Oxford Textbook of Neurologic and Neuropsychiatric Epidemiology

Edited by Carol Brayne, Valery L. Feigin, Lenore J. Launer, and Giancarlo Logroscino

Publisher: Oxford University Press
Print Publication Date: Nov 2020
Print ISBN-13: 9780198749493
Published online: Oct 2020
DOI: 10.1093/med/9780198749493.001.0001

Epidemiology of schizophrenia and related disorders

Chapter: Epidemiology of schizophrenia and related disorders

Author(s):

Assen Jablensky, Hannah E Jongsma, James B Kirkbride, and Peter B Jones

DOI: 10.1093/med/9780198749493.003.0028

Introduction

Epidemiological research into schizophrenia has had a long and productive history over many decades, since Kraepelin's formulation of the disease concept of *dementia praecox* in 1896 and the renaming of the disorder as *schizophrenia* by Bleuler in 1911.[1] Being a counterpart to clinical and biological research, the focus of epidemiology is on the population frequency of the disorder and the distribution of its incidence, prevalence, course, outcome, and associated risk factors. The hallmark of the 'classical' epidemiological method is the referral of a counting measure (numerator) of the occurrence of a disorder and any associated characteristics to a population base (denominator), yielding its epidemiological 'signature' which enables the testing of hypotheses about risk factors and causes. The epidemiology of schizophrenia and other psychotic disorders aims to address three essential questions: (1) does the incidence, manifestations, and course of these disorders vary in

relation to factors of the physical and social environment? (2) who is at risk and what forces determine or influence the risk of developing schizophrenia or other psychotic disorders? (3) can epidemiological research contribute to the understanding of the aetiology of psychotic disorders and their prevention?

While epidemiological investigations to address these questions have been conducted for over a century, they are still encountering difficulties related to the nature of the disease concept of schizophrenia. Recurring problems include the dependence of the diagnosis on self-reported subjective experience; the clinical and genetic heterogeneity of the disorder; the absence of validated biological markers; and its tenuous delineation from other psychotic disorders and bipolar affective disorder. Although the ICD-10 and DSM-V criteria have clinical utility, a resolution of these difficulties is currently provided by the schizophrenia spectrum concept that embraces schizophrenia, schizoaffective disorder, schizotypal disorder, and acute transient psychotic disorders. One further challenge is creating valid and reliable nosological entities of disorder, warranting clinical intervention, which differentiate ‘healthy’ from ‘disordered’ populations.

Psychotic phenomena in the general population are relatively common,[2] may be very brief, and usually do not persist or warrant clinical intervention. As such, it has been proposed that psychotic phenomena exist more as dimensional constructs, as reflected in the recently revised DSM-V, rather than as binary (present/absent) diagnoses. Nonetheless, it remains both clinically and aetiologically important to be able to target appropriate treatment and prevention to groups whose symptomatology presents sufficient distress, disability, or disruption to impact their lives. Classification systems, such as ICD-10 and DSM-V, although not perfect, present evidence-based attempts to draw these nosological lines according to a set of agreed, standardized criteria. Notwithstanding the outstanding classificatory issues, there is at present a broad consensus that schizophrenia is a genetically complex disease, with variants and mutations in multiple genes and gene networks, as well as with a significant neurodevelopmental and environmental contribution to its phenotypic expression. The findings of epidemiological research provide a useful background for the interpretation of genetic, neurobiological, and social research, as well as aiding clinicians in making evidence-based diagnostic and treatment decisions.

In this chapter we survey a broad range of findings that jointly outline the composite epidemiological profile of schizophrenia and its spectrum. In the second section we outline the major historical milestones in the epidemiology of psychotic disorders. Next, in the third section, we review the main findings with respect to the incidence (new) and prevalence (total) burden of such disorders worldwide. In the fourth section we review the major risk factors which have been identified for psychotic disorders, and the strength of evidence to support these. We also discuss major public health issues surrounding, course, outcome, and mortality in

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

people who develop a psychotic disorder, before presenting our concluding remarks on the direction of psychiatric epidemiology in this field in the section entitled Future Prospects.

Historical 'Milestones' of Epidemiological Research into Psychotic Disorders

Measuring the burden—or disease frequency—of psychotic disorders in the population is a challenging issue in psychiatric epidemiology. Studies of incidence—the rate of new cases in a defined population over a defined period—require large samples, or relatively long time periods of observation, given the absolutely rarity of psychotic disorders (in England for example, the pooled incidence of all adult-onset (16–64 years) psychotic disorders has been placed at 31.7 new cases per 100,000 people per year).[3]

The most accurate method of estimating the true incidence of psychotic disorder in the population would be to identify all new cases wherever they may occur in the community. However, since it is impractical to contact and screen every person in a population, the gold standard for estimating true incidence rates typically involves establishing a case ascertainment procedure which monitors several informal or formal potential points of contact for psychosis. This may include primary and secondary healthcare providers, religious organizations, charitable and government welfare providers, and the police and judicial system. Because it is often argued that the severity of a first episode of psychosis (FEP) is sufficiently severe to warrant mental healthcare at some point—even when an untreated disorder may be longstanding—many incidence studies may restrict case ascertainment to those coming into contact with secondary mental healthcare services, which may lead to the estimation of 'treated' incidence rates which are assumed to sufficiently approximate the true underlying incidence of disorder in the population. The validity of this methodology is open to debate, and may lead to issues when inferring differences in treated incidence rates between groups of aetiological importance, if this methodology has introduced differential case ascertainment between the groups under study.

Prevalence studies—which estimate the total burden of psychotic disorder in a population at a given point, or over a given period, are typically ascertained via household surveys.[4,5,6] While such studies use sampling strategies which lead to the identification of representative samples for many psychiatric conditions, this methodology may lead to an underestimation of the prevalence of psychotic disorders,[7] since people with such conditions may be less likely to respond to household surveys as a function of paranoia or other related symptoms often inherent to the disorder.

The various case finding strategies employed in the early epidemiological studies of psychoses fall into three categories: (1) birth cohort studies; (2) surveys of whole communities; and (3) population sample surveys. *Birth*

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

cohort studies were first introduced by Klemperer,[8] who selected a random sample of 1000 individuals from the birth register of Munich but succeeded in tracing and examining only about 30% of them. This approach was used with greater success by Fremming,[9] who collected life history data on 92% of the 5500 persons born on the island of Bornholm during 1883–7. In Iceland, Helgason[10] compiled a cohort of all 5395 individuals born 1895–97 who had survived into adulthood and traced their life history and psychiatric data until 1957 from admission records and interviews. A further step was taken during the 1990s when this approach encompassed national, general population birth cohorts established for reasons other than psychiatric research, including the study of many physical and mental health outcomes over the life course.[11] Linked to means of identifying psychiatric outcomes, nested case control studies within these cohorts have illuminated questions of aetiology and mechanism, particularly in a developmental context.[12] *Surveys of whole communities* involving a census and personal interviewing of every adult person were pioneered by Brugger[13,14] in small rural towns in Thuringia and Bavaria. However, the major share of such studies took place in the Scandinavian countries, owing to their excellent population statistics.[15,16] A special variety of the comprehensive survey was the *prospective repeat survey*, of which the Lundby study in Sweden[17,18] and Böök's re-examinations of the entire population of a North Swedish genetic isolate[20,21] remain as the best examples. *Population sample surveys* involved the selection of random samples of individuals without regard to their health, and the collection of data on the mental morbidity of all of their first-degree relatives.[16,21,22] The most striking finding of all of these study designs was the relatively good agreement across studies between prevalence estimates, incidence rates, and morbid risk of schizophrenia—regardless of the ongoing arguments about its definition and diagnostic boundaries. Thus, in most population studies the point prevalence of schizophrenia was estimated within the range of 1.4–4.6 per 1000.[23] Incidence rates were reported within the range of 17–57 per 100,000 per year, and morbid risk for the general population between 0.36% and 1.87%. In addition, repeat surveys of the same population using very similar designs suggested the possibility of a real decrease of the morbid risk for schizophrenia during the 30 or more years separating the individual studies,[24] although other studies have found the rate of all non-affective psychoses may be relatively stable over time.[25]

The data on the frequency of schizophrenia in different communities are probably among the best documented evidence of early psychiatric epidemiology. However, their interpretation at the time was contentious. On one hand, the similarity of prevalence, incidence, and expectancy rates of schizophrenia in different populations was seen as evidence favouring a predominantly genetic (Mendelian) causation of the disorder. On the other hand, a hypothesis proposed by Böök,[20] but never properly tested, proposed that the operation of an environmental aetiological factor would be manifested in disproportionately elevated morbid risks for the siblings, parents, and children of schizophrenia patients,

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

particularly in settings characterized by higher than average incidence of schizophrenia and some sort of social upheaval.

Generally, past epidemiological research has demonstrated that psychotic disorders, including schizophrenia, are ubiquitous (no human group, society, or culture has been convincingly shown to be free of such disorders), although more recent literature has identified pronounced—and replicable—heterogeneity in risk,[26] between and within populations (see the next two sections). Furthermore, it has shown that the phenomenology and natural history of these disorders appear to be less uniform than current classifications and diagnostic concepts tend to assume. This provides evidence that many aspects of the enduring burden of psychotic disorders are the result of adverse social reactions to the phenomena of illness, rather than intrinsic characteristics of the disease process. This suggests that much of the disability associated with schizophrenia and related disorders can be contained, reduced, or even prevented.

The Current State of Neuropsychiatric Epidemiology of Psychotic Disorders

Incidence

The ubiquity of schizophrenia and other psychotic disorders worldwide should not be confused with uniformity in their distribution. In the early epidemiological evidence presented in the previous section, variation in the *incidence rate* of schizophrenia across studies was more than three-fold, implying that social or biological factors might lead to the exact rate at which psychotic disorders manifest in different populations. The identification of these features—whether genetic, social, or environmental—would also be important for understanding the aetiology of these disorders. Early epidemiological studies which focused on the micro-level geographical distribution of psychotic disorders across neighbourhoods within cities, observed strong social and spatial gradients in incidence, with cases over-represented from more socially deprived and socially fragmented or isolated areas.[27,28,29,30] During the latter half of the 20th century interest grew in comparing the global distribution, incidence, course, and outcome of schizophrenia and other psychotic disorders using a standardized methodology. Such advances were a critical exercise in benchmarking the occurrence and manifestation of psychotic disorders globally,[31,32,33] and in conducting multisite studies in different countries using a singular methodology, in an attempt to minimize biases which may have been introduced in comparing incidence rates from different studies, which used different case finding approaches, inclusion criteria, estimation of the population at-risk, and diagnostic instruments.

Following a successful pilot study in the 1960s, the WHO set out to conduct an even more ambitious international comparison of cross-cultural variation in incidence rates and course in the late 1970s, the WHO “10-country” study.[33] This study encompassed twelve centres in ten

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

countries, including both urban and rural settings, and developed and developing nations, under an umbrella methodology. Case finding was based on the gold standard for epidemiological research, and included:

(1) Defined geographical catchment areas from which cases and the population at-risk were estimated.
(2) Standardized inclusion criteria, including restrictions on age (15–54), minimum residency in the catchment (six months) and first contact with a 'helping agency' for suspected psychosis of recent onset (12 months).
(3) Defined case ascertainment period (two years).
(4) Exclusion of people presenting with psychotic disorders of organic origin.
(5) Standardized diagnostic assessment, assessed for reliability, using clinical information (obtained from the Present State Examination[34]) to produce comparable, that is, standardized diagnoses across settings via a computerized diagnostic algorithm known as CATEGO.
(6) Use of a 'leakage' protocol, to return to all participating agencies and any others to identify potentially missed cases during the initial screen.
(7) Training and inter-centre reliability estimates across all instruments used in the study.

Such was the rigour of the WHO ten-country study, that data quality assurance meant that only seven of the original twelve sites were deemed appropriate to provide incidence rate comparisons. The WHO ten-country study[33] found that incidence rates of narrowly-defined schizophrenia varied across these centres from 7 (Aarhus, Denmark) to 14 (Nottingham, UK) per 100,000 population at-risk, while a broader definition was associated with more variation, ranging from 16 (Honolulu, Hawaii, USA) to 35 (rural Chandigarh, India) per 100,000 population at-risk, respectively. Although these studies suggested a two-fold variation in rates globally, consistent with earlier studies,[23] findings of the WHO ten-country study were popularly misinterpreted as evidence of a uniform distribution of psychosis incidence worldwide. Inspection of incidence rates from the study, based on four diagnostic categories from the broadest to narrowest definitions of schizophrenia, actually revealed statistically significant ($p<0.001$) variation in incidence across all but the narrowest definition of schizophrenia (CATEGO: 'S+') for men, and similarly strong evidence for women in the two broadest CATEGO classes of psychotic disorder. Subsequently the earlier, erroneous interpretation of these findings have been challenged by carefully conducted systematic reviews which reveal substantial variation in the incidence of non-affective psychotic disorders between populations.[3,26,35]

The decade following the publication of the WHO findings almost completely eschewed further investigation into global variation in the incidence of psychotic disorders, and ushered in technological breakthroughs in the hunt for what some presumed would be a singular

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

genetic cause, which penetrated populations with such uniform regularity that it led some influential thinkers[36] to state that: 'The evidence points to the singular conclusion that, contrary to almost any other common condition, the incidence of schizophrenia is independent of the environment and a characteristic of human populations. Perhaps it is the human condition.'

This view was not, of course, held by all. Many suggested that the genetic architecture leading to psychosis would be as exquisitely complicated and heterogeneous,[37,38,39] as it has thus far proved to be.[40] Indeed, one common feature of the genetic and epidemiological landscape of psychotic disorders is the marked heterogeneity in risk at multiple levels of causation.

During the late 1990s and first decade of the 21st century important epidemiological findings built an evidence base which strongly suggested that the incidence of psychotic disorders was not equally distributed in the population (see section entitle Future Prospects for an overview). Of particular note, the Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) study[41,42,43] sought to estimate first contact incidence rates of psychotic disorder, in an ambitious study to provide definitive estimates of epidemiological risk, and investigate the neural, biological, and social correlates of excess risks experienced in some population groups, most notably amongst people of black Caribbean and black African ethnicity living in England.[44] The study used a similar case finding design to the WHO 10-country study to investigate variation in incidence in three settings in England over a two-year case ascertainment period: south-east London, Nottinghamshire, and Bristol (over the first nine months of this period). The authors found variation between[43] and within settings,[45] such that rates tended to be higher in more urban, socially fragmented, and densely populated regions of the catchment areas;[46] findings which could not be explained by differences in the age, sex, or ethnic composition of the population in those areas.

Other seminal epidemiological studies of schizophrenia have used longitudinal or cohort designs—the gold standard for observational epidemiology—to investigate the association between urban living and risk of disorder.[47,48] Unlike previous studies, which estimated psychosis incidence close to the time of presentation to healthcare services, these longitudinal studies—often utilizing routinely collected register-based data on the entire population of a nation—were able to investigate the association between schizophrenia risk in adulthood and urban birth[48] and upbringing.[47] These designs overcame some weaknesses of the more conventional 'first contact' designs above.[33,43] Notably, the longitudinal nature of these studies ensured that the exposure under investigation (urban living) occurred temporally before the outcome (schizophrenia) in these studies, all but excluding the possibility that any association between the two factors could be attributed to people with schizophrenia

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

moving into more urban settings as a result (i.e. consequence) of their disorder, known in epidemiology as reverse causation.

This process, also termed *social drift*, has long been thought to play a role in the unequal distribution of psychotic disorders in the population, since people who begin to develop psychotic symptoms eventually leading to disorder may also be more likely to become unemployed, drop out of school, or struggle to afford access to better quality housing. While there is some evidence that this process exists as an unwanted and even preventable consequence of psychosis onset,[49,50] the pioneering work by Lewis et al.[47] in Sweden and Mortensen et al.[48] in Denmark suggested that this type of social drift could not explain the longitudinal association between urban birth or upbringing and later risk of schizophrenia. Moreover, these study designs were also able to adjust for several potential confounders—alternative explanations—of the relationship between urban birth and upbringing and later psychosis risk, including family history of psychiatric disorder, family income, parental divorce, paternal age and even, in one study,[47] cannabis use; the relationship between urban living and future schizophrenia risk persisted.

More recently, in the first major international comparison of the incidence of psychotic disorders in the 40 years since the WHO ten-country study, the European Network of National Schizophrenia Networks Studying Gene-Environment Interactions (EU-GEI) study has reported over an eight-fold variation in the incidence of psychotic disorders across 17 centres in 6 countries, including the UK, France, Netherlands, Spain, Italy, and Brazil.[51] As in earlier first contact designs, the study employed a comprehensive approach to identifying all new cases of potential psychotic disorder presenting to mental health services in defined catchment areas. Although, unlike earlier first contact designs,[33,43] the study did not systematically include a leakage methodology, it extended previous knowledge by showing substantial international variation in incidence which could not be explained by age, sex, or ethnic differences between settings. Here, rates were substantially higher in three major northern European cities (London, Amsterdam, and Paris) than in southern European cities (Madrid, Barcelona, and Palermo) or rural catchment areas. Furthermore, the study investigated whether a range of putative risk factors measured at the ecological (i.e. setting) level were correlated with variation in incidence.

In univariable analyses, greater incidence across settings was predicted by higher levels of social isolation (percentage of people living alone), lower unemployment, and lower levels of home ownership, for which only the latter persisted in fully adjusted analyses (see Fig. **28.1**). These results raise the possibility that the level of socioeconomic instability or disadvantage, or other closely-correlated factors* in a population may predict the incidence of psychotic disorders, though further research is required to understand the causal implications of such associations (see the next section).

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

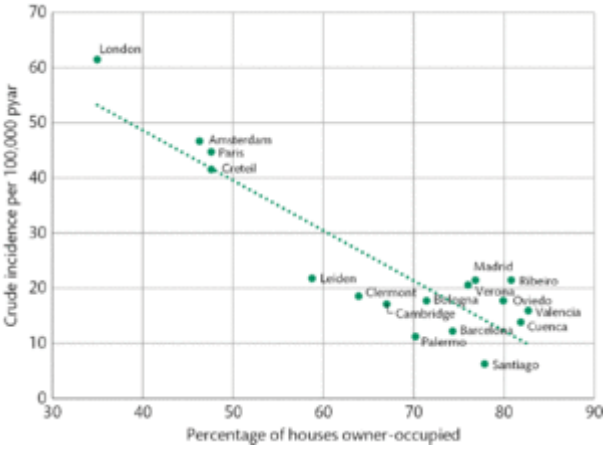

Fig. 28.1
Correlation between crude incidence of psychotic disorders and proportion of owner-occupied homes across 17 settings in the EU-GEI study.[51]

Legend: crude incidence rates are plotted per 100,000 person-years at risk. Percentage of home ownership is plotted along the x-axis. Correlation between crude incidence rates and % owner-occupied homes was -0.79.

Adapted from Jongsma H.E., Gayer-Anderson, C., Lasalvia, A. et al. Treated Incidence of Psychotic Disorders in the Multinational EU-GEI Study. *JAMA Psychiatry*, 75(1): 36–46. Copyright © 2017 Jongsma HE et al. Distributed under the terms of the Creative Commons Attribution 4.0 International (CC BY 4.0) https://creativecommons.org/licenses/by/4.0/

Several well-conducted systematic reviews have synthesized all the available evidence on variation in incidence rates of psychotic disorders between people and places published over the last 70 years.[3,26,35] All these reviews have concluded that the incidence of non-affective psychotic disorders vary along both these dimensions. In general, the affective psychoses (including bipolar disorder and severe depression with psychotic features) seem to show less variation with regard to place,[35] and have a somewhat different age-sex distribution to non-affective psychoses (see the next section), suggesting that while these disorders share some genetic[52] and environmental origins,[42] they may also differ in their exact aetiology.[53,54]

Prevalence

While epidemiological studies of incidence can provide rich information about variation of psychotic disorders, and even clues as to their aetiology, they typically rely on first-contact or register-based designs to ascertain caseloads. Thus, most such studies, even those that work closely with a range of help-seeking agencies to identify cases missed by

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

initial screening procedures, formally provide estimates of the *treated* incidence of psychotic disorder. Whether this rate is close to the true rate of disorder in the underlying population will depend both on the severity of the illness (with more severe illnesses more likely to come into contact with care services) and the design of the case ascertainment phase of the study. Because the absolute incidence of psychotic disorders is typically low (placed at around 31.7 new case per 100,000 in a review of English rates published between 1950–2009[3]) it is prohibitively expensive to design truly population-based surveys (e.g. via household surveys and screening) to establish the true, population-based incidence of psychotic disorders. Here, however, surveys to establish the prevalence of psychotic disorders in the population are more feasible, though not without challenges. Prevalence—the proportion of people in a given population over a given time period with a new or existing occurrence of disorder—is an essential measure of establishing overall psychiatric morbidity between and within populations. Prevalence is typically estimated at a given point in time (*point prevalence*), over a given period (i.e. *period prevalence;* when over a year typically denoted as *annual prevalence*) or over the entire life course (*lifetime prevalence*).

Several major studies of the prevalence of psychotic and other psychiatric disorders have been made. Amongst these, two in the USA, the Epidemiological Catchment Area (ECA) study and the National Comorbidity Surveys (NCS) have provided estimates of the lifetime and period prevalence of broadly defined schizophrenia. The ECA study, based on a representative sample of over 18,000 adults living in private households or institutionalized settings in five US cities (New Haven, Baltimore, St Louis, Durham, and Los Angeles), used the Diagnostic Interview Schedule (DIS) to estimate the prevalence of major psychiatric disorders according to DSM-III criteria at the beginning of the 1980s.[55] Lifetime prevalence estimates of schizophrenia spectrum disorders were published for three of these sites (New Haven, Baltimore, and St Louis),[56] which were found to vary from 1.1% in St Louis (Missouri) to 2.0% in New Haven (Connecticut).

The lifetime prevalence of non-affective psychosis in the first NCS study, based on a representative sample of over 8000 Americans aged 15–54 living in non-institutionalized settings in the 48 contiguous states of the USA, was placed at 2.2%, with lifetime prevalence of schizophrenia estimated to be 1.3%.[5] These prevalence estimates, which used a similar diagnostic algorithm to the ECA study, were somewhat higher than estimates based on clinical diagnoses alone (0.7% and 0.2%, respectively, for non-affective psychoses and schizophrenia), and highlight the important issue surrounding methods of assessment used in epidemiological studies. Kendler and colleagues[5] went on to show that clinician-rated diagnoses tended to agree poorly with computerized diagnoses based on the DIS in the NCS studies.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

Concerned by the high sensitivity and low specificity of the DIS instrument used in the earlier ECA and NCS studies,[55,57] the NCS-R replication study used tighter screening criteria in the WHO's Composite International Diagnostic Interview (CIDI 3.0) in an attempt to minimize the introduction of false positive cases to estimate prevalence.[7] In a representative sample of 9000 respondents aged 18 and older, the lifetime prevalence of non-affective disorders using the CIDI was much smaller, estimated as 0.5%.[7] This variation highlights the importance of using carefully designed epidemiological studies which use well-validated screening and follow-up assessments to make psychiatric (particularly, here, psychotic) diagnoses.

In a systematic review of the available literature, Saha et al.[58] observed that the median lifetime prevalence of schizophrenia, identified from 29 unique estimates, was placed at 0.4% (10–90th percentile: 0.2–1.2%), but they reported that better quality studies tended to find higher estimates. Moreover, until recently, the scientific community has tended to prioritize understanding of the lifetime prevalence of schizophrenia, or other related non-affective psychotic disorders, over the affective psychosis. In both the ECA and NCS (and NCS-R) studies the lifetime prevalence of manic episodes, for example, has been placed at between 0.6% (Baltimore, ECA,[56]) and 1.6%.[57]

In addition to the aforementioned design issues which may have a bearing on prevalence estimates, other issues may also affect variation in lifetime prevalence, as observed, including the age, sex, and ethnic composition of the underlying population at risk, level of urbanization or other factors such as deprivation, which may affect the burden of disorder in different populations. One further substantive problem inherent in many household survey designs is response or ascertainment bias. This problem is particularly pertinent in the estimation of the prevalence of psychotic disorders, whereby people with paranoid beliefs or suspicious thoughts may be less likely to respond to survey invitations. This could lead to the substantial underestimation of the prevalence of psychotic disorders.

While analytical methods to weight estimates by survey non-response exist, these are chiefly to recover representative prevalence estimates and confidence intervals by adjusting the distribution of parameters of interest (say, age or sex) in the sample, based on known values of these distributions in the target population (i.e. *post-stratification*). Such methods do not necessarily resolve the issue of whether non-responders to a survey were more likely to have the outcome of interest, precisely because the value of this estimate in the target population is unknown, and the object of interest to be estimated.

One novel methodology to partially overcome these issues utilized a hybrid household survey design with linkage to national population registers in Finland.[59] Thus, in this study of over 8000 participants, of whom 93% took part, people who screened positive for potential

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

psychosis were invited for re-interview to confirm the presence of diagnosis via the CIDI. For those who refused or could not be contacted, the study had permission to examine evidence of a history of a diagnosis for psychotic disorder in the Finnish hospital registers. Using this method, the lifetime prevalence of any psychotic disorder, including bipolar disorders, rose from 3.06% to 3.48%, with total figures for all non-affective psychoses and schizophrenia only, placed at 1.44% and 0.87%, respectively. This design is likely to provide closer insights into the true prevalence of psychotic disorders, albeit in a particular context (i.e. Finland).

Alternatively, we may look to other epidemiological designs, such as cohort studies, to estimate the lifetime (and other) morbid risk of psychotic disorders. *Lifetime prevalence* estimates the proportion of all people with the disorder of interest at a given point in time. Necessarily, its estimate depends on survival, since people who have died prior to this point will not contribute to lifetime prevalence.

In contrast, *morbid risk* (sometimes referred to as *disease expectancy*) estimates the proportion of the population who will experience the disorder of interest at some point in their lifetime. In this respect, morbid risk is similar to *lifetime risk*, a measure of *cumulative incidence*, which estimates the proportion of people alive and disease free at a certain point in time (typically, birth) who will subsequently experience the disorder over their lifetime. Morbid risks of broadly-defined schizophrenia in the WHO ten-country study[33] for the population aged 15–54 years ranged from 0.5% in Honolulu (Hawaii, USA) to 1.72% in rural Chandigarh (India). Saha and colleagues[58] observed similar variation in their review of the international literature. They reported a median morbid risk of 0.72% for schizophrenia (10–90th percentile: 0.31–2.71%), based on 27 estimates.

The Impact of Epidemiological Research

Aetiology

Age and sex

While schizophrenia onset can start at almost any age,72 over 70% of cases will occur between early adolescence and before 35 years old.[43,60] This finding has had a substantial impact on the provision of EIP services in several countries.[61] Although childhood-onset schizophrenia (onset before age 12) and late-onset schizophrenia (onset after age 50) have lower incidences, they appear to present with similar clinical features and risk factors that characterize schizophrenia arising in young adults;[62,63] nonetheless, psychotic disorganization symptoms may be more common in early onset cases while systematized paranoid delusions predominate in late onset cases.[64]

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

It remains unclear whether this robust age-at-onset distribution comprises variation determined by random genetic, developmental, or environmental effects unique to the individual,[5] or whether the apparent continuum masks underlying discontinuities. At younger ages, typically before 35 years old, rates of schizophrenia and other non-affective psychoses are twice as common in men than women, although the peak in risk for both sexes probably occurs before 20 years old.[60] Nonetheless, attenuated or even inverted sex effects, that is, a female preponderance of cases in younger age groups, has been consistently reported from India[65,66] and China,[67] and these findings have received little recent attention.

Generally, in the mid-forties incidence rates for men and women become more similar, or even higher amongst women. This later peak for women, robustly demonstrated in a meta-analytic approach[68] coincides with the menopausal epoch, which may be associated with biopsychosocial changes, including a possible cessation of a neuroprotective role of oestrogen around this time.[69,70] In very late onset psychosis (after age 60 years old) cohort studies suggest a higher cumulated lifetime risk in women, compared to men.[71,72]

Genetic factors

The genetic risk for psychotic disorders is complex and, with the exception of rare syndromes such as 22q11 deletion syndrome,[73,74,75] involves a large number of genes each carrying a small effect size.[76,77,78] Schizophrenia, for instance, is highly heritable, with 50% monozygotic twin concordance.[79] Recent advances in genetic research, particularly the increased availability and decreased cost of carrying out GWASs, mean that understanding of genetics of psychotic disorders has improved substantially.[80] Yet, heritability is considered complex and non-Mendelian.[81] There is also considerable overlap in genetic risk between schizophrenia and bipolar I[76,82] and other psychiatric disorders.[83]

The landmark meta-analysis of GWASs in schizophrenia identified 108 independently associated loci,[40] which each explained a very small part of the genetic variance. With larger samples becoming available for GWAS the number of loci identified will increase.[84] The largest meta-analysis of bipolar-I GWASs has established 56 independently associated loci across five regions,[85] and further study estimates there might be as many as 105 loci,[86] but these have not yet been discovered (largely, due to the large sample sizes needed for such discoveries).

A common way of combining these genetic loci with small effect sizes and improving predictive ability is via so-called polygenic risk scores (PRSs; a weighted sum of genetic variance of disease risk). The PRS for schizophrenia is derived from the aforementioned meta-analysis of GWASs[40] and contains genes for known neurobiological mechanisms involved in psychosis, such as dopamine-2 receptors,[87] genes involved in

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

glutamatergic neurotransmission and synaptic plasticity,[88] and genes involved in immune function—also implicated in psychosis.[89]

Nonetheless, PRS is no panacea: current PRS for schizophrenia is thought to explain only about 8% of the total variance in genetic predisposition to schizophrenia, with the remainder most likely explained by, as of yet, undiscovered genetic loci, rare variants, and gene-gene and gene-environment interactions.[77] It is also susceptible to population stratification effects whereby allele frequency differences between cases and controls are due to systematic genetic ancestry differences and spurious disease correlations,[90] although it is possible to control for such effects to an extent. PRS for schizophrenia scores are beginning to be used in population-based epidemiological studies, in at least three ways. First, and most classically, it has been possible to examine whether greater PRS for schizophrenia was associated with psychotic experiences and disorders in population-based samples. For example, Vassos and colleagues[80] suggested that PRS for schizophrenia had good discriminant validity to distinguish between first episode psychosis cases and controls of European ancestry, and to predict diagnoses of schizophrenia amongst the control group. PRS scores currently lack validity in people of non-European ancestry. Curiously, data from a longitudinal, population-based birth cohort (the Avon Longitudinal Study of Parents and Children (ALSPAC) study) found that PRS scores were not predictive of psychotic experiences in adolescence, although they did predict negative symptoms associated with schizophrenia, as well as anxiety.[91]

This leads to the second potential use of PRS scores. In the same study, PRS for schizophrenia significantly predicted depressive symptoms, thus providing confirmation of the likely polygenic basis of generalized psychiatric morbidity. Genetic and family risk of a range of neurodevelopmental and psychiatric disorders are known to predict the full spectrum of mental health outcomes,[52,92,93] and PRS for schizophrenia are highly predictive of, and share overlap with, genes for bipolar disorder.[94] Schizophrenia PRS has also been associated with lower cognitive ability, though it appears to explain less of the genetic variance here than for schizophrenia.[95]

Finally, and perhaps most interestingly, PRS may allow us to test causal inference about putative relationships between environmental risk factors and psychiatric outcomes, including schizophrenia. For example, evidence that PRS for schizophrenia are associated with known risk factors for schizophrenia such as cannabis use, or urban living, may suggest that genetic factors are implicated in both the development of psychosis, and independently, the choice to smoke cannabis or live in a more urban environment. Such gene-environment correlation could imply that unmeasured genetic confounders are the causal drivers of the association between factors previously presumed to be solely environmental and subsequent schizophrenia risk. While this is still an emerging literature, some, though not all, early examples support the possibility that higher PRS for schizophrenia predicts exposure to both cannabis use and urban

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

living.[95,96] Larger studies, free of selection biases, with even better characterized genetic and environmental measures are still required to elucidate the main, interactive, and potentially mediating effects of these variables on schizophrenia risk. This includes the PRS for any disorder, which is also liable to change as studies become larger and technologically improved.[84] Recent evidence suggests that even when controlling for PRS for schizophrenia, associations between urban birth and adolescent psychotic experiences in the general population remain evident.*

Substance use

Concern about the harmful effects of un-prescribed drugs on the mental state has a long history. Some substances, such as amphetamine, can lead to a psychotic state in virtually all users in a dose-dependent manner as part of intoxication. Others, such as alcohol, have aspects of the schizophrenia syndrome as part of relatively rare states associated with chronic, heavy use. Much focus has been placed on the role of cannabis (marijuana, hashish, etc.) that has, for at least a century, attracted particular attention.

It is clear that use of alcohol and cannabis alongside other drugs is common in people with schizophrenia. For instance, the Australian Survey of High Impact Psychosis[97] collected nationally representative data on 1825 people with psychotic illness, mainly schizophrenia. Alcohol and substance abuse or dependence were common, with lifetime prevalence of 51% and 55%, respectively.[97] It is accepted that drug use, particularly cannabis, can complicate the management of schizophrenia, but whether or not it can cause the disorder in those otherwise at the same risk as the healthy population has been contentious for at least a century, with the Indian Hemp Drugs Commission Report, completed in 1894, concluding that the evidence was nuanced.[98]

As in many investigations of personal risk factors and schizophrenia, the question of cause and effect is hard to answer with surveys and case control designs, some of which indicate that people with schizophrenia may stop using the drug around onset of psychosis.[99,100] Furthermore, the question as to whether cannabis can lead to schizophrenia remotely, after the acute effects of intoxication have settled, is complicated by the recognition of a dependence syndrome, particularly for preparations of cannabis containing higher levels of pro- versus anti-psychotic components that are increasingly available.[101]

Recent epidemiological data, again relying on birth cohort designs, indicates that there is an elevated risk associated with cannabis consumption, particularly in the early teenage years. Andreasson et al.[102] contributed a seminal study of military conscripts in Sweden and demonstrated an increased risk of schizophrenia in those who reported cannabis use by age 18 years of age; a systematic review including further cohort studies confirmed a modestly increased increase in risk.[103]

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

Nevertheless, the public health implications remain unclear.[104] The prevalence of use and potency of cannabis is increasing in many countries, while it remains a moot point as to whether incidence of schizophrenia is increasing, the *sine qua non* of a causal association between the two. While an increasing number of US states, Canada, and Uruguay are legalizing cannabis use, with a variety of preparations and potencies available, the debate on causality[105,106] will continue. It remains crucial that relevant epidemiological data continue to be scrupulously collected while natural experiments are underway.

Neurodevelopmental issues and milestones

Psychotic disorders are thought to have important neurodevelopmental factors in their origin,[107] and risk factors for development of psychosis can be identified *in utero*. Severe maternal malnutrition[108] and prenatal exposure to infection increase risk of later disorder.[109] Obstetric complications and other perinatal hazards such as complications in pregnancy, abnormal foetal growth and complications during labour,[119,111] markers of disordered motor development and neurodevelopment in childhood,[112,113,114] and cognitive problems predating the onset of disorder[115] have also been associated with increased risk of disorder. High educational attainment in childhood is considered protective against the development of psychosis,[116,117] and study authors have suggested this might link to neurodevelopmental origins of disorder and the existence of a ‘cognitive reserve’ which increases available coping strategies.[116] These developmental risk factors for schizophrenia appear to act in a dose-response manner, arguing against a specific developmental subtype of schizophrenia.

Childhood trauma

Childhood adversities are also strongly associated with later psychosis risk,[118,119,120] including emotional, psychological abuse, physical and sexual abuse, neglect, peer victimization, and bullying.[120] A longitudinal study (n<1,000 adolescents) suggested a bidirectional relation between childhood trauma and psychotic experiences in adolescence: trauma both predicted these experiences and later trauma was a consequence of them. After accounting for this bidirectionality, trauma was still strongly predictive of psychotic experiences in a dose-response relationship, suggesting a causal role.[121] Trauma characterized by intention to harm (maltreatment, bullying) was particularly associated with increased psychotic symptoms in a longitudinal twin study,[121] and people experiencing more than one type of trauma (poly-victimization) are particularly at risk of adverse outcomes.[121,122] This poly-victimization is common, as is re-victimization of maltreated children in adulthood.[123]

Research into childhood maltreatment is often done by either prospective informant-reports or retrospective self-reports, and neither of these are perfect. Informant reports may lead to underestimation of the prevalence of childhood maltreatment, and self-report might be subject to memory or

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

recall bias (cases might be more likely to remember maltreatment than controls). Recent research from the E-Risk study (the longitudinal twin study mentioned above) suggests that these measure largely non-overlapping populations (people who say they experienced childhood maltreatment are not considered to be maltreated by key informants) and those who self-report maltreatment appear most at risk of adverse mental health outcomes.[124]

Inflammation

An emerging body of evidence is accumulating regarding the association between inflammation and psychiatric illness including schizophrenia. Early pointers to this association, that may have considerable therapeutic impact, included the increased risk of schizophrenia following pandemic infections such as the global 1918 influenza outbreak.[125] While there is now clear evidence that a pro-inflammatory state exists during acute episodes of depression and psychosis, and that conventional psychiatric treatments normalize cytokine levels, circulating protein markers of infection,[126] the direction of causality in this association was not, until recently, clear.

Khandaker and colleagues[89] demonstrated that higher childhood inflammatory markers (interleukin 6 and C-reactive protein) were associated with depression, psychotic experiences, and psychotic disorder in young adulthood,[89,127] indicating a potential causal or pathogenic role for inflammation; this was later supported through a Mendelian randomization approach.[128] In addition to illuminating the mechanism through which causal factors may operate, this may illuminate the sometimes lethal comorbidity between schizophrenia cardiovascular disease and metabolic disorders.[89] There is also interest in the adaptive immune response and schizophrenia,[129] with auto-antibodies to neuronal surface antigens (largely neurotransmitter receptors) being demonstrated in 5–10% of people with first episode psychosis.[130] Randomized controlled trials of immune therapy for this group will establish whether or not this represents stratification of schizophrenia based on a cause, and echoes robust and long-standing epidemiological evidence of associations between the disorder and a variety of auto-immune disorders.[131]

Urban living

Neighbourhood-level risk factors have long been associated with the incidence of psychotic disorders, and appear to hold some specificity to non-affective psychotic disorders.[35] Limited evidence of a role in the affective psychosis[132] points towards possible mechanisms which are specific to non-affective psychotic disorders, such as the possibility that cognitive impairments or early developmental delays (see above) interact with exposure to neighbourhood social adversities. This research tenet started in the early 20th century, with Faris and Dunham’s seminal work in Chicago.[133] They established that neighbourhoods with increased

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

residential mobility and percentage of African-Americans and those of no fixed abode faced an increased incidence of psychosis.[133]

This work was later replicated in Bristol,[27] Nottingham,[30] and Mannheim in Germany,[134] amongst others. More recent studies have used advances in multilevel modelling[135] and spatial epidemiology[45,136] to show that environmental-level variance in non-affective psychosis risk remains even after accounting for compositional characteristics of the people within those areas, such as lower socioeconomic status, minority position (see below), or younger age. While neighbourhoods typically explain less than 10% of the variance in schizophrenia and other psychoses,[135] this effect seems to be relatively robust.

Most such multilevel studies have focused on the role of socio-environmental factors, finding support for exposures such as population density,[47,48,137] deprivation,[136,138] inequality,[136,139] low social cohesion,[140] crime rates,[140] social fragmentation,[142,143] and ethnic density: the size of a particular ethnic group in proportion to the total population in a specified area.[144] A low ethnic density is hypothesized to be associated with increased incidence of psychotic disorders in ethnic minorities.[145,146] It is thought that a high ethnic density is associated with strong support networks, alleviating the effects of discrimination.[146] Results of recent epidemiological investigations are mixed: some studies established a relationship,[145,147,148] but others showed a more nuanced picture of differential effects of ethnic density by ethnic group.[136] Non-social environmental risk factors for psychosis have received less attention to date, but factors such as air pollution, noise, and vitamin D deficiencies, to which urban populations may be more likely to be exposed ,have also been proposed as potential risk factors for psychosis; little evidence currently supports these findings,[149] but this may be due to difficulties in reliably and validly measuring such exposures.

Interestingly, these patterns of association are beginning to be replicated in both non-clinical samples of adolescent psychotic symptoms,[150,151,152] and in social neuroscience,[153,154,155] suggesting that exposure to adverse environmental factors over the early life course may lead to tangible changes in key brain regions known to be associated with the continuum of risk of psychotic experiences. Nonetheless, many, though not all,[47,48,132] of epidemiological studies investigating neighbourhood risk factors have been cross-sectional, meaning any observed association could at least partially be due to downward social drift whereby individuals in the prodromal stages of disorder move to neighbourhoods with higher levels of the exposure of interest. Prospectively collected longitudinal studies have shown that urban birth and upbringing [47,48] are associated with future risk of schizophrenia, meaning that the association cannot be fully attributable to social drift of individuals in the early stages of psychosis. Nonetheless, recent advances in the availability of genetic data (see above) and causal inference techniques in epidemiology[156] have suggested that some risk factors, including urban upbringing, might be subject to a degree of gene-environment selection. Here, individuals with

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

a higher genetic risk of schizophrenia might be more likely to move to more densely populated areas,[156,157] or alternatively might be more likely to develop a substance use issues[158] which precipitate a downward social cascade.

Moreover, recent research has shone further light onto the role of urban factors in the onset of psychotic disorders across the world. In the 17-centre EU-GEI incidence study,[51] an eight-fold variation in rates across Europe and Brazil was not simply explained by population density; instead urban-rural differences were found in northern European countries (the UK, Netherlands) but not their southern counterparts (Spain, Italy). Instead, the strongest predictor of inter-centre variation in rates was owner-occupancy, a strong marker of social stability, not urbanicity per se. This finding accords with recent research in East Anglia[137] which shows that higher rates of psychosis exist in more deprived and fragmented rural populations, suggesting urbanicity alone may be one of a set of socio-environmental markers which alter incidence.

The importance of local context in driving environmental associations with psychosis risk may also be borne out in emerging evidence from LMICs. For example, in a recent large meta-analysis of World Health Survey data from 42 LMIC settings,[159] no overall effect of urban-rural living was found on the prevalence of psychotic experiences or disorder, though high between-country heterogeneity highlights the importance of measuring specific contextual factors which may drive rates in some, but not all urban environments. In a population survey of Chinese men, urban birth was a stronger predictor of psychotic symptoms in adulthood than current urban residency.[160]

Migration and ethnicity

One of the most consistent epidemiological findings in the epidemiology of psychotic disorders is the excess risk experienced by migrants and their descendants. This finding is long-established,[161] and well replicated.[162,163] Excess rates in some migrant and minority group (such as those of black Caribbean and African origin in the UK[3,164] and elsewhere[165,166,167]) may be up to five times greater than in the majority white population, making this one of the greatest structural and cultural injustices in public mental health. There are no reasons to assume this increased incidence is an artefact of demographics, as incidence is still higher after adjusting for age and sex[42] and socio-economic status.[46,168] Moreover, rates do not appear to be elevated in the countries of origin from which migrant groups originated,[161,169,170,171] though further research in more diverse settings is needed on this topic, or due to selective emigration of people predisposed to psychosis.[172,173]

These findings argue strongly against a genetic explanation for excess rates in many black and ethnic minority (BME) groups. Furthermore, whilst it appears to be true that there are, for instance, ethnic differences in pathways to care[174,175] and worse treatment when accessing mental

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

health services,[175,176,177,178,179,180] there is little evidence that there are systemic racist diagnostic biases (at least, not concerning black Caribbeans in the UK).[181,182]

Timing of exposure to such effects may be important, although it is not currently clear at which age migration conveys the greatest risk, but childhood appears to be a key time. A Dutch study showed that an earlier age of migration (0–4 years) is associated with the highest risk,[183] whereas a Danish study demonstrated that in immigrants from the developed world, those who migrated aged 10–14 appeared to be at a similarly high risk,[184] and findings from East Anglia indicated that those who migrated during childhood (5–12 years) carried the highest risk.[168] Interestingly, internal migration—measured via greater residential instability in childhood and adolescence also has independent effects on later psychosis risk,[185,186] though this may also extend to other psychiatric disorders.[189]

Observations that the relative increase in psychosis risk is highly correlated with visible minority status[163] and perceived levels of discrimination[188] have led authors to investigate whether exposure to a range of pre-migratory and post-migratory social adversities increases psychosis risk amongst migrants and their descendants. Refugees are likely to be at increased risk of psychosis compared with the general migrant population,[189,190] and this is thought to be due to a combination of increased exposure to pre-migratory stressors and a more traumatic migration experience (although post-migratory factors may also play a role).[191] Post-migratory stressors may also play a role.

Several studies have found support for an ethnic density effect in psychosis,[192,193] whereby BME risk is conditional upon the proportion of people from one’s ethnic group living in the neighbourhood. Although this finding could be explained by differential help-seeking and case ascertainment, one possibility is that greater social support from people with more similar social, economic and cultural backgrounds, or immigrant experiences, buffers against psychosis risk. Interestingly, in healthy volunteers, recent social neuroscience has shown that ethnic density results in lower activation of amygdala activity during stress responses.[155] Migrant and minority groups may face exposure to a range of increased social stressors relevant to psychosis risk,[194] and more longitudinal research is required to understand the pathways through which exposure to social adversities over the life course may disproportionately increase psychosis risk for these groups.

Course and outcome

While schizophrenia is largely defined on the basis of abnormal mental phenomena, disability in terms of restricted everyday activities and social functioning may be driven as much by cognitive dysfunction and so-called negative features as it is by the key diagnostic components of the syndrome. Studies investigating the long-term course and outcome of

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

psychotic disorders for many years focused on prevalent cases with a diagnosis of schizophrenia or non-affective psychosis[195] where the degree of chronicity required to merit an operational diagnosis of schizophrenia heavily conditioned the outcomes achieved. This approach systematically excludes those developing a psychotic syndrome but who recover promptly and may bias our view towards a poorer outcome, skewing our understanding of the true long-term prognosis of these.[196,197] We may have been too pessimistic about outcome and so give an overly gloomy answer to questions family members ask about outcome when their relative first seeks help.[198]

The WHO ten-country study follow-up in people 12–26 years after diagnosis[197] demonstrated good symptomatic outcomes in over half of those with schizophrenia and other psychotic disorders. Indeed, the report was titled 'Recovery From Schizophrenia: An International Perspective'. Kraepelin's assertion of the deteriorating course of schizophrenia as its hallmark appears inconsistent with such data, and a likely consequence of the individuals with chronic conditions on which his descriptions relied;[199] modern models of course and outcome need to incorporate notions of remission and recovery.[200]

As the results of the WHO study show, the answer to the question as to what might happen after onset of schizophrenia or a first episode of any psychosis is anything, from complete recovery to a relapsing and remitting or even chronic course of psychosis over many years. Unfortunately, while *symptomatic* recovery is possible for some, the outcomes of schizophrenia in terms of the *social* and *functional* spheres are discrepant and often poor. For instance, Morgan et al.[201] followed up over ten years the AESOP study described above in terms of incidence. Symptomatic outcome was generally good. Three-quarters of participants experienced at least one period of sustained remission a decade after onset; at follow-up 141 (46%) had been symptom free for at least two years. In contrast, most (72%) had been unemployed for more than 75% of the follow-up period. This emphasizes the importance of considering a broad range of outcomes, and the factors that may determine the facets of outcome that are of importance in everyday life that may not see symptoms of psychosis as core.

Mortality

Although the effects of schizophrenia and other psychotic disorders on premature mortality have been known for over 175 years,[202] it is only relatively recently that this issue has returned to public prominence. Farr[202] demonstrated a six-fold excess of deaths among asylum inmates, compared with the general population of England and Wales. He concluded—obliquely—that a lack of medical supervision and treatment was to blame. Nearly two centuries later, studies still provide compelling evidence for excess mortality associated with psychosis, culminating in reduced life expectancy estimates for people with serious mental illness of between 10–25 years.[203,204,205] In a systematic review of 37 studies

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

emanating from 25 different countries, Saha et al.[58] calculated a median standardized mortality ratio (SMR) of 2.58 for all-cause mortality in schizophrenia patients. Using the UK's General Practice Research Database, Osborn et al.[206] estimated a hazard ratio (HR) of 3.22 for increased risk of death from coronary heart disease and stroke in people with severe mental illness that could not be wholly explained by antipsychotic medication, smoking, or social deprivation. Unnatural causes apart, there is a nearly five-fold increase (SMR 4.68) of 'avoidable' natural deaths, due to hypertension, cerebrovascular disease, and smoking-related disease.[207] The phenomenon of 'sudden unexplained death' among schizophrenic patients[208] may also be related to cardiotoxic effects of antipsychotic drugs, especially in patients receiving more than one antipsychotic concurrently.[203,209,210]

Unnatural causes, including suicide (particularly in the early phase of illness),[211] accidents, and homicide (particularly high risk in men with schizophrenia), accounted for 25% of all deaths of people with psychoses over a 20-year period, according to a study based on the Danish Psychiatric Case Register.[212] In recent decades, the suicide rate in schizophrenia patients has become at least equal to, or possibly higher, than the suicide rate in major depression (SMR 9.60 in males, 6.80 in females).[213] Data from Scotland[214] and Australia[215] point to an increasing suicide rate in schizophrenia patients, mostly within the first year after discharge from hospital. Several risk factors have been suggested as relatively specific to suicide in schizophrenia suicide: being young and male, the experience of a disabling mental illness with multiple relapses and remissions, awareness of the deteriorating course of the condition, comorbid substance use, and loss of faith in treatment.[211,216,217] These recent findings have led to the notion of a persistent 'mortality gap' between people with schizophrenia and the general population,[218] leading to calls for parity of esteem in the treatment for (and research into) mental as compared with physical illness.[219]

Future Prospects

The epidemiology of schizophrenia and other psychotic disorders has a set of distinct features which provided important clues for aetiology and information for the provision, care, treatment, and intervention for people at risk of, or who experience first episode psychosis. As we have highlighted in this chapter, the causes of psychosis are likely to be multifaceted and complex, probably invoking multiple genetic, biological, and environmental risk factors and pathways which may lead to the onset of alterations in perception, beliefs, and cognitive schema which give rise to psychotic symptoms and in some cases, the persistence of disorder.

The most recent epidemiological data reveals a particularly challenging landscape, whereby established environmental risk factors for psychosis, including urban living and cannabis use, may be under a degree of genetic control.[156,220] This has not been universally replicated,[221] and such environmental factors appear to have independent effects on

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

psychosis risk.[96,222] Many of these risk factors for schizophrenia and other psychotic disorders appear to begin early in life, consistent with current socio-neurodevelopmental theories of disorder.[107,223,224] Life course epidemiological approaches have been critical in elucidating some of these factors.[48,112,225] However, psychiatric epidemiology needs to adapt to both the realistic complexity of neuropsychiatric disorders and the availability of modern causal inference methods in epidemiology[226,227] if progress in the identification of the risk factors and pathways which lead to psychosis are to be fully understood and ameliorated at a population level.

Part of the solution to these problems will be the development of sufficiently powered, modern birth cohorts with well-characterized, reliable, and validated psychiatric outcomes over the life course. Such cohorts would need to collect information on a range of genetic, biological, and environmental measures over early childhood and adolescence—the period at which most mental health disorders, including psychosis, emerge—and acknowledge the multitude of individual, familial, school-based, and societal and cultural layers through which risk and protective factors may influence mental health.[228,229,230] Such samples may need to be huge in order to have sufficient statistical power to investigate interactive effects and, to constrain this, they will need to draw on as well as contribute to basic science investigations of causal heterogeneity. These goals are ambitious, but no more so than the large investments made in psychiatric genetics and neuroscience over the past three decades that must now incorporate environmental measures. Integrating a population-based understanding of psychotic disorders with these two domains will yield fruitful insights into their aetiology.

References

1. Bleuler E. *Dementia Praecox Oder Gruppe Der Schizophrenien*. Tubingen: Diskord, 1911.

2. Van Os J, Reininghaus U. Psychosis as a transdiagnostic and extended phenotype in the general population. *World Psychiatry*. 2016; 15: 118–24.

3. Kirkbride JB, Errazuriz A, Croudace TJ, et al. Incidence of schizophrenia and other psychoses in England, 1950–2009: A systematic review and meta-analyses. *PLOS One*. 2012; 7: e31660.

4. Regier DA, Boyd JH, Burke Jr JD, et al. One-month prevalence of mental disorders in the United States. Based on five Epidemiologic Catchment Area sites. *Arch Gen Psychiatry*. 1988; 45: 977–86.

5. Kendler KS, Gallagher TJ, Abelson JM, et al. Lifetime prevalence, demographic risk factors, and diagnostic validity of nonaffective psychosis as assessed in a US community sample. The National Comorbidity Survey. *Arch Gen Psychiatry*. 1996; 53: 1022–31.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

6. McManus S, Bebbington PE, Jenkins R, et al. *Mental Health and Wellbeing in England: Adult Psychiatric Morbidity Survey 2014 Executive Summary*. Leeds: NHS Digital, 2016.

7. Kessler RC, Birnbaum H, Demler O, et al. The prevalence and correlates of nonaffective psychosis in the national comorbidity survey replication (NCS-R). *Biol Psychiatry*. 2005; 58: 668–76.

8. Klemperer J. Zur Belastungsstatistik der Durchschnittsbevölkerung: Psychosenhäufigkeit unter 1000 stichprobenmäßig aus den Geburtsregistern der Stadt München (Jahrgang 1881–1890) ausgelesenen Probanden. *Zeitschrift für die gesamte Neurol und Psychiatr*. 1933; 146: 277–316.

9. Fremming K. *Sygdomsrisikoen for Sindslidelser Og Andre Sjaelelige Abnormtilstande in Den Danske Gennemsnitsbefolkning*. London: Munksgaard, 1947.

10. Helgason T. Epidemiology of mental disorders in Iceland. A psychiatric and demographic investigation of 5395 Icelanders. *Acta Psychiatr Scand*. 1964; 40: (Suppl 173): 1+.

11. Mann A. The evolving face of psychiatric epidemiology. *Br J Psychiatry*. 1997; 171: 314–18.

12. Colman I, Jones PB. Birth cohort studies in psychiatry: beginning at the beginning. *Psychol Med*. 2004; 34: 1375–83.

13. Brugger C. Versuch einer Geisteskrankenzahlung in Turingen. *J Neurol Psychiatry*. 1931; 133: 252–390.

14. Brugger C. Psychiatrische Ergebnisse einer medizinischen, anthropologischen und soziologischen Bevolkerungsuntersuchung. *Zschr Ges Neurol Psychiatr*. 1933; 146.

15. Strömgren E. Beiträge zur psychiatrischen Erblehre, auf Grund von Untersuchungen an einer Inselbevölkerung. *Acta Psychiatr Neurol Scand*. 1938; Suppl. 19.

16. Sjögren T. Genetic-statistical and psychiatric investigations of a West Swedish population. *Acta Psychiatr Neurol Scand*. 1948; Suppl. 52.

17. Esson-Moller E, Larsson H, Uddenberg CE, et al. Individual traits and morbidity in a Swedish rural population. *Acta Psychiatr Neurol Scand Suppl*. 1956; 100: 1–160.

18. Hagnell O. *A Prospective Study of the Incidence of Mental Disorder*. Stockholm: Scand Univ Books, Svenska Bokförlaget/Norstedts-Bonniers, 1966.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

19. Hagnell O. The incidence and duration of episodes of mental illness in a total population. In: Hare EH, Wing JK (eds). *Psychiatric Epidemiology*. Lund: Oxford University Press, 1970. pp213–24.

20. Böök JA. A genetic and neuropsychiatric investigation of a North-Swedish population. with special regard to schizophrenia and mental deficiency. *Acta Genet Stat Med*. 1953; 4: 1–100.

21. Böök JA, Wettererg L, Modrzewska K. Schizophrenia in a North Swedish geographical isolate, 1900–77: epidemiology, genetics and biochemistry. *Clin Genet*. 1978; 14: 373–94.

22. Rüdin E. *Studien Über Vererbung Und Entstehung Geistiger Störungen*. London: Springer, 1916.

23. Jablensky A. Epidemiology of schizophrenia: the global burden of disease and disability. *Eur Arch Psychiatry Clin Neurosci*. 2000; 250: 274–85.

24. Eagles JM. Is schizophrenia disappearing? *Br J Psychiatry*. 1991; 158: 834–5.

25. Kirkbride JB, Croudace T, Brewin J, et al. Is the incidence of psychotic disorder in decline? Epidemiological evidence from two decades of research. *Int J Epidemiol*. 2009; 38: 1255–64.

26. McGrath J, Saha S, Welham J. et al. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med*. 2004; 2: 1–22.

27. Hare EH. Mental illness and social conditions in Bristol. *J Ment Sci*. 1956; 102: 349–57.

28. Faris R, Dunham H. Ecology of Mental Disorders in Urban Areas. Chicago: Chicago University Press, 1969.

29. Häfner H, Reimann H, Immich H, et al. Inzidenz seelischer Erkrankungen in Mannheim 1965. *Soc Psychiatr*. 1969; 4: 127–35.

30. Giggs JA, Cooper JE. Ecological structure and the distribution of schizophrenia and affective psychoses in Nottingham. *Br J Psychiatry*. 1987; 151: 627–33.

31. Baudiš P, Matesová A, Škoda C, et al. A comparison of first admissions of Mania in Prague, Aarhus and London—A transcultural study linked up with the International Pilot Study of Schizophrenia of WHO. *Soc Psychiatry*. 1977; 12: 185–93.

32. Sartorius N, Jablensky A, Korten A, et al. Early manifestations and first-contact incidence of schizophrenia in different cultures. A preliminary report on the initial evaluation phase of the WHO

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

Collaborative Study on determinants of outcome of severe mental disorders. *Psychol Med.* 1986; 16: 909–28.

33. Jablensky A, Sartorius N, Ernberg G, et al. *Schizophrenia: Manifestations, Incidence and Course in Different Cultures A World Health Organization Ten-Country Study*. Psychological Medicine. Monograph Supplement.1992; 20: 1–97. http://www.journals.cambridge.org/abstract_S0264180100000904

34. Wing JK, Cooper JE, Sartorius N. *The Measurement and Classification of Psychiatric Symptoms*. Cambridge & London: Cambridge University Press, 1974.

35. March D, Hatch SL, Morgan C, et al. Psychosis and Place. *Epidemiol Rev.* 2008; 30: 84–100.

36. Crow TJ. Schizophrenia as the price that homo sapiens pays for language: a resolution of the central paradox in the origin of the species. *Brain Res Rev.* 2000; 31: 118–29.

37. Gottesman II, Shields J. A polygenic theory of schizophrenia. *Proc Natl Acad Sci U S A.* 1967; 58: 199–205.

38. Risch N, Rao DC. Genetic linkage and complex diseases, with special reference to psychiatric disorders. *Genet Epidemiol.* 1990; 7: 3–16.

39. McGuffin P, Owen M, Farmer A. Genetic basis of schizophrenia. *Lancet.* 1995; 346: 678–82.

40. Ripke S, Neale BM, Corvin A, et al. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014; 511: 421–7.

41. Lloyd T, Kennedy N, Fearon P, et al. Incidence of bipolar affective disorder in three UK cities: Results from the ÆSOP study. *Br J Psychiatry.* 2005; 186: 126–131.

42. Fearon P, Kirkbride JB, Morgan C, et al. Incidence of schizophrenia and other psychoses in ethnic minority groups: results from the MRC AESOP Study. *Psychol Med.* 2006; 36: 1541–50.

43. Kirkbride JB, Fearon P, Morgan C, et al. Heterogeneity in incidence rates of schizophrenia and other psychotic syndromes: findings from the 3-center AeSOP study. *Arch Gen Psychiatry.* 2006; 63: 250–8.

44. Harrison G, Owens D, Holton A, et al. A prospective study of severe mental disorder in Afro-Caribbean patients. *Psychol Med.* 1988; 18: 643–57.

45. Kirkbride JB, Fearon P, Morgan C, et al. Neighbourhood variation in the incidence of psychotic disorders in Southeast London. *Soc Psychiatry Psychiatr Epidemiol.* 2007; 42: 438–45.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

46. Kirkbride JB, Barker D, Cowden F, et al. Psychoses, ethnicity and socio-economic status. *Br J Psychiatry.* 2008; 193: 18–24.

47. Lewis G, David A, Andreasson S, et al. Schizophrenia and city life. *Lancet.* 1992; 340: 137–40.

48. Mortensen PB, Pedersen CB, Westergaard T, et al. Effects of family history and place and season of birth on the risk of schizophrenia. *N Engl J Med.* 1999; 340: 603–8.

49. Goldberg EM, Morrison SL. Schizophrenia and Social Class. *Br J Psychiatry.* 1963; 109.

50. Ngamini Ngui A, Cohen AA, Courteau J, et al. Does elapsed time between first diagnosis of schizophrenia and migration between health territories vary by place of residence? A survival analysis approach. *Heal Place.* 2013; 20: 66–74.

51. Jongsma HE, Gayer-Anderson C, Lasalvia A, et al. Treated incidence of psychotic disorders in the multinational EU-GEI Study. *JAMA Psychiatry.* 2018; 75: 36–46.

52. Lee SH, Ripke S, Neale BM, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nat Genet.* 2013; 45: 984–94.

53. Murray RM, Sham P, Van Os J, et al. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr Res.* 2004; 71: 405–16.

54. Kaymaz N, Krabbendam L, de Graaf R, et al. Evidence that the urban environment specifically impacts on the psychotic but not the affective dimension of bipolar disorder. *Soc Psychiatry Psychiatr Epidemiol.* 2006; 41: 679–85.

55. Regier DA, Myers JK, Kramer M, et al. The NIMH Epidemiologic Catchment Area program. Historical context, major objectives, and study population characteristics. *Arch Gen Psychiatry.* 1984; 41: 934–41.

56. Robins LN, Helzer JE, Weissman MM, et al. Lifetime prevalence of specific psychiatric disorders in three sites. *Arch Gen Psychiatry.* 1984; 41: 949.

57. Kessler RC, McGonagle KA, Zhao S, et al. Lifetime and 12-month prevalence of DSM-III-R psychiatric disorders in the United States. Results from the National Comorbidity Survey. *Arch Gen Psychiatry.* 1994; 51: 8–19.

58. Saha S, Chant D, Welham J, et al. A systematic review of the prevalence of schizophrenia. *PLOS Med.* 2005; 2: e141.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

59. Perälä J, Suvisaari J, Saarni SI, et al. Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch Gen Psychiatry.* 2007; 64: 19–28.

60. Kirkbride JB, Hameed Y, Ankireddypalli G, et al. The epidemiology of first-episode psychosis in early intervention in psychosis services: findings from the Social Epidemiology of Psychoses in East Anglia [SEPEA] Study. *Am J Psychiatry.* 2017; 174: 143–53.

61. Csillag C, Nordentoft M, Mizuno M, et al. Early intervention services in psychosis: from evidence to wide implementation. *Early Interv Psychiatry.* 2016; 10: 540–546.

62. Brodaty H, Sachdev P, Rose N, et al. Schizophrenia with onset after age 50 years. I: Phenomenology and risk factors. *Br J Psychiatry.* 1999; 175: 410–15.

63. Nicolson R, Rapoport JL. Childhood-onset schizophrenia: rare but worth studying. *Biol Psychiatry.* 1999; 46: 1418–28.

64. Häfner H, Löffler W, Riecher-Rössler A, et al. Schizophrenia and delusions in middle aged and elderly patients. Epidemiology and etiological hypothesis. *Nervenarzt* 2001; 72: 347–57.

65. Murthy G V, Janakiramaiah N, Gangadhar BN, et al. Sex difference in age at onset of schizophrenia: discrepant findings from India. *Acta Psychiatr Scand.* 1998; 97: 321–5.

66. Gangadhar BN, Panner Selvan C, Subbakrishna DK, et al. Age-at-onset and schizophrenia: reversed gender effect. *Acta Psychiatr Scand.* 2002; 105: 317–19.

67. Phillips MR, Yang G, Li S, et al. Suicide and the unique prevalence pattern of schizophrenia in mainland China: a retrospective observational study. *Lancet.* 2004; 364: 1062–8.

68. Jackson D, Kirkbride J, Croudace T, et al. Meta-analytic approaches to determine gender differences in the age-incidence characteristics of schizophrenia and related psychoses. *Int J Methods Psychiatr Res.* 2013; 22(1): 36–45.

69. Häfner H, Riecher-Rossler A, An Der Heiden W, et al. Generating and testing a causal explanation of the gender difference in age at first onset of schizophrenia. *Psychol Med.* 1993; 23: 925–40.

70. Chua WLLC, Izquierdo de Santiago A, Kulkarni J, et al. Estrogen for schizophrenia. *Cochrane Database Syst Rev.* 2005; DOI: 10.1002/14651858.CD004719.pub2.

71. Helgason T, Magnússon H. The first 80 years of life. A psychiatric epidemiological study. *Acta Psychiatr Scand Suppl.* 1989; 348: 85–94; discussion 167–78.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

72. Stafford J, Howard R, Kirkbride JB. The incidence of very late-onset psychotic disorders: a systematic review and meta-analysis, 1960–2016. *Psychol Med.* 2018; 48: 1775–86.

73. Bassett AS, Chow EWC, AbdelMalik P, et al. The schizophrenia phenotype in 22q11 deletion syndrome. *Am J Psychiatry.* 2003; 160: 1580–6.

74. Bassett AS, Chow EWC, Husted J, et al. Clinical features of 78 adults with 22q11 deletion syndrome. *Am J Med Genet Part A.* 2005; 138A: 307–13.

75. Baker KD, Skuse DH. Adolescents and young adults with 22q11 deletion syndrome: psychopathology in an at-risk group. *Br J Psychiatry.* 2005; 186.

76. Craddock N, Sklar P. Bipolar disorder 1: Genetics of bipolar disorder. *Lancet.* 2013; 381: 1654–62.

77. Harrison PJ. Recent genetic findings in schizophrenia and their therapeutic relevance. *J Psychopharmacol.* 2015; 29: 85–96.

78. Schizophrenia Working Group of the Psychiatric Genomic Consortium, 2015. https://pubmed.ncbi.nlm.nih.gov/25056061-biological-insights-from-108-schizophrenia-associated-genetic-loci/.

79. Dean L, Pratt V Mcleod H, et al. *Schizophrenia.* National Center for Biotechnology Information (US), 2012. https://pubmed.ncbi.nlm.nih.gov/28520342-schizophrenia/.

80. Vassos E, Di Forti M, Coleman J, et al. An examination of polygenic score risk prediction in individuals with first-episode psychosis. *Biol Psychiatry.* 2017; 81: 470–7.

81. Giegling I, Hosak L, Mössner R, et al. Genetics of schizophrenia: A consensus paper of the WFSBP Task Force on Genetics. *World J Biol Psychiatry.* 2017: 1–14.

82. International Schizophrenia Consortium. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature.* 2009; 460: 748–52.

83. Cross-Disorder Group of the Psychiatric Genetics Consortium. Identification of risk loci with shared effects on five major psychiatric disorders: a genome-wide analysis. *Lancet.* 2013; 381: 1371–9.

84. Pardiñas AF, Holmans P, Pocklington AJ, et al. Common schizophrenia alleles are enriched in mutation-intolerant genes and in regions under strong background selection. *Nat Genet.* 2018; 50: 381–9.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

85. Mühleisen TW, Leber M, Schulze TG, et al. Genome-wide association study reveals two new risk loci for bipolar disorder. *Nat Commun.* 2014; 5: DOI: 10.1038/ncomms4339.

86. Chen DT, Jiang X, Akula N. et al. Genome-wide association study meta-analysis of European and Asian-ancestry samples identifies three novel loci associated with bipolar disorder. *Mol Psychiatry.* 2013; 18: 195–205.

87. Howes OD, McCutcheon R, Owen MJ, et al. the role of genes, stress, and dopamine in the development of schizophrenia. *Biol Psychiatry.* 2017; 81: 9–20.

88. Howes OD, Kapur S. A neurobiological hypothesis for the classification of schizophrenia: type A (hyperdopaminergic) and type B (normodopaminergic). *Br J Psychiatry.* 2014; 205: 1–3.

89. Khandaker GM, Pearson RM, Zammit S, et al. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life. *JAMA Psychiatry.* 2014; 71: 1121–8.

90. Price AL, Patterson NJ, Plenge RM, et al. Principal components analysis corrects for stratification in genome-wide association studies. *Nat Genet.* 2006; 38: 904–9.

91. Jones HJ, Stergiakouli E, Tansey KE, et al. Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. *JAMA Psychiatry.* 2016; 73: 221.

92. Dean K, Stevens H, Mortensen PB, et al. Full spectrum of psychiatric outcomes among offspring with parental history of mental disorder. *Arch Gen Psychiatry.* 2010; 67: 822.

93. Mistry S, Harrison JR, Smith DJ, et al. The use of polygenic risk scores to identify phenotypes associated with genetic risk of schizophrenia: Systematic review. *Schizophr Res*. 2018; 197: 2–8.

94. Neale BM, Sklar P. Genetic analysis of schizophrenia and bipolar disorder reveals polygenicity but also suggests new directions for molecular interrogation. *Curr Opin Neurobiol.* 2015; 30: 131–8.

95. Sariaslan A, Fazel S, D'Onofrio BM, et al. Schizophrenia and subsequent neighborhood deprivation: revisiting the social drift hypothesis using population, twin and molecular genetic data. *Transl Psychiatry.* 2016; 6: e796.

96. Paksarian D, Trabjerg BB, Merikangas KR, et al. The role of genetic liability in the association of urbanicity at birth and during upbringing with schizophrenia in Denmark. *Psychol Med.* 2018; 48: 305–14.

97. Morgan VA, Waterreus A, Carr V, et al. Responding to challenges for people with psychotic illness: Updated evidence from the Survey of High Impact Psychosis. *Aust N Z J Psychiatry.* 2017; 51: 124–40.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

98. Indian Hemp Drugs Commission Report of the Indian Hemp Drugs Commission 1893–1894. Simla: Government Central Printing Office; 1894.

99. McGuire PK, Jones P, Harvey I, et al. Cannabis and acute psychosis. *Schizophr Res.* 1994; 13: 161–7.

100. Dekker N, de Haan L, van den Berg S, et al. Cessation of cannabis use by patients with recent-onset schizophrenia and related disorders. *Psychopharmacol Bull.* 2008; 41: 142–53.

101. ElSohly MA, Mehmedic Z, Foster S, et al. Changes in cannabis potency over the last 2 decades (1995–2014): analysis of current data in the United States. *Biol Psychiatry.* 2016; 79: 613–19.

102. Andreasson S, Allebeck P, Engstrom A, et al. Cannabis and schizophrenia. A longitudinal study of Swedish conscripts. *Lancet.* 1987; 2: 1483–6.

103. Moore THM, Zammit S, Lingford-Hughes A, et al. Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet.* 2007; 370: 319–28.

104. Hickman M, Vickerman P, MacLeod J, et al. If cannabis caused schizophrenia—How many cannabis users may need to be prevented in order to prevent one case of schizophrenia? England and Wales calculations. *Addiction.* 2009; 104: 1856–61.

105. Hill M. Perspective: Be clear about the real risks. *Nature.* 2015; 525: S14.

106. Murray RM, Quigley H, Quattrone D, et al. Traditional marijuana, high-potency cannabis and synthetic cannabinoids: increasing risk for psychosis. *World Psychiatry.* 2016; 15: 195–204.

107. Howes OD, Murray RM. Schizophrenia: an integrated sociodevelopmental-cognitive model. *Lancet.* 2014; 383:1677–87.

108. Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch Hunger Winter of 1944–1945. *Arch Gen Psychiatry.* 1992; 49: 983–8.

109. Khandaker GM, Zimbron J, Lewis G, et al. Prenatal maternal infection, neurodevelopment and adult schizophrenia: A systematic review of population-based studies. *Psychol Med.* 2013; 43: 239–57.

110. Brown AS, Derkits EJ. Prenatal infection and schizophrenia: a review of epidemiologic and translational studies. *Am J Psychiatry.* 2010; 167: 261–80.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

111. Cannon M, Jones PB, Murray RM. Obstetric complications and schizophrenia: historical and meta-analytic review. *Am J Psychiatry.* 2002; 159: 1080–92.

112. Jones P, Rodgers B, Murray R, et al. Child development risk factors for adult schizophrenia in the British 1946 birth cohort. *Lancet.* 1994; 344: 1398–402.

113. Bramon E, Walshe M, Mcdonald C, et al. Dermatoglyphics and schizophrenia: A meta-analysis and investigation of the impact of obstetric complications upon a–b ridge count. *Schizophr Res.* 2005; 75: 399–404.

114. Filatova S, Koivumaa-Honkanen H, Hirvonen N, et al. Early motor developmental milestones and schizophrenia: A systematic review and meta-analysis. *Schizophr Res.* 2017; 188: 13–20.

115. Reichenberg A, Caspi A, Harrington H, et al. Static and Dynamic Cognitive Deficits in Childhood Preceding Adult Schizophrenia: A 30-year Study. *Am J Psychiatry.* 2010; 167: 160–9.

116. Khandaker GM, Stochl J, Zammit S, et al. A population-based longitudinal study of childhood neurodevelopmental disorders, IQ and subsequent risk of psychotic experiences in adolescence. *Psychol Med.* 2014; 44: 3229–38.

117. Khandaker GM, Barnett JH, White IR, et al. A quantitative meta-analysis of population-based studies of premorbid intelligence and schizophrenia. *Schizophr Res.* 2011; 132: 220–7.

118. Bendall S, Jackson HJ, Hulbert CA, et al. Childhood trauma and psychotic disorders: a systematic, critical review of the evidence. *Schizophr Bull.* 2008; 34: 568–79.

119. Matheson SL, Shepherd AM, Pinchbeck RM, et al. Childhood adversity in schizophrenia: a systematic meta-analysis. *Psychol Med.* 2013; 43: 225–238.

120. Varese F, Smeets F, Drukker M, et al. Childhood adversities increase the risk of psychosis: a meta-analysis of patient-control, prospective- and cross-sectional cohort studies. *Schizophr Bull.* 2012; 38: 661–71.

121. Kelleher I, Keeley H, Corcoran P, et al. Childhood trauma and psychosis in a prospective cohort study: cause, effect, and directionality. *Am J Psychiatry.* 2013; 170: 734–41.

122. Arseneault L, Cannon M, Fisher HL, et al. Childhood trauma and children’s emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *Am J Psychiatry.* 2011; 168: 65–72.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

123. Fisher HL, Caspi A, Moffitt TE, et al. Measuring adolescents' exposure to victimization: The Environmental Risk (E-Risk) Longitudinal Twin Study. *Dev Psychopathol.* 2015; 27: 1399–416.

124. Newbury JB, Arseneault L, Moffitt TE, et al. Measuring childhood maltreatment to predict early-adult psychopathology: Comparison of prospective informant-reports and retrospective self-reports. *J Psychiatr Res.* 2018; 96: 57–64.

125. Menninger KA. Influenza and schizophrenia. An analysis of post-influenzal "dementia precox," as of 1918, and five years later further studies of the psychiatric aspects of influenza. 1926. *Am J Psychiatry.* 1994; 151: 182–7.

126. Köhler CA, Freitas TH, Stubbs B, et al. Peripheral alterations in cytokine and chemokine levels after antidepressant drug treatment for major depressive disorder: systematic review and meta-analysis. *Mol Neurobiol.* 2017; 55: 4195–206.

127. Khandaker GM, Zammit S, Lewis G, et al. A population-based study of atopic disorders and inflammatory markers in childhood before psychotic experiences in adolescence. *Schizophr Res.* 2014; 152: 139–45.

128. Khandaker GM, Zammit S, Burgess S, et al. Association between a functional interleukin 6 receptor genetic variant and risk of depression and psychosis in a population-based birth cohort. *Brain Behav Immun.* 2018; 69: 264–72.

129. Khandaker GM, Cousins L, Deakin J, et al. Inflammation and immunity in schizophrenia: implications for pathophysiology and treatment. *Lancet Psychiatry.* 2015; 2: 258–70.

130. Lennox BR, Palmer-Cooper EC, Pollak T, et al. Prevalence and clinical characteristics of serum neuronal cell surface antibodies in first-episode psychosis: a case-control study. *Lancet Psychiatry.* 2017; 4: 42–8.

131. Benros ME, Eaton WW, Mortensen PB. The Epidemiologic Evidence Linking Autoimmune Diseases and Psychosis. *Biol Psychiatry.* 2014; 75: 300–6.

132. Pedersen CB, Mortensen PB. Urbanicity during upbringing and bipolar affective disorders in Denmark. *Bipolar Disord.* 2006; 8: 242–7.

133. Faris R, Dunham H. *Mental Disorders in Urban Areas: An Ecological Study of Schizophrenia and Other Psychoses*. Chicago: University of Chicago Press, 1939.

134. Weyerer S, Häfner H. The stability of the ecological distribution of the incidence of treated mental disorders in the city of Mannheim. *Soc Psychiatry Psychiatr Epidemiol.* 1989; 24: 57–62.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

135. Zammit S, Lewis G, Rasbash J, et al. Individuals, schools, and neighborhood: a multilevel longitudinal study of variation in incidence of psychotic disorders. *Arch Gen Psychiatry.* 2010; 67: 914–22.

136. Kirkbride JB, Jones PB, Ullrich S, et al. Social deprivation, inequality, and the neighborhood-level incidence of psychotic syndromes in East London. *Schizophr Bull.* 2014; 40: 169–80.

137. Richardson L, Hameed Y, Perez J, et al. Association of environment with the risk of developing psychotic disorders in rural populations: Findings from the social epidemiology of psychoses in east anglia study. *JAMA Psychiatry* 2018; 75: 75–83.

138. Lasalvia A, Bonetto C, Tosato S, et al. First-contact incidence of psychosis in north-eastern Italy: influence of age, gender, immigration and socioeconomic deprivation. *Br J Psychiatry.* 2014; 205: 127–34.

139. Burns JK, Esterhuizen T. Poverty, inequality and the treated incidence of first-episode psychosis: an ecological study from South Africa. *Soc Psychiatry Psychiatr Epidemiol.* 2008; 43: 331–5.

140. Kirkbride JB, Morgan C, Fearon P, et al. Neighbourhood-level effects on psychoses: re-examining the role of context. *Psychol Med.* 2007; 37: 1413–25.

141. Bhavsar V, Boydell J, Murray R, et al. Identifying aspects of neighbourhood deprivation associated with increased incidence of schizophrenia. *Schizophr Res.* 2014; 156: 115–21.

142. Allardyce J, Gilmour H, Atkinson J, et al. Social fragmentation, deprivation and urbanicity: Relation to first-admission rates for psychoses. *Br J Psychiatry.* 2005; 187: 401–6.

143. Veling W, Susser E, Selten J-P, et al. Social disorganization of neighborhoods and incidence of psychotic disorders: a 7-year first-contact incidence study. *Psychol Med.* 2015; 45: 1789–98.

144. Bhugra D, Gupta S, Bhui K, et al. WPA guidance on mental health and mental health care in migrants. *World Psychiatry.* 2011; 10: 2–10.

145. Boydell J, Van Os J, Lambri M, et al. Incidence of schizophrenia in south-east London between 1965 and 1997. *Br J Psychiatry.* 2003; 182: 45–9.

146. Bécares L, Nazroo J, Stafford M. The buffering effects of ethnic density on experienced racism and health. *Heal Place.* 2009; 15: 670–8.

147. Schofield P, Ashworth M, Jones R. Ethnic isolation and psychosis: re-examining the ethnic density effect. *Psychol Med.* 2011; 41: 1263–9.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

148. Veling W, Susser E, van Os J, et al. Ethnic density of neighborhoods and incidence of psychotic disorders among immigrants. *Am J Psychiatry.* 2008; 165: 66–73.

149. Pedersen C, Mortensen P. Urbanization and traffic related exposures as risk factors for schizophrenia. *BMC Psychiatry.* 2006; 6: 2.

150. Newbury J, Arseneault L, Caspi A, et al. Why Are children in urban neighborhoods at increased risk for psychotic symptoms? Findings from a UK Longitudinal Cohort Study. *Schizophr Bull.* 2016; 42: 1372–83.

151. Newbury J, Arseneault L, Caspi A *et al*. Cumulative Effects of Neighborhood social adversity and personal crime victimization on adolescent psychotic experiences. *Schizophr Bull.* 2018; 44: 348–358.

152. Solmi F, Colman I, Weeks M, et al. Trajectories of neighborhood cohesion in childhood, and psychotic and depressive symptoms at age 13 and 18 years. *J Am Acad Child Adolesc Psychiatry.* 2017; 56: 570–7.

153. Lederbogen F, Kirsch P, Haddad L, et al. City living and urban upbringing affect neural social stress processing in humans. *Nature.* 2011; 474: 498–501.

154. Haddad L, Schafer A, Streit F, et al. Brain structure correlates of urban upbringing, an environmental risk factor for schizophrenia. *Schizophr Bull.* 2014; 41: 115–122.

155. McCutcheon R, Bloomfield MAP, Dahoun T, et al. Amygdala reactivity in ethnic minorities and its relationship to the social environment: an fMRI study. *Psychol Med.* 2018: 1–8.

156. Sariaslan A, Larsson H, D'Onofrio B, et al. Does population density and neighborhood deprivation predict schizophrenia? A nationwide Swedish family-based study of 2.4 million individuals. *Schizophr Bull.* 2015; 41: 494–502.

157. Colodro-Conde L, Couvy-Duchesne B, Whitfield JB, et al. Association Between Population Density and Genetic Risk for Schizophrenia. *JAMA Psychiatry*. 2018; 75: 901–910.

158. Hartz SM, Horton AC, Oehlert M, et al. Association between substance use disorder and polygenic liability to schizophrenia. *Biol Psychiatry.* 2017; 82: 709–15.

159. DeVylder JE, Kelleher I, Lalane M, et al. Association of urbanicity with psychosis in low- and middle-income countries. *JAMA Psychiatry*. 2018; 75: 678–686.

160. Coid JW, Hu J, Kallis C, et al. Urban birth, urban living, and work migrancy: differential effects on psychotic experiences among young Chinese men. *Schizophr Bull.* 2018; 44: 1123–1132.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

161. Ødegaard Ø. Emigration and insanity. *Acta Psychiatr Neurol.* 1932; Supp: 1–206.

162. Cantor-Graae E, Selten J-PP. Schizophrenia and migration: A meta-analysis and review. *Am J Psychiatry.* 2005; 162: 12–24.

163. Bourque F, Van Der Ven E, Malla A. A meta-analysis of the risk for psychotic disorders among first- and second-generation immigrants. *Psychol Med.* 2011; 41: 897–910.

164. Tortelli A, Errazuriz A, Croudace T, et al. Schizophrenia and other psychotic disorders in Caribbean-born migrants and their descendants in England: systematic review and meta-analysis of incidence rates, 1950–2013. *Soc Psychiatry Psychiatr Epidemiol.* 2015; 50: 1039–55.

165. Tortelli A, Morgan C, Szoke A, et al. Different rates of first admissions for psychosis in migrant groups in Paris. *Soc Psychiatry Psychiatr Epidemiol.* 2014; 49: 1103–9.

166. Zolkowska K, Cantor-Graae E, McNeil TF. Increased rates of psychosis among immigrants to Sweden: is migration a risk factor for psychosis? *Psychol Med.* 2001; 31: 669–78.

167. Dykxhoorn J, Hollander A-C, Lewis G, et al. Does risk of schizophrenia, schizoaffective, and bipolar disorders vary by migrant status, age-at-migration, and region of origin? A national cohort study of 1.8 million people. *Psychol Med.* 2019; 49(14): 2354–63.

168. Kirkbride JB, Hameed Y, Ioannidis K, et al. Ethnic minority status, age-at-immigration and psychosis risk in rural environments: evidence from the SEPEA study. *Schizophr Bull.* 2017; 43: 1251–61.

169. Hickling FW, Rodgers-Johnson P. The incidence of first contact schizophrenia in Jamaica. *Br J Psychiatry.* 1995; 167: 193–196.

170. Bhugra D, Hilwig M, Hossein B, et al. First-contact incidence rates of schizophrenia in Trinidad and one-year follow-up. *Br J Psychiatry.* 1996; 169: 587–92.

171. Mahy GE, Mallett R, Leff J, et al. First-contact incidence rate of schizophrenia on Barbados. *Br J Psychiatry.* 1999; 175: 28–33.

172. Selten J-P, Cantor-Graae E, Slaets J, et al. Odegaard's selection hypothesis revisited: schizophrenia in Surinamese immigrants to the Netherlands. *Am J Psychiatry.* 2002; 159: 669–71.

173. van der Ven E, Dalman C, Wicks S, et al. Testing Ødegaard's selective migration hypothesis: a longitudinal cohort study of risk factors for non-affective psychotic disorders among prospective emigrants. *Psychol Med.* 2015; 45: 727–34.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

174. Morgan C, Mallett R, Hutchinson G, et al. Negative pathways to psychiatric care and ethnicity: the bridge between social science and psychiatry. *Soc Sci Med.* 2004; 58: 739–52.

175. Morgan C, Mallett MR, Hutchinson G, et al. Pathways to care and ethnicity II. Source of referral and help-seeking: Report from the ÆSOP study. *Br J Psychiatry.* 2005; 186: 290–6.

176. Morgan C, Mallett MR, Hutchinson G, et al. Pathways to care and ethnicity I. Sample characteristics and compulsory admission: Report from the AESOP study. *Br J Psychiatry.* 2005; 186: 281–9.

177. Koffman J, Fulop NJ, Pashley D, et al. Ethnicity and use of acute psychiatric beds: one-day survey in north and south Thames regions. *Br J Psychiatry.* 1997; 171: 238–41.

178. Takei N, Persaud R, Woodruff P, et al. First episodes of psychosis in Afro-Caribbean and White people. An 18-year follow-up population-based study. *Br J Psychiatry.* 1998; 172: 147–53.

179. Kuno E, Rothbard AB. Racial disparities in antipsychotic prescription patterns for patients with schizophrenia. *Am J Psychiatry.* 2002; 159: 567–72.

180. Mallinger JB, Fisher SG, Brown T, et al. Racial disparities in the use of second-generation antipsychotics for the treatment of schizophrenia. *Psychiatr Serv.* 2006; 57: 133–6.

181. Lewis G, Croft-Jeffreys C, David A. Are British psychiatrists racist?. *Br J Psychiatry.* 1990; 157: 410–15.

182. Hickling FW, McKenzie K, Mullen R, et al. A Jamaican psychiatrist evaluates diagnoses at a London psychiatric hospital. *Br J Psychiatry.* 1999; 175: 283–5.

183. Veling W, Hoek HW, Selten JP, et al. Age at migration and future risk of psychotic disorders among immigrants in the Netherlands: A 7-year incidence study. *Am J Psychiatry.* 2011; 168: 1278–85.

184. Pedersen CB, Cantor-Graae E. Age at migration and risk of schizophrenia among immigrants in Denmark: A 25-year incidence study. *Am J Psychiatry.* 2012; 169: 1117–18.

185. Price C, Dalman C, Zammit S, et al. Residential mobility and non-affective psychosis over the life course in 1.4 m young people in Sweden. *JAMA Psychiatry*. 2018; 75(11): 1128–36.

186. Paksarian D, Eaton WW, Mortensen PB, et al. Childhood residential mobility, schizophrenia, and bipolar disorder: a population-based study in Denmark. *Schizophr Bull.* 2015; 41: 346–54.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

187. Mok PLH, Webb RT, Appleby L, et al. Full spectrum of mental disorders linked with childhood residential mobility. *J Psychiatr Res.* 2016; 78: 57–64.

188. Veling W, Selten J-P, Susser E, et al. Discrimination and the incidence of psychotic disorders among ethnic minorities in the Netherlands. *Int J Epidemiol.* 2007; 36: 761–8.

189. Anderson KK, Cheng J, Susser E, et al. Incidence of psychotic disorders among first-generation immigrants and refugees in Ontario. *CMAJ.* 2015; 187: E279–E286.

190. Hollander A-C, Dal H, Lewis G, et al. Refugee migration and risk of schizophrenia and other non-affective psychoses: cohort study of 1.3 million people in Sweden. *BMJ.* 2016; 352: i1030.

191. Rechel B, Mladovsky P, Ingleby D, et al. Migration and health in an increasingly diverse Europe. *Lancet.* 2013; 381: 1235–45.

192. Boydell J, van Os J, McKenzie K, et al. Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *Br Med J.* 2001; 323: 1336–8.

193. Kirkbride JB, Boydell J, Ploubidis GB, et al. Testing the association between the incidence of schizophrenia and social capital in an urban area. *Psychol Med.* 2008; 38: 1083–94.

194. Hjern A, Wicks S, Dalman C. Social adversity contributes to high morbidity in psychoses in immigrants -a national cohort study of two generations of Swedish residents. *Psychol Med.* 2004; 34: 1025–33.

195. Hegarty JD, Baldessarini RJ, Tohen M, et al. One hundred years of schizophrenia: a meta-analysis of the outcome literature. *Am J Psychiatry.* 1994; 151: 1409–16.

196. Cohen P, Cohen J. The clinician's illusion. *Arch Gen Psychiatry.* 1984; 41: 1178–82.

197. Hopper K, Harrison G, Janca A, et al. *Recovery from Schizophrenia: an International Perspective: a Report from the WHO Collaborative Project, the International Study of Schizophrenia*. New York: Oxford University Press, 2007.

198. Revier CJ, Reininghaus U, Dutta R, et al. Ten-Year outcomes of first-episode psychoses in the MRC AESOP-10 study. *J Nerv Ment Dis.* 2015; 203: 379–86.

199. Jablensky A. The diagnostic concept of schizophrenia: its history, evolution, and future prospects. *Dialogues Clin Neurosci.* 2010; 12: 271–87.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

200. Barber ME. Recovery as the new medical model for psychiatry. *Psychiatr Serv.* 2012; 63: 277–9.

201. Morgan C, Lappin J, Heslin M, et al. Reappraising the long-term course and outcome of psychotic disorders: the AESOP-10 study. *Psychol Med.* 2014; 44: 2713–26.

202. Farr W. Report on the mortality of lunatics. *Lancet.* 1841; 36: 332–5.

203. Tiihonen J, Lönnqvist J, Wahlbeck K, et al. 11-year follow-up of mortality in patients with schizophrenia: a population-based cohort study (FIN11 study). *Lancet.* 2009; 374: 620–7.

204. Laursen TM, Munk-Olsen T, Vestergaard M. Life expectancy and cardiovascular mortality in persons with schizophrenia. *Curr Opin Psychiatry.* 2012; 25: 83–8. 10.1097/YCO.0b013e32835035ca.

205. Laursen TM, Wahlbeck K, Hällgren J, et al. Life expectancy and death by diseases of the circulatory system in patients with bipolar disorder or schizophrenia in the Nordic countries. *PLOS One.* 2013; 8: e67133.

206. Osborn DPJ, Levy G, Nazareth I, et al. Relative risk of cardiovascular and cancer mortality in people with severe mental illness from the United Kingdom’s General Practice Research Database. *Arch Gen Psychiatry.* 2007; 64: 242.

207. Brown S, Inskip H, Barraclough B. Causes of the excess mortality of schizophrenia. *Br J Psychiatry.* 2000; 177: 212–17.

208. Appleby L, Thomas S, Ferrier N, et al. Sudden unexplained death in psychiatric in-patients. *Br J Psychiatry.* 2000; 176: 405–6.

209. Waddington JL, Youssef HA, Kinsella A. Mortality in schizophrenia. Antipsychotic polypharmacy and absence of adjunctive anticholinergics over the course of a 10-year prospective study. *Br J Psychiatry.* 1998; 173: 325–9.

210. Joukamaa M, Heliövaara M, Knekt P, et al. Schizophrenia, neuroleptic medication and mortality. *Br J Psychiatry.* 2006; 188: 122–7.

211. Simon GE, Stewart C, Yarborough BJ. et al. Mortality rates after the first diagnosis of psychotic disorder in adolescents and young adults. *JAMA Psychiatry.* 2018; 75: 254.

212. Hiroeh U, Appleby L, Mortensen PB, et al. Death by homicide, suicide, and other unnatural causes in people with mental illness: a population-based study. *Lancet.* 2001; 358: 2110–12.

213. Mortensen PB, Juel K. Mortality and causes of death in first admitted schizophrenic patients. *Br J Psychiatry.* 1993; 163: 183–9.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

214. Geddes JR, Juszczak ED. Period trends in rate of suicide in first 28 days after discharge from psychiatric hospital in Scotland, 1968–92. *BMJ.* 1995; 311: 357.

215. Lawrence D, Holman CD, Jablensky AV, et al. Increasing rates of suicide in Western Australian psychiatric patients: a record linkage study. *Acta Psychiatr Scand.* 2001; 104: 443–51.

216. Caldwell CB, Gottesman II. Schizophrenics kill themselves too: a review of risk factors for suicide. *Schizophr Bull.* 1990; 16: 571–89.

217. Hawton K, Sutton L, Haw C, et al. Schizophrenia and suicide: Systematic review of risk factors. *Br J Psychiatry.* 2005; 187: 9–20.

218. Chwastiak LA, Tek C. The unchanging mortality gap for people with schizophrenia. *Lancet.* 2009; 374: 590–2.

219. Royal College of Psychiatrists. Whole person care: from rhetoric to reality, 2013. https://www.basw.co.uk/system/files/resources/basw_103627-6_0.pdf.

220. Power RA, Verweij KJH, Zuhair M, et al. Genetic predisposition to schizophrenia associated with increased use of cannabis. *Mol Psychiatry.* 2014; 19: 1201–4.

221. French L, Gray C, Leonard G, et al. Early Cannabis Use, Polygenic Risk Score for Schizophrenia and Brain Maturation in Adolescence. *JAMA Psychiatry.* 2015; 72: 1002.

222. Solmi F, Lewis G, Kirkbride JB. Neighbourhood characteristics at birth and positive and negative psychotic symptoms in adolescence: findings from the ALSPAC birth cohort. 2018: DOI: 10.17605/OSF.IO/NMH9Y.

223. Howes OD, Kapur S. The dopamine hypothesis of schizophrenia: Version III—the final common pathway. *Schizophr Bull.* 2009; 35: 549–62.

224. Morgan C, Charalambides M, Hutchinson G, et al. Migration, ethnicity, and psychosis: toward a sociodevelopmental model. *Schizophr Bull.* 2010; 36: 655–664.

225. Susser E, Hoek HW, Brown A. Neurodevelopmental disorders after prenatal famine: The story of the Dutch Famine Study. *Am J Epidemiol.* 1998; 147: 213–16.

226. Kendler KS. The structure of psychiatric science. *Am J Psychiatry.* 2014; 171: 931–8.

227. Petersen ML, van der Laan MJ. Causal models and learning from data. *Epidemiology.* 2014; 25: 418–26.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020

228. Susser E, Schwartz S, Morabia A. Eco-epidemiology. In: Susser E, Schwartz S, Morabia A, et al. (eds). *Psychiatric Epidemiology*. Oxford: Oxford University Press, 2006.

229. Susser M, Susser E. Choosing a future for epidemiology: I. Eras and paradigms. *Am J Public Health*. 1996; 86: 668–73.

230. Susser M, Susser E. Choosing a future for epidemiology: II. From black box to Chinese boxes and eco-epidemiology. *Am J Public Health*. 1996; 86: 674–7.

PRINTED FROM OXFORD MEDICINE ONLINE (www.oxfordmedicine.com). © Oxford University Press, 2020. All Rights Reserved. Under the terms of the licence agreement, an individual user may print out a PDF of a single chapter of a title in Oxford Medicine Online for personal use (for details see Privacy Policy and Legal Notice).

Subscriber: James Kirkbride; date: 18 November 2020