Irish Journal of Psychological Medicine (2019), **36**, 293–303. doi:10.1017/ipm.2019.11

REVIEW ARTICLE

The Cavan-Monaghan First Episode Psychosis Study (CAMFEPS): arbitrary diagnostic boundaries across the gene–environment interface and within evolving models of care

John L. Waddington[1,2,3,*] **and Vincent Russell**[4,5]

[1] *Molecular and Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin, Ireland*
[2] *Cavan-Monaghan Mental Health Service, St. Davnet's Hospital, Monaghan, Ireland*
[3] *Jiangsu Key Laboratory of Translational Research & Therapy for Neuropsychiatric Disorders and Department of Pharmacology, College of Pharmaceutical Sciences, Soochow University, Suzhou, China*
[4] *Cavan-Monaghan Mental Health Service, Cavan General Hospital, Cavan, Ireland*
[5] *Department of Psychiatry, Royal College of Surgeons in Ireland, Education and Research Centre, Beaumont, Dublin, Ireland*

As research into psychotic illness evolves along established lines, insights are emerging that deviate from those lines and challenge more fundamentally our understanding. On the background of a new generation of studies on first-episode psychosis, investigations across the gene–environment interface and the intersection with 'normal' human mentation heighten these concerns. Using findings from the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS) as an exemplar, we here review the complexity of these challenges from the perspective of this real-world setting. They range from trans-diagnostic epidemiology and clinical characterisation, through molecular genetics, social milieu, developmental pathobiology and functional outcome across arbitrary diagnostic boundaries, to the evidence base for early intervention and more radical conceptualisations and structures for provision of mental health care.

Received 11 September 2018; Revised 19 February 2019; Accepted 25 February 2019; First published online 12 April 2019

Key words: At-risk mental state, clinical high risk, diagnostic boundaries, early intervention, epidemiology, first-episode studies, functional outcome, molecular genetics, psychotic illness, social milieu.

Introduction

Contemporary research into psychotic illness is both elaborating and altering long-standing concepts of its psychopathology, pathobiology and trajectory, both before and after initiating treatment (Kahn *et al.* 2015; Owen *et al.* 2016). We have recently proposed (Zhen & Waddington, 2018) that this reflects two types of processes: *evolving* insights increase our understanding incrementally along established lines with which we feel comfortable, typically in the context of conventional diagnostic categories such as schizophrenia; in contrast, *emerging* insights act heuristically by deviating from established lines to challenge fundamentally our understanding and can engender discomfiture.

On a background that extends to the earliest concepts of psychotic illness (Ram *et al.* 1992; Million *et al.* 2004), one important vehicle for elaboration and alteration has been the emergence of a new generation of systematic studies of first-episode psychosis that seek to define, prospectively, the nature and course of illnesses such as schizophrenia from what was conceptualised conventionally as 'onset', through the early phases of treatment, to long-term care and outcome. Following initial appreciation by 1992 that this vehicle had 'taken to the road' (Keshavan & Schooler, 1992; Kirch *et al.* 1992), by 2005 no less than 25 such studies had begun their journey. Among these, the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS; Baldwin *et al.* 2005), a collaboration between Cavan-Monaghan Mental Health Services (CMMHS) and the Royal College of Surgeons in Ireland (RCSI), adopted what was then an idiosyncratic and heuristic approach: it sought to ascertain and evaluate 'all' incident cases of psychosis within the counties of Cavan and Monaghan, on an epidemiological basis, with diagnosis being just one of multiple post-inception assessments rather than any criterion for entry; furthermore, the study was embedded within CMMHS during a period of progressive evolution into a home-based model of care with substantive primary care liaison, and subsequently into a new service model for the early detection and treatment of psychosis.

Why did CAMFEPS adopt this then idiosyncratic approach? One of the most challenging contemporary

*Address for correspondence: John L. Waddington, Molecular & Cellular Therapeutics, Royal College of Surgeons in Ireland, Dublin 2, Ireland.
(Email: jwadding@rcsi.ie)

concepts, sustained and elaborated by increasing evidence, is that psychotic psychopathology, underlying developmental pathobiology and associated risk genes are not only disrespectful to conventional diagnostic boundaries but also indicate the arbitrary nature of our diagnostic categories, both cross-sectionally and prospectively. As clinical practice evolves (see our companion article, Russell *et al.* 2019), it is likely to continue to involve the establishment of psychotic diagnoses, as enshrined in DSM-5 and ICD-11; these provide a guide to treatment, generate much useful data that can inform on the above challenges and have pragmatic value such as for reimbursements from health insurers. Yet they are under increasing scrutiny. This is exemplified by current research emphasis on the increasingly blurred and porous schizophrenia-bipolar interface (Cross-Disorder Group of the Psychiatric Genomics Consortium, 2013a, 2013b; Owen 2014; Pearlson, 2015; Birur *et al.* 2017) that is at variance with and challenging to classical nosology (the 'Kraepelinian dichotomy'; Craddock & Owen, 2010).

Further concepts and increasing evidence are equally challenging: that psychotic ideation and associated psychopathology can be present in young persons across the general population and, according to nature and intensity, may be early harbingers of risk for clinical psychosis (Fusar-Poli *et al.* 2013; van Os & Reininghaus, 2016); and that early intervention for features associated with clinical high risk/at-risk mental state and at the first psychotic episode may, respectively, ameliorate the emergence of diagnostic psychotic symptoms and improve long-term outcome (Clarke *et al.* 2016; Millan *et al.* 2016). Additionally, this evolving evidence base continues to influence how service models for both early intervention and subsequent longer-term care for psychotic illness should be conceptualised and applied; should conventional models of care be modified to incorporate such new insights; or do these insights suggest more radical restructuring of service provision within an alternative concept of mental health and dysfunction (McGorry *et al.* 2018)? Here we review several of these challenges using findings from CAMFEPS to illustrate their complexity in a real-world setting.

Outline of CAMFEPS

In 1991, the Health Research Board funded the Schizophrenia Research Unit, a collaborative endeavour involving *inter alia* RCSI/CMMHS and St. John of God Hospitaller Ministries/Cluain Mhuire Community Mental Health Services. On the basis of studies carried out by the Unit (Waddington & Larkin, 1993) in 1995, the [then] Theodore & Varda Stanley Foundation [subsequently the Stanley Medical Research Institute] awarded philanthropic funding to initiate and sustain two parallel first-episode psychosis studies: one (CAMFEPS) based in two contiguous rural counties in the Northeast of Ireland having a total population of approximately 109,000; the demographic and socioeconomic characteristics of these counties have been described previously in detail (Baldwin *et al.* 2005); the other based in a more urban setting proximal to Dublin (St. John of God Hospitaller Ministries/Cluain Mhuire Community Mental Health Services, Co. Dublin; Browne *et al.* 2000). These two studies operated in parallel for 4 years, after which the St. John of God Hospitaller Ministries/Cluain Mhuire Community Mental Health Services study began a process of evolution into the Dublin and East Treatment and Early Care Team (DETECT) early intervention service (Renwick *et al.* 2008), while CAMFEPS continued for a total of 15 years, during which it evolved into the Carepath for Overcoming Psychosis Early (COPE) early intervention service (Nkire *et al.* 2015), as outlined below (see Early intervention) and elaborated in a companion article (Russell *et al.* 2019). The structure of CAMFEPS involved a Clinical Research Fellow/Registrar embedded within CMMHS and having both a research role and sessional service commitment; the service model involved two community mental health teams, a specialist service for the elderly and a community rehabilitation team, with primary care liaison and use of home-based treatment as an alternative to hospital admission being central to the delivery of health services in this model (McCauley *et al.* 2003; Nwachukwu *et al.* 2014; see Russell *et al.* 2019).

While the operation of CAMFEPS in terms of case identification and assessment has been described previously in detail (Baldwin *et al.* 2005; Owoeye *et al.* 2013), essential points include (a) case ascertainment via all routes to care [i.e. public (CMMHS: home-based, outpatient and inpatient), private (St. John of God Hospital, Co. Dublin; St. Patrick's University Hospital, Dublin) and forensic (Central Mental Hospital, Dublin)]; inception throughout the adult lifespan (age 16 and above, i.e. no arbitrary upper age cut-off); inception of all 12 DSM-IV psychotic diagnoses [schizophrenia; schizophreniform disorder; schizoaffective disorder; delusional disorder; brief psychotic disorder; bipolar disorder; major depressive disorder, with psychotic features; 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; psychotic disorder not otherwise specified].

Epidemiology

Classical research and literature on the epidemiology of psychotic illness derives primarily from studies of schizophrenia and indicates a disorder having the

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

following profile: an incidence that can vary across countries and cultures, has its onset primarily in young adulthood, and occurs earlier in men than in women. However, while some of these features have been generally sustained by contemporary studies, they now appear to be simplistic and incomplete, particularly in relation to diversity in case ascertainment, social milieu and 'strictness' of diagnostic criteria, over-representation of data on schizophrenia vis-à-vis other diagnoses in which psychosis can occur, and application of arbitrary upper age cut-offs (Baldwin *et al.* 2005; McGrath 2005; Kirkbride *et al.* 2012).

In CAMFEPS, on ascertaining cases via all routes to care, dispensing with diagnostic restriction and arbitrary upper age cut-off and applying internationally recognised DSM-IV diagnostic criteria, a more complex and nuanced epidemiological landscape is apparent. Over the 15-year period (1995–2010), CAMFEPS incepted 432 cases: 92 major depressive disorder with psychotic features (MDDP); 89 bipolar disorder (BD); 81 schizophrenia (SZ); 25 schizoaffective disorder (SA); 25 delusional disorder; 25 substance-induced psychotic disorder; 23 brief psychotic disorder; 20 schizophreniform disorder; 13 psychotic disorder due to a general medical condition; 8 substance-induced mood disorder with manic features; 4 mood disorder due to a general medical condition, with manic features; and 25 psychotic disorder not otherwise specified. There were also two cases of simple deteriorative disorder, a DSM-IV Appendix category characterised by all the hallmarks of schizophrenia in terms of negative symptoms and functional decline but without sufficiently prominent positive symptoms to satisfy criteria for SZ; this condition overlaps with attenuated psychosis syndrome, a DSM-5 Condition for Further Study. The overall incidence of any psychotic illness was 34.1/100,000 of population age over 15 years (Baldwin *et al.* 2005; Kingston *et al.* 2013; Owoeye et al. 2013; Nkire *et al.* in preparation).

An unexpected finding on applying such methodology in this 'real-world' setting was the breadth of diagnoses under which psychotic psychopathology was manifest, with the incidence of psychosis under the three most populous diagnoses being indistinguishable between SZ, BD and MDDP. Yet each of these diagnostic categories showed a distinct profile: SZ was threefold more common and was first diagnosed at a younger mean age in men than in women; BD was indistinguishably common and first diagnosed at an indistinguishable mean age in men and women; MDDP was indistinguishably common and first diagnosed at an indistinguishable mean age in men and women but that mean age was substantially older, by some 20 years, than for SZ and BD. This later finding illustrates the impact of arbitrary upper age cut-offs in studies of psychotic illness through exclusion of many MDDP cases and this artefact applies also to a smaller, but not inconsequential, number of SZ and BD cases. Critically, these distinct epidemiological 'signatures' in CAMFEPS should not be misinterpreted as validating these diagnostic categories; when ascertained appropriately these differences are quantitative rather than qualitative, such that each diagnosis of SZ, BD and MDDP (and also SA, schizophreniform disorder, delusional disorder and psychosis not otherwise specified) can and does occur in either sex, with the onset of psychosis occurring at any age over the adult lifespan, from the teens through to the ninth or, occasionally, the tenth decade (Baldwin *et al.* 2005; Kingston *et al.* 2013; Owoeye *et al.* 2013; Nkire *et al.* in preparation).

These findings from CAMFEPS have contributed to a recent international collaborative analysis of SZ across 43 methodologically diverse datasets amounting to 133,693 cases, which elaborates differential susceptibility to SZ for men and women with age (van der Werf *et al.* 2014). Additionally, CAMFEPS shows that while these relationships differ quantitatively in BD and MDDP vis-à-vis SZ, they do not constitute qualitative discriminators between them; rather, these, together with other psychotic diagnoses encountered less commonly, are in epidemiological continuity with each other in the absence of any points of rarity (Waddington *et al.* 2019).

Diagnostic instability

An important aspect of psychotic illness is the stability or otherwise of such diagnoses on a long-term basis; in particular, do initial diagnoses remain stable, diverge or converge to a smaller number of more highly populated categories that might be considered more fundamental diagnostic nodes? In a 6-year follow-up of the first 202 cases incepted into CAMFEPS, similar robust ascertainment methods allowed diagnostic reassessments for 196 (97%) cases with quantification of prospective and retrospective consistency. While the 12 initial psychotic diagnoses were characterised by numerous transitions, these were diverse with only limited convergence towards a smaller number of more stable diagnostic nodes, most commonly SZ. Notably, for 85% of cases having an initial diagnosis of brief psychotic disorder this was the harbinger of long-term evolution to a serious psychotic illness of diagnostic diversity (SZ, SA, delusional disorder, BD, MDDP), as were the two cases of simple deteriorative disorder. Furthermore, 15% of cases having an initial diagnosis of MDDP were deceased at 6 years due to diverse causes, a concern that may not simply reflect cases of MDDP being a mean of some 20 years older at inception than cases of SZ and BD. Enigmatically, 31% of cases having an initial diagnosis of psychotic disorder not otherwise specified continued over 6 years to defy any other DSM-IV diagnosis (Kingston *et al.* 2013).

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

These findings from CAMFEPS have contributed to a recent international meta-analysis of diagnostic stability across 42 methodologically diverse first-episode psychosis datasets amounting to 14,484 cases, which provides estimates of diagnostic stabilities and transitions across diverse periods of follow-up for a circumscribed range of DSM-IV psychotic diagnoses, among which BD and MDDP are compacted into a single category of 'affective spectrum psychosis' (Fusar-Poli *et al.* 2016). Across all 12 DSM-IV psychotic diagnoses, CAMFEPS reveals a diversity of stabilities in, and transitions between, these diagnoses over a 6-year period that indicates some 'fluidity' in and thus longitudinal disrespect to such categorisation; in particular, a first episode of brief psychotic disorder or MDDP may be an indicator for vigorous and sustained interventions (Kingston *et al.* 2013; Waddington *et al.* 2019).

Clinical characteristics

That CAMFEPS methodology reveals MDDP to be just as common as SZ and BD at a first psychotic episode indicates that recent emphasis on the SZ-BD interface (see Introduction) may need to be broadened yet further. Indeed, we have argued that MDDP is an archetype for the challenge of confluence between psychotic and affective domains of psychopathology, even more so than BD or the long-standing conundrum of SA (Waddington & Buckley, 2013; Waddington *et al.* 2019). Current theory emphasises dimensional rather than solely diagnostically based perspectives of psychotic illness (van Os & Kapur, 2009; Barch *et al.* 2013; Owen, 2014; Owen *et al.* 2016; Waddington *et al.* 2019) in a manner complementary to the above epidemiological evidence. On this basis, CAMFEPS has undertaken systematic, heuristic comparisons between SZ, BD and MDDP at the first episode across the clinical domains of psychopathology, neuropsychology, neurology, premorbid adjustment and quality of life, the interim results of which can be summarised as follows (Baldwin *et al.* 2005; Owoeye *et al.* 2013):

Psychopathology

SZ, BD and MDDP evidenced indistinguishable severity of positive symptoms, with negative symptom severity being highest in SZ, slightly less so in MDDP and less so in BD; assessment of negative symptom severity in MDDP may be confounded with symptoms of depression.

Neuropsychology

SZ, BD and MDDP were indistinguishable on screening for current general cognitive function and on the estimation of premorbid intellectual functioning prior to the onset of psychotic symptoms; SZ and MDDP evidenced indistinguishable severity of executive dysfunction, with BD appearing somewhat less impaired.

Neurology

SZ and MDDP evidenced indistinguishable prominence of neurological soft signs (minor neurological signs that indicate non-localising cerebral dysfunction), with BD appearing somewhat less impaired; each of SZ, BD and MDDP showed indistinguishably low levels of extrapyramidal movement disorder and abnormal involuntary movements, as expected given no or only brief exposure to antipsychotic drugs when evaluated at the first psychotic episode.

Premorbid adjustment

SZ, BD and MDDP evidenced only subtle differences in impairment of premorbid adjustment, which varied slightly between the age ranges of up to 11 years *versus* 12–15 years.

Quality of life

SZ and MDDP evidenced indistinguishable impairment in quality of life, with BD appearing less impaired.

Overview

In CAMFEPS, interim findings in SZ, BD and MDDP indicate very similar clinical profiles, with any differences being quantitative rather than qualitative in the presence of considerable overlap and no points of rarity between them (Owoeye *et al.* 2013). While every diagnosis of SZ indicates, by definition, an intrinsically psychotic disorder, independent of severity, this is less clear for BD across all severities of illness in relation to presence or absence of the DSM-IV specifier for BD 'severe, with psychotic features' (Pearlson, 2015; Anderson *et al.* 2018; Waddington *et al.* 2019). To clarify this issue, CAMFEPS has investigated BD cases divided according to the presence or absence of this DSM-IV specifier and compared these subgroups across the same clinical domains as above: at the first manic episode, BD patients with the specifier 'severe with psychotic features' (the majority of cases) showed, by definition, greater severity, but overlapping extents, of positive symptoms than BD patients without this specifier; furthermore, these two subgroups were indistinguishable in terms of negative symptoms, neuropsychology, neurology, premorbid adjustment and quality of life (Owoeye *et al.* 2013). The same question can be asked for major depressive disorder (MDD) in relation to presence or absence of the DSM-IV specifier 'severe with psychotic features'. While CAMFEPS, like essentially all first-episode studies, does not ascertain and incept

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

cases of MDD in the absence of psychosis, review of the available evidence suggests a similar conclusion (Waddington *et al.* 2019).

Gene–environment interface

Current theory posits in SZ a gene–environment interaction process that may take many forms, from the heterogeneity of pathobiological processes, through subsequently converging pathways, to a more homogeneous, down-stream pathobiological process (Tost & Meyer-Lindenberg, 2012; Howes *et al.* 2017). Among many attendant challenges are how to specify the relevant process(es) and if/how they might generalise to psychotic illness occurring under differing diagnoses (European Network of National Networks Studying Gene-Environment Interactions in Schizophrenia, 2014).

Classical research and literature on the origins of psychotic illness derive primarily from studies of SZ in twins; studies on concordance for SZ among monozygotic *versus* dizygotic twin pairs constitute the naturalistic experimental paradigm *par excellence* for partitioning the relative roles of genetic *versus* common/unique (non-shared) environmental factors in the origin(s) of the disorder. In the most recent and most extensive study, involving all pairs in the Danish Nationwide Twin Register, comparison of monozygotic *versus* dizygotic concordance rates indicates that additive genetic effects account for 78.9% and unique environmental effects for 21.1% of variance in liability for SZ, in elaboration of the classical literature (Hilker *et al.* 2017). While the same approach indicates generally similar partitioning of variance in liability for genetic *versus* unique environmental effects in BD (Craddock & Sklar, 2013), there are only limited data in SA (Cardno & Owen, 2014) and even less so in MDDP (Domschke, 2013).

Molecular genetics

The impact of genome-wide association studies (GWAS) on our understanding of SZ, BD and an increasing number of other neuropsychiatric disorders continues to be profound (Sullivan et al. 2018). CAMFEPS and other centres in Ireland have contributed data, via a national dataset assembled and curated by colleagues at Trinity College Dublin, to several recent global meta-analyses of the molecular genetics of psychotic illness, under the auspices of the Psychiatric Genomics Consortium and the Brainstorm Consortium.

Among the studies to which CAMFEPS contributed was the then-largest GWAS of SZ undertaken, which identified 108 independent genetic loci among 128 loci associated with risk for the disorder among 36,989 cases and 113,075 controls (Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2014). However, this finding, though of enduring import, should no longer be considered in isolation. CAMFEPS has also contributed to a more recent GWAS meta-analysis of 265,218 patients having one of 25 neuropsychiatric disorders and 784,643 control participants, which found that psychiatric disorders share an unexpected degree of common genetic risk: for example, genes associated with risk for SZ are also associated, to varying extents, with risk for BD, MDD, autism spectrum disorder, attention-deficit/hyperactivity disorder, obsessive-compulsive disorder and anorexia nervosa; in contrast, neurological disorders such as epilepsy, stroke, Parkinson's disease, migraine and multiple sclerosis appear more genetically distinct (Brainstorm Consortium, 2018).

More specifically, CAMFEPS has also contributed to a recent GWAS meta-analysis that identified 32 independent genetic loci among 114 loci associated with risk for a single diagnostic phenotype obtained by combining 33,426 cases of SZ with 20,129 cases of BD in comparison with 54,065 controls (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018); this study also identified polygenic risk scores for SZ that are associated with psychotic symptoms in BD and polygenic risk scores in BD that are associated with manic symptoms in SZ, together with a small number of loci that differentiated between these diagnostic phenotypes.

These GWAS studies elaborate the clinical challenges to diagnostic orthodoxy in, and the alternative dimensional construct for, psychotic illness identified above (see Epidemiology, Diagnostic instability and Clinical characteristics) by indicating SZ and BD to be neither independent nor the same but, rather, sharing particular symptom dimensions that can be reflected in genetic architecture (Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium, 2018). However, they throw less light on putative mechanisms of gene–environment interactions.

Social milieu

Though genetics clearly holds' 'centre stage' in relation to the origins of psychotic illness, the very small extent of risk associated with each genetic locus (other than extremely rare copy number variations; Sullivan *et al.* 2018) and robust evidence for unique environmental effects (see Gene–environment interface) requires that non-genetic factors continue to receive appropriate investigation. The epidemiology of psychotic illness, deriving primarily from studies in SZ, now encompasses a wide range of characteristics and exposures that involve all phases of the illness, from the intrauterine environment, through infancy, childhood and 'onset', to adulthood (McGrath, 2005; Brown, 2011; Kirkbride *et al.* 2012; Owen et al. 2016); these exposures

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

may act independent of genetic risk, or, more likely, via gene–environment interactions (European Network of National Networks Studying Gene-Environment Interactions in Schizophrenia, 2014). The epidemiology of BD has also received extensive study (Bortolato *et al.* 2017; Vieta *et al.* 2018), though only occasionally from a systematically trans-diagnostic perspective (Baldwin *et al.* 2005; Kirkbride *et al.* 2012), while the epidemiology of SA and particularly of MDDP has received considerably less attention (Waddington *et al.* 2019).

Among environmental factors associated with increased incidence of SZ, one currently attracting renewed attention is that of neighbourhood-level social factors, particularly greater social deprivation and lower social capital-cohesion/fragmentation (O'Donoghue *et al.* 2016; Radua *et al.* 2018). These factors are closely associated with urbanicity and ethnicity/in-migration, each of which has been related consistently with risk for SZ (Kelly *et al.* 2010; Castillejos *et al.* 2018; Radua *et al.* 2018). As the region in which CAMFEPS is embedded is characterised by no major urban centres or ethnic diversity, with the vast majority of cases being white Irish, it constitutes an important rural resource for investigating social deprivation and lower social capital-cohesion/fragmentation at a neighbourhood level in the absence of urbanicity or associated issues relating to ethnicity/in-migration. Furthermore, the majority of studies to date have not been able to disentangle reliably whether these socioeconomic factors are most important in relation to the neighbourhood where the case was born [in accordance with a developmental model for psychosis (Waddington *et al.* 2012; Weinberger, 2017)] *versus* where he/she experienced the 'onset' of their psychotic illness [as a proximal 'trigger', perhaps interacting with developmental risk (Davis *et al.* 2016)]; CAMFEPS has been able to address this issue also.

Across the 155 Electoral Divisions constituting the CAMFEPS region, increase in risk for psychosis (SZ + BD + MDDP pooled) was related to increase in neighbourhood deprivation at 'onset', subject to some differences of detail between ecological analysis and multilevel modelling; while ecological analysis indicated an additional relationship to increasing neighbourhood social fragmentation, this was not evident in multilevel modelling on incorporating the highly correlated factor of material deprivation and there were no relationships to extent of neighbourhood rurality (Omer *et al.* 2014). In contrast, an increase in risk for psychosis was related to a decrease in neighbourhood rurality at birth, in the absence of urbanicity; while there were no relationships to neighbourhood social fragmentation or deprivation at birth, older age at 'onset' (as age at first presentation) was associated prominently with lower parental social class (as paternal occupation at birth of the case; Omer *et al.* 2016).

These findings from CAMFEPS indicate effects of neighbourhood- and individual-level socioeconomic factors on risk for psychosis within a rural environment and these relationships differ between neighbourhoods at 'onset' and at birth. Thus, such findings are not confined to large urban settings and apply not only across the urban–rural continuum but also across gradations of rurality. One influential theory posits that genetic and environmental factors interact to sensitise the dopaminergic system so that it is vulnerable to acute stressors, leading to progressive dopaminergic dysregulation and the 'onset' of psychosis (Howes & Murray, 2014; Howes *et al.* 2017). It appears that these stressors may act diversely from the pre-/perinatal period through to proximity to 'onset'. Furthermore, a gradient of socioeconomic position appears to influence delay in presentation to mental health services and initiation of treatment.

Developmental pathobiology

While the neurodevelopmental model continues to hold 'centre stage' in relation to schizophrenia (Waddington *et al.* 2012; Weinberger, 2017), controversy endures regarding the extent to which BD might also have developmental origins (Demjaha *et al.* 2012; Murray *et al.* 2017; Parellada *et al.* 2017). While genetic risk for SZ is commonly interpreted in terms of developmental dysregulation that interacts with environmental adversities (Birnbaum & Weinberger, 2017; Howes *et al.* 2017), clarification would be facilitated by a 'hard' biological index of a developmental abnormality. Anatomical dysmorphologies indicate developmental disruption during early foetal life and are over-represented in SZ (Waddington *et al.* 2008; Xu *et al.* 2011). Among these, craniofacial dysmorphologies bear the closest embryological relationship to brain dysmorphogenesis (Marcucio *et al.* 2011, 2015). Thus, CAMFEPS has contributed to studies in which we have applied 3D laser surface imaging and geometric morphometrics to resolve the topography of craniofacial dysmorphology in SZ (Hennessy *et al.* 2007) and show that in BD this appears more similar to than different from dysmorphology evident in SZ (Hennessy *et al.* 2010). These findings complement evidence for considerable overlap in genetic risk for SZ and BD (see Molecular genetics) by indicating shared disruptive events operating over early foetal life.

Functional outcome and service models

Though these intricacies of psychopathology, diagnosis, developmental pathobiology, genetics and gene–environment interaction are fundamental to our understanding of psychotic illness, it is functional outcome and the model of care applied to optimise such

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

outcome that are the primary concerns of patients, their families and health service providers.

While functionality and quality of life are well recognised as critical indices of outcome in all medical conditions and have been widely studied in relation to psychotic illness, this literature derives primarily from studies in SZ, less so in SA and BD, with MDDP receiving little attention (Lally *et al.* 2017; Santesteban-Echarri *et al.* 2017; Waddington *et al.* 2019). Therefore, we have systematically compared functional outcome, quality of life and service engagement across these four diagnoses during a 6-year follow-up of the first 202 cases in the CAMFEPS cohort (Kingston *et al.* 2018): positive psychotic symptoms were most prominent in SZ and SA, and less prominent in MDDP and BD; negative symptoms, impaired functioning and reduction in objectively determined quality of life were most prominent in SZ, intermediate in SA and less prominent in MDDP and BD; in contrast, subjectively determined quality of life was indistinguishable across diagnoses. Service engagement was lowest for SZ, intermediate for SA and BD, and highest for MDDP. However, these measures showed considerable overlap across diagnoses, with no quantitative points of rarity between them. Indeed, on pooling all cases of SZ, SA, BD and MDDP into a single psychotic composite, an increasingly heuristic practice (see e.g. Molecular genetics), higher general (i.e. less diagnostically specific) psychopathology, together with higher negative but not positive psychopathology, and lower service engagement predicted poor functioning in association with lower educational attainment, never having married and living in unsupported living conditions (Kingston *et al.* 2018).

These findings relate to studies carried out over a period during which the underlying model of mental health care provision, in which CAMFEPS was embedded, has been progressively revised. This journey, involving primary care liaison and use of home-based treatment as an alternative to hospital admission as central to the delivery of health services (McCauley *et al.* 2003; Nwachukwu *et al.* 2014), is described in detail in a companion article; the challenges encountered and opportunities afforded in the course of these innovations are instructive, both locally and nationally, when considered in the context of current professional, public and political debate (Russell *et al.* 2019).

Early intervention

At the 'core' of priorities for Ireland in relation to psychotic illness is the National Clinical Programme for Early Intervention in Psychosis, which is driven by assumptions of dual import:

Firstly, that longer duration of untreated psychosis (DUP) at first clinical presentation is associated with poorer long-term outcome, such that reduction in DUP through earlier case identification and initiation of treatment can improve outcome (Millan *et al.* 2016). DETECT and CAMFEPS-COPE have recently pointed out that opinion on this issue is diverse, ranging from scepticism, through agnosticism, to proselytism (Clarke *et al.* 2016), but what is the evidence? The most recent meta-analysis indicates that among available interventions (standalone first-episode psychosis services, standalone clinical high risk services, community interventions, healthcare professional training and multi-focus interventions), there is no summary evidence that they are successful in reducing DUP, though a single, standalone clinical high-risk services study was positive but remains to be replicated (Oliver *et al.* 2018). The CAMFEPS dataset, which contains 15 years of measurement of DUP prior to the introduction of an early intervention service, followed by the COPE dataset, which contains 5 years of measurement of DUP following introduction of the COPE early intervention service, will allow further systematic investigation of this issue. In contrast, the most recent meta-analysis indicates that early intervention services are superior to treatment as usual across multiple indices of outcome (treatment discontinuation, psychiatric hospitalisation, improvement at school or in work, and total, positive and negative symptom severity) over periods up to 24 months (Correll *et al.* 2018). This suggests that early intervention services may have clinical impact through processes other than or additional to a reduction in DUP. Comparisons between the CAMFEPS and COPE datasets will allow further systematic investigation of the relationships between early intervention and outcome vis-à-vis DUP.

Secondly, as psychotic ideation and associated subclinical psychopathology and dysfunction can be present in young persons across the general population (van Os & Reininghaus 2016) and, in some individuals, may be early harbingers of risk for clinical psychosis (i.e. clinical high risk/at-risk mental state; Fusar-Poli *et al.* 2013), early detection of and interventions for such individuals may reduce and even prevent transition to a psychotic diagnosis (Millan *et al.* 2016; Carpenter, 2018). The most recent meta-analysis indicates that among diverse interventions at this stage [needs-based interventions (supportive psychotherapy, psychosocial assistance, brief family psychoeducation, non-antipsychotic medications), cognitive behavioural therapy, integrated psychological interventions, family-focussed therapy, and pharmacological interventions (currently licensed medications, experimental pharmacotherapies, nutritional supplements, or placebo)] no specific intervention is superior to any other (Davies *et al.* 2018).

Experience in these areas in Ireland is limited but evolving under the National Clinical Programme for

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

Early Intervention in Psychosis. Given the challenges to date in implementing this programme, it may be helpful to note that the first two early intervention services have their origins in two substantive and complementary first-episode psychosis studies: the evolution of the St. John of God Hospitaller Ministries/Cluain Mhuire Community Mental Health Services study (Browne *et al.* 2000) into DETECT (Renwick *et al.* 2008) and the evolution of CAMFEPS (Baldwin *et al.* 2005) into COPE (Nkire *et al.* 2015). These issues are considered in greater detail in a companion article (Russell *et al.* 2019)

Synthesis

Perhaps the greatest challenge is increasing congruence between studies of psychotic illness across conventional diagnoses and psychotic ideation across the population at large. By way of example, the common manifestation of both psychosis and depression in a given individual can lead to a variety of diagnoses by DSM-IV criteria (the version of DSM on which the great majority of published studies are based, with DSM-5 containing only minor variations): (a) depression in schizophrenia is so widely recognised that its presence may not engender any concern as to a primary diagnosis of *Schizophrenia*; (b) occasionally, when depressive symptoms in schizophrenia meet criteria for a major depressive episode, an additional diagnosis of *Depressive disorder not otherwise specified* may be made together with a diagnosis of *Schizophrenia*; (c) where psychotic symptoms are manifested both concurrently with a major depressive episode and in the absence of prominent mood symptoms, the diagnosis may be *SA*; (d) where a major depressive episode includes concurrent manifestation of psychotic symptoms but psychosis is not evident in the absence of prominent mood symptoms, the diagnosis may be *MDD, severe with psychotic features*; (e) the subsequent manifestation of a manic or hypomanic episode may lead to diagnostic revision to *bipolar I* or *II disorder, depressed, severe with psychotic features*; (f) where the interplay of psychotic and mood symptoms is unclear, is the subject of contradictory information or does not allow determination of whether it is primary or secondary, the diagnosis may be *Psychotic disorder not otherwise specified*. To what extent can we be confident that such intricacies and subtleties of diagnosis constitute real and impactful differences, or else reflect mercurial designations within a rich *milieu* of developmental outcomes at the level of mentation, behaviour and function?

Psychotic illness and associated risk factors across the gene–environment interface are disrespectful to conventional diagnostic categories, with any differences between them being quantitative rather than qualitative, in the presence of substantive overlap and absence of points of rarity between them. Thus, our efforts to impose some underlying order through diagnostic categories constitute, in reality, a series of arbitrary boundaries. Building on previous conceptualisations (Owen, 2014; Brainstorm Consortium, 2018; Waddington *et al.* 2019), evidence increasingly suggests a continuum of developmental outcomes characterised by variations in pathobiological processes, psychopathological dimensions and functional characteristics. Furthermore, these outcomes, including what we term 'psychosis', appear in continuity or intersection with the limits of 'normal' human mentation and functioning, with attendant implications for how we conceive and optimally structure provision of mental health services (Arango *et al.* 2018; McGorry *et al.* 2018).

Acknowledgements

We thank the Stanley Medical Research Institute for funding the first 10 years of CAMFEPS; Clinical Research Fellows/Registrars Drs. Paul Scully, John Quinn, Maria Morgan, Patrizia Baldwin, David Browne, Tara Kingston, Olabisi Owoeye and Nnamdi Nkire who so capably operated CAMFEPS for 15 years and carried out and authored the studies described in this article; and all our colleagues in Cavan-Monaghan Mental Health Service who supported and fostered CAMFEPS and its transition to COPE. We dedicate this article to the memory of the late Dr. Hanafy A. Youssef, Consultant Psychiatrist, St. Davnet's Hospital, Monaghan, who, through his dedication to and enthusiasm for mental health research, fostered the initial clinical collaboration between Cavan-Monaghan Mental Health Service and the Royal College of Surgeons in Ireland that led to CAMFEPS.

Conflict of interest

The authors have no conflicts of interest to declare.

Ethical standards

All study protocols relating to the Cavan-Monaghan First Episode Psychosis Study 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 University Hospital, Dublin, St. John of God Hospital, Co. Dublin, and the Central Mental Hospital, Dublin, The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committee on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008.

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

Financial support

The first 10 years of the Cavan-Monaghan First Episode Psychosis Study were supported by the Stanley Medical Research Institute.

References

Anderson AE, Marder S, Reise SP, Savitz A, Salvadore G, Fu DJ, Li Q, Turkoz I, Han C, Bilder RM (2018). Bifactor modeling of the Positive and Negative Syndrome Scale: generalized psychosis spans schizoaffective, bipolar and schizophrenia diagnoses. *Schizophrenia Bulletin* **44**, 1204–1216. doi: 10.1093/schbul/sbx163.

Arango C, Diaz-Caneja CM, McGorry PD, Rapoport J, Sommer IE, Vorstman JA, McDaid D, Marion O, Serrano-Drozdowskyj E, Freedman R, Carpenter WT (2018). Preventive strategies for mental health. *Lancet Psychiatry* **5**, 591–604.

Baldwin P, Browne D, Scully PJ, Quinn JF, Morgan MG, Kinsella A, Owens JM, Russell V, O'Callaghan E, Waddington JL (2005). Epidemiology of first-episode psychosis: illustrating the challenges across diagnostic boundaries through the Cavan/Monaghan study at 8 years. *Schizophrenia Bulletin* **31**, 624–638.

Barch DM, Bustillo J, Gaebel W, Gur R, Heckers S, Malaspina D, Owen MJ, Schultz S, Tandon R, Tsuang M, van Os J, Carpenter W (2013). Logic and justification for dimensional assessment of symptoms and related phenomena in psychosis: relevance to DSM-5. *Schizophrenia Research* **150**, 31–35.

Bipolar Disorder and Schizophrenia Working Group of the Psychiatric Genomics Consortium (2018). Genomic dissection of bipolar disorder and schizophrenia, including 28 subphenotypes. *Cell* **173**, 1705–1715.

Birnbaum R, Weinberger DR (2017). Genetic insights into the neurodevelopmental origins of schizophrenia. *Nature Reviews Neuroscience* **18**, 727–740.

Birur B, Kraguljac NV, Shelton RC, Lahti AC (2017). Brain structure, function, and neurochemistry in schizophrenia and bipolar disorder—a systematic review of the magnetic resonance neuroimaging literature. *NPJ Schizophrenia* **3**, 15 doi: 10.1038/s41537-017-0013-9.

Bortolato B, Kohler CA, Evangelou E, Leon-Caballero J, Solmi M, Stubbs B, Belbasis L, Pacchiarotti I, Kessing LV, Berk M, Vieta E, Carvalho AF (2017). Systematic assessment of environmental risk factors for bipolar disorder: an umbrella review of systematic reviews and meta-analyses. *Bipolar Disorders* **19**, 84–96.

Brainstorm Consortium (2018). Analysis of shared heritability in common disorders of the brain. *Science* **360**, pii: eaap8757. doi: 10.1126/science.aap8757.

Brown AS (2011). The environment and susceptibility to schizophrenia. *Progress in Neurobiology* **93**, 23–58.

Browne S, Clarke M, Gervin M, Waddington JL, Larkin C, O'Callaghan E (2000). Determinants of quality of life at first presentation with schizophrenia. *British Journal of Psychiatry* **176**, 173–176.

Cardno AG, Owen MJ (2014). Genetic relationship between schizophrenia, bipolar disorder, and schizoaffective disorder. *Schizophrenia Bulletin* **40**, 504–515.

Carpenter WT (2018). Clinical high risk controversies and challenges for the experts. *Schizophrenia Bulletin* **44**, 223–225.

Castillejos MC, Martin-Perez C, Moreno-Kustner B (2018). A systematic review and meta-analysis of the incidence of psychotic disorders: the distribution of rates and the influence of gender, urbanicity, immigration and socio-economic level. *Psychological Medicine* **48**, 2101–2115. doi: 10.1017/S0033291718000235.

Clarke M, McDonough CM, Doyle R, Waddington JL (2016). Are we really impacting duration of untreated psychosis and does it matter? Longitudinal perspectives on early intervention from the Irish public health services. *Psychiatric Clinics of North America* **39**, 175–186.

Correll CU, Galling B, Pawar A, Krivko A, Bonetto C, Ruggeri M, *et al.* (2018). Comparison of early intervention services vs treatment as usual for early-phase psychosis: A systematic review, meta-analysis and meta-regression. *JAMA Psychiatry* **75**, 555–565.

Craddock N, Owen MJ (2010). The Kraepelinian dichotomy – going, going . . . but still not gone. *British Journal of Psychiatry* **196**, 92–95.

Craddock N, Sklar P (2013). Genetics of bipolar disorder. *Lancet* **381**, 1654–1662.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013a). Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet* **381**, 1371–1379.

Cross-Disorder Group of the Psychiatric Genomics Consortium (2013b). Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature Genetics* **45**, 984–994.

Davies C, Cipriani A, Ioannidis JPA, Radua J, Stahl D, Provenzani U, McGuire P, Fusar-Poli P (2018). Lack of evidence to favor specific preventive interventions in psychosis: a network meta-analysis. *World Psychiatry* **17**, 196–209.

Davis J, Eyre H, Jacka FN, Dodd S, Dean O, McEwen S, Debnath M, McGrath J, Maes M, Amminger P, McGorry PD, Pantelis C, Berk M (2016). A review of vulnerability and risks for schizophrenia: beyond the two hit hypothesis. *Neuroscience & Biobehavioral Reviews* **65**, 185–194.

Demjaha A, MacCabe JH, Murray RM (2012). How genes and environmental factors determine the different neurodevelopmental trajectories of schizophrenia and bipolar disorder. *Schizophrenia Bulletin* **38**, 209–214.

Domschke K (2013). Clinical and molecular genetics of psychotic depression. *Schizophrenia Bulletin* **39**, 766–775.

European Network of National Networks Studying Gene-Environment Interactions in Schizophrenia (2014). Identifying gene-environment interactions in schizophrenia: contemporary challenges for integrated, large-scale investigations. *Schizophrenia Bulletin* **40**, 729–736.

Fusar-Poli P, Borgwardt S, Bechdolf A, Addington J, Riecher-Rössler A, Schultze-Lutter F, *et al.* (2013). The

psychosis high-risk state: a comprehensive state-of-the-art review. *JAMA Psychiatry* **70**, 107–120.

Fusar-Poli P, Cappucciati M, Rutigliano G, Heslin M, Stahl D, Brittenden Z, Caverzasi E, McGuire P, Carpenter WT (2016). Diagnostic stability of ICD/DSM first episode psychosis diagnoses: meta-analysis. *Schizophrenia Bulletin* **42**, 1395–1406.

Hennessy RJ, Baldwin PA, Browne DJ, Kinsella A, Waddington JL (2007). Three-dimensional laser surface imaging and geometric morphometrics resolve frontonasal dysmorphology in schizophrenia. *Biological Psychiatry* **61**, 1187–1194.

Hennessy RJ, Baldwin PA, Browne DJ, Kinsella A, Waddington JL (2010). Frontonasal dysmorphology in bipolar disorder by 3D laser surface imaging and geometric morphometrics: comparisons with schizophrenia. *Schizophrenia Research* **122**, 63–71.

Hilker R, Helenius D, Fagerlund B, Skytthe A, Christensen K, Werge TM, Nordentoft M, Glenthoj B (2017). Heritability of schizophrenia and schizophrenia spectrum based on the nationwide Danish twin register. *Biological Psychiatry* **83**, 492–498.

Howes OD, McCutcheon R, Owen MJ, Murray RM (2017). The role of genes, stress, and dopamine in the development of schizophrenia. *Biological Psychiatry* **81**, 9–20.

Howes OD, Murray RM (2014). Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet* **383**, 1677–1687.

Kahn RS, Sommer IE, Murray RM, Meyer-Lindenberg A, Weinberger DR, Cannon TD, O'Donovan M, Correll CU, Kane JM, van Os J, Insel TR (2015). Schizophrenia. *Nature Reviews Disease Primers* **1**, 15067. doi: 10.1038/nrdp.2015.67.

Kelly BD, O'Callaghan E, Waddington JL, Feeney L, Browne S, Scully PJ, Clarke M, Quinn JF, McTigue O, Morgan MG, Kinsella A, Larkin C (2010). Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophrenia Research* **116**, 75–89.

Keshavan MS, Schooler NR (1992). First-episode studies in schizophrenia: criteria and characterization. *Schizophrenia Bulletin* **18**, 491–513.

Kingston T, Scully PJ, Browne D, Baldwin PA, Kinsella A, O'Callaghan E, Waddington JL (2018). Functional outcome and service engagement inn major depressive disorder with psychotic features: comparisons with schizophrenia, schizoaffective disorder and bipolar disorder in a 6-year follow-up of the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *CNS Neuroscience & Therapeutics* **24**, 633–640.

Kingston T, Scully PJ, Browne D, Baldwin P, Kinsella A, Russell V, O'Callaghan E, Waddington JL (2013). Diagnostic trajectory, interplay and convergence/divergence across all 12 DSM-IV psychotic diagnoses: 6-year follow-up of the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Psychological Medicine* **43**, 2523–2533.

Kirch DG, Lieberman JA, Matthews SM (1992). First-episode psychosis. *Schizophrenia Bulletin* **18**, 177–178.

Kirkbride JB, Errazuriz A, Croudace TJ, Morgan C, Jackson D, Boydell J, Murray RM, Jones PB (2012). Incidence of schizophrenia and other psychoses in England, 1950-2009: a systematic review and meta-analyses. *PLOS One* **7**, e31660. doi: 10.1371/journal.pone.0031660.

Lally J, Ajnakina O, Stubbs B, Cullinane M, Murphy KC, Gaughran F, Murray RM (2017). Remission and recovery from first-episode psychosis in adults: systematic review and meta-analysis of long-term outcome studies. *British Journal of Psychiatry* **211**, 350–358.

Marcucio R, Hallgrimsson B, Young NM (2015). Facial morphogenesis: physical and molecular interactions between the brain and face. *Current Topics in Developmental Biology* **115**, 299–320.

Marcucio RS, Young NM, Hu D, Hallgrimsson B (2011). Mechanisms that underlie co-variation of the brain and face. *Genesis* **49**, 177–189.

McCauley M, Rooney S, Clarke C, Carey T, Owens J (2003). Home-based treatment in Monaghan: the first two years. *Irish Journal of Psychological Medicine* **20**, 11–14.

McGorry PD, Hartmann JA, Spooner R, Nelson B (2018). Beyond the "at risk mental state" concept: transitioning to transdiagnostic psychiatry. *World Psychiatry* **17**, 133–142.

McGrath JJ (2005). Myths and truths about schizophrenia epidemiology. *Acta Psychiatrica Scandinavica* **111**, 4–11.

Millan MJ, Andrieux A, Bartzokis G, Cadenhead K, Dazzan P, Fusar-Poli P, *et al.* (2016). Altering the course of schizophrenia: progress and perspectives. *Nature Reviews Drug Discovery* **15**, 485–515.

Million T, Grossman S, Meagher S (2004). *Masters of the Mind: Exploring the Story of Mental Illness from Ancient Times to the New Millennium*. John Wiley: Hoboken, NJ.

Murray RM, Bhavsar V, Tripoli G, Howes O (2017). 30 years on: How the neurodevelopmental hypothesis of schizophrenia morphed into the developmental risk factor model of psychosis. *Schizophrenia Bulletin* **43**, 1190–1196.

Nwachukwu I, Nkire N, Russell V (2014). Profile and activities of a rural home-based treatment service in Ireland. *International Journal of Psychiatry in Clinical Practice* **18**, 125–130.

Nkire N, Sardinha S, Nwosu B, McDonough CM, De Coteau PA, Duffy I, Waddington JL, Russell V (2015). Evaluation of knowledge and attitudes among primary care physicians in Cavan-Monaghan as 'gatekeepers-in-waiting' for the introduction of Carepath for Overcoming Psychosis Early (COPE). *Early Intervention in Psychiatry* **9**, 141–150.

O'Donoghue B, Roche E, Lane A (2016). Neighbourhood level social deprivation and the risk of psychotic disorders: a systematic review. *Social Psychiatry and Psychiatric Epidemiology* **51**, 941–950.

Oliver D, Davies C, Crossland G, Lim S, Gifford G, McGuire P, Fusar-Poli P (2018). Can we reduce the duration of untreated psychosis? A systematic review and meta-analysis of controlled intervention studies. *Schizophrenia Bulletin* **44**, 1362–1372. doi: 10.1093/schbul/sbx166.

Omer S, Finnegan M, Pringle DG, Kinsella A, Fearon P, Russell V, O'Callaghan E, Waddington JL (2016).

https://doi.org/10.1017/ipm.2019.11 Published online by Cambridge University Press

Socioeconomic status at birth and risk for first episode psychosis in rural Ireland: eliminating the features of urbanicity in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophrenia Research* **173**, 84–89.

Omer S, Kirkbride JB, Pringle DG, Russell V, O'Callaghan E, Waddington JL (2014). Neighbourhood-level socio-environmental factors and incidence of first episode psychosis by place at onset in rural Ireland: the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophrenia Research* **152**, 152–157.

Owen MJ (2014). New approaches to psychiatric diagnostic classification. *Neuron* **84**, 564–571.

Owen MJ, Sawa A, Mortensen PB (2016). Schizophrenia. *Lancet* **388**, 86–97.

Owoeye O, Kingston T, Scully PJ, Baldwin P, Browne D, Kinsella A, Russell V, O'Callaghan E, Waddington JL (2013). Epidemiological and clinical characterization following a first psychotic episode in major depressive disorder: comparisons with schizophrenia and bipolar I disorder in the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Schizophrenia Bulletin* **39**, 756–765.

Parellada M, Gomez-Vallejo S, Burdeus M, Arango C (2017). Developmental differences between schizophrenia and bipolar disorder. *Schizophrenia Bulletin* **43**, 1176–1189.

Pearlson GD (2015). Etiologic, phenomenologic, and endophenotypic overlap of schizophrenia and bipolar disorder. *Annual Review of Clinical Psychology* **11**, 251–281.

Radua J, Ramella-Cravaro V, Ioannidis JPA, Reichenberg A, Phiphopthatsanee N, Amir T, Yenn Thoo H, Oliver D, Davies C, Morgan C, McGuire P, Murray RM, Fusar-Poli P (2018) What causes schizophrenia? An umbrella review of risk and protective factors. *World Psychiatry* **17**, 49–66.

Ram R, Bromet EJ, Eaton WW, Pato C, Schwartz JE (1992). The natural course of schizophrenia: a review of first admission studies. *Schizophrenia Bulletin* **18**, 185–207.

Renwick L, Gavin B, McGlade N, Lacey P, Goggins R, Jackson D, Turner N, Foley S, McWilliams S, Behan C, Lawlor E, Cullen W, O'Callaghan E (2008). Early intervention service for psychosis: views from primary care. *Early Intervention in Psychiatry* **2**, 285–290.

Russell V, Nkire N, Kingston T, Waddington JL (2019). Forging successful partnerships in psychosis research: lessons from the Cavan-Monaghan First Episode Psychosis Study (CAMFEPS). *Irish Journal of Psychological Medicine* (in press).

Santesteban-Echarri O, Paino M, Rice S, Gonzalez-Blanch C, McGorry P, Gleeson J, Alvarez-Jimenez M (2017). Predictors of functional recovery in first-episode psychosis: a systematic review and meta-analysis of longitudinal studies. *Clinical Psychology Reviews* **58**, 59–75.

Schizophrenia Working Group of the Psychiatric Genomics Consortium (2014) Biological insights from 108 schizophrenia-associated genetic loci. *Nature* **511**, 421–427.

Sullivan PF, Agrawal A, Bulik CM, Andreassen OA, Borglum AD, Breen G, Cichon S, Edenberg HJ, Faraone SV, Gelernter J, Mathews CA, Nievergelt CM, Smoller JW, O'Donovan MC, Psychiatric Genomics Consortium (2018). Psychiatric genomics: an update and agenda. *American Journal of Psychiatry* **175**, 15–27.

Tost H, Meyer-Lindenberg A (2012). Puzzling over schizophrenia: schizophrenia, social environment and the brain. *Nature Medicine* **18**, 211–213.

Van der Werf M, Hanssen M, Kohler S, Verkaaik M, Verhey FR, RISE Investigators, van Winkel R, van Os J, Allardyce J (2014). Systematic review and collaborative recalculation of 133693 incident cases of schizophrenia. *Psychological Medicine* **44**, 9–16.

van Os J, Kapur S (2009). Schizophrenia. *Lancet* **374**, 635–645.

van Os J, Reininghaus U (2016). Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry* **15**, 118–124.

Vieta E, Berk M, Scxhulze TG, Carvalho AF, Suppes T, Calabrese JR, Gao K, Miskowiak KW, Grande I (2018). Bipolar disorders. *Nature Reviews Disease Primers* **4**, 18008. doi: 10.1038/nrdp.2018.8.

Waddington JL, Brown AS, Schaefer CA, Goetz RR, Bresnahan M, Susser ES (2008). Congenital anomalies and early functional impairments in a prospective birth cohort: risk of schizophrenia-spectrum disorder in adulthood. *British Journal of Psychiatry* **192**, 264–267.

Waddington JL, Buckley PF (2013). Psychotic depression: an underappreciated window to explore the dimensionality and pathobiology of psychosis. *Schizophrenia Bulletin* **39**, 754–755.

Waddington JL, Hennessy RJ, O'Tuathaigh CMP, Owoeye O, Russell V (2012). Schizophrenia and the lifetime trajectory of psychotic illness: developmental neuroscience and pathobiology. In *The Origins of Schizophrenia* (ed. A. S. Brown and P. H. Harrison), pp. 3–21. Columbia University Press: New York.

Waddington JL, Larkin C (1993). A new developmental epidemiology of schizophrenia: the HRB Schizophrenia Research Unit, 1991-92, and contemporary perspectives of the disease. *Irish Journal of Psychological Medicine* **10**, 56–59.

Waddington JL, Kingston T, Nkire N, Russell V (2019). Major depressive disorder with psychotic features: confronting and resolving the dimensional challenge. In *Psychotic Disorders: Comprehensive Conceptualization and Treatments* (ed. J. van Os, C. A. Tamminga, E. I. Ivleva and U. Reininghaus). Oxford University Press: Oxford. (in press)

Weinberger DR (2017). Future of days past: neurodevelopment and schizophrenia. *Schizophrenia Bulletin* **43**, 1164–1168.

Xu T, Chan RCK, Compton MT (2011). Minor physical anomalies in patients with schizophrenia, unaffected first-degree relatives, and healthy controls: a meta-analysis. *PLoS ONE* **6**, e24129.

Zhen XC, Waddington JL (2018). Emerging and evolving concepts in the pathobiology and treatment of psychosis. *CNS Neuroscience & Therapeutics* **24**, 583–585.