was more graded across these diagnoses, in a manner similar to negative symptoms with which quality of life has been associated across diagnostically undifferentiated FEP (Malla & Payne, 2005; Watson et al., 2018); higher quality of life for SF and BrP may reflect their lower scores for negative symptoms, while higher quality of life for BD may reflect phenomenological incompatibility between lower quality of life and elation/grandiosity.

Many theories have been offered to explain the well-recognized association between SZ and SIP (Khokhar, Dwiel, Henricks, Doucette, & Green, 2018). In the absence of any comparable study, it is notable that the clinical profile of SIP did not differ materially from that for SZ, SA, BD, MDDP, DD or PNOS in terms of positive and general symptoms, cognitive dysfunction, neurological features, premorbid features and insight, with SIP having a profile similar to that for SF and BrP in terms of negative symptoms. These findings would be consistent with the proposition that SZ and SIP arise from shared susceptibility via discrete or overlapping components in a common, dysfunctional neuronal network (Khokhar et al., 2018) and elaborate this notion across the full complement of DSM-IV functional psychotic diagnoses and PNOS. In contrast, SIM has received less systematic study; though the number of cases in the present study was small, including not just substances of abuse but also prescribed steroid-induced (Brown & Chandler, 2001) and antidepressant-induced (Barbuti et al., 2017) psychopathology, the overall profile for SIM tracked that for SIP with somewhat lower levels of severity other than for executive dysfunction.

Similarly, recent reviews have documented the wide spectra of both PGMC (Joyce, 2018) and MGMC (Sami et al., 2015). As expected, the numbers of cases here were modest and of diverse aetiology, including epilepsy, multiple sclerosis, cerebral trauma, cerebral tumours and cerebrovascular events, and occurred primarily in middle-old age. Yet PGMC demonstrated a psychopathological profile similar to that of its functional and

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substance-induced counterparts. This may reflect the impact of these diverse aetiologies on discrete or overlapping components of a common, dysfunctional neuronal network implicated in the pathobiology of functional and substance-induced psychosis (see Conclusions section) to result in shared psychopathology.

Cases of SDD were ascertained naturalistically. They were included to inform on the extent to which this exploratory DSM-IV entity, which overlaps with the exploratory DSM-5 entity APS and the 'psychosis high-risk state' (Fusar-Poli et al., 2013), might reflect in clinical practice the inevitable uncertainties around the threshold between potential prodromal features and overt psychosis. That only two such cases were identified (both transitioning to SZ on long-term follow-up; see Kingston et al., 2013) may complement a recent report that only a small proportion of FEP cases are identified via services structured to address these uncertainties (Ajnakina et al., 2017).

Strengths of the study

The strengths of the present study include epidemiological completeness with case inception via all routes to care (i.e. whether public, private or forensic; home-based, outpatient or inpatient), no arbitrary upper age cut-off (i.e. cases incepted throughout the adult lifespan) and limited impact of factors associated with variations in social milieu, ethnicity and urbanicity. This was combined with a full diagnostic scope to allow systematic comparisons between all 12 DSM-IV psychotic diagnoses across several domains of clinical assessment.

Limitations of the study

The limitations of the study are typical of many investigations of FEP. The range of assessment instruments had to be concise so that it would be feasible, at any given time, for a single Clinical Research Fellow to conduct the study; thus, for example, assessment of affective symptoms lacked depth and neuropsychological assessment lacked breadth. Similarly, it was not feasible to assess every case immediately on inception; thus, while the effects of medication are likely limited, measurements of psychopathology may have been influenced by initial consequences of the clinical imperative to begin treatment at the earliest possible stage. While epidemiological data were available for all cases, there was inevitable attrition among those assessed with any given instrument due to consent and the varying demands of those instruments on each subject. Additionally, the socioeconomic milieu of this rural region may limit generalization to other settings. Furthermore, given meta-analytic evidence for varying degrees of diagnostic instability across seven of the 12 diagnoses studied here (Fusar-Poli et al., 2016), we cannot exclude that more robust diagnostic discontinuities might emerge during later phases in the trajectory of psychotic illness as diagnostic changes ensue consequent to such instability. Finally, we cannot exclude that more robust diagnostic discontinuities might emerge on the application of individual instruments having yet greater sensitivity and reliability than the standard, widely applied instruments adopted here. Future studies should further address these issues.

Conclusions

In CAMFEPS, the functional psychotic diagnoses of SZ, SF, BrP, SA, BD, MDDP and DD, the substance-induced disorders of SIP and SIM, the medical conditions of PGMC and MGMC, together with PNOS that defied any more specific DSM-IV criterion, showed profiles that were more similar than distinct.

One explanation for the present findings may be the DSM-5 conceptualization of the breadth of psychotic disorders, which proposes that all such disorders are characterized by six distinct dimensions [positive symptoms (delusions, hallucinations), disorganization, negative symptoms, cognitive impairment, motor symptoms and mood symptoms (depression, mania)], which are shared to varying extents (Heckers et al., 2013). This conceptualization is complemented by a scale for measuring the individual elements that constitute these dimensions (Barch et al., 2013), use of which may produce findings that differ from those reported here.

An alternative explanation for the present findings elaborates a conceptualization from earlier clinical studies (Guloksuz & van Os, 2018; Owen, 2014) and from recent meta-analyses of genome-wide association studies that indicate shared heritability among SZ (including SF and SA), BD and major depressive disorder (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018; Brainstorm Consortium, 2018). Cases of PNOS challenge whether their defiance reflects not any inadequacy in DSM-IV criteria or their application but, rather, exemplifies a reality: the extent of similarities and overlap across these diagnostic categories indicates psychotic illness may be of such continuity that it cannot be fully captured by operational diagnostic algorithms that, at least in part, assume discontinuities. This continuity may reflect the impact of factors that (a) operate in an overlapping genetic and environmental milieu (Brainstorm Consortium, 2018; Castillejos et al., 2018; Guloksuz & van Os, 2018; Jongsma et al., 2018; Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014) and (b) act on one or more overlapping components of a common, dysfunctional prefrontal/anterior cingulate cortical-striatal-hippocampal neuronal network that has been implicated in the pathobiology of psychosis and responsivity to antipsychotic drugs (Goodkind et al., 2015; Joyce, 2018; Khokhar et al., 2018; Kraguljac et al., 2016; Sarpal et al., 2015; Sheffield et al., 2017).

Both explanations are plausible and require further study.

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