

Environmental risk factors for schizophrenia: implications for prevention

Simona A Stilo¹, Marta Di Forti¹ & Robin M Murray^{*1}

Practice points

- Risk factors for schizophrenia in fetal life consist of:
 - Prenatal maternal complications (e.g., diabetes, rhesus incompatibility, pre-eclampsia or bleeding);
 - Prenatal maternal infection;
 - Prenatal maternal nutrition (e.g., nutrition deprivation, hypovitaminosis D or folate deficiency);
 - Abnormal fetal development;
 - Delivery complications;
 - Season of birth;
 - Advanced paternal age.
- Risk factors for schizophrenia in early life consist of:
 - Hearing impairment;
 - Childhood trauma.
- Risk factors for schizophrenia in later childhood/adolescence consist of:
 - Social factors (e.g., parental separation and loss or social exclusion);
 - Stressful life events;
 - Migration;
 - Urbanicity.

SUMMARY The most important risk factor for schizophrenia is a positive family history, but only a minority of people with schizophrenia have an affected relative and no single gene of large effect has been consistently associated with psychosis risk. Epidemiological research has elucidated putative biological and psychosocial candidate risk factors for schizophrenia. Biological factors include advanced paternal age, exposure to obstetric events and abuse of drugs such as stimulants and cannabis. Recent evidence indicates that social factors such as migration, urban living and victimization also increase the risk. However, neither individual susceptibility genes nor individual environmental risk factors appear sufficient or necessary to cause schizophrenia. Both genetic and environmental risk factors are mostly of small effect, but the latter offer more tangible targets for prevention.

¹Division of Psychological Medicine, Institute of Psychiatry, King's College London, London, UK

*Author for correspondence: robin.murray@iop.kcl.ac.uk

Incidence & prevalence

Epidemiological studies have examined the prevalence, incidence and lifetime risk of schizophrenia across different populations and geographic areas [1]. The distribution of the disease is generally expressed in terms of incidence (new cases per year) and prevalence (total number of existing and new cases at a specified time or during a specified period).

Schizophrenia most commonly manifests in late adolescence or early adult life, with the peak age of risk between 18 and 35 years. It is accompanied by subtle brain structural and neurocognitive abnormalities. A wealth of data show that the incidence of schizophrenia is higher in men compared with women, higher in urban than rural areas and higher in migrants than native-born individuals. Indeed, there are substantial variations in the incidence of schizophrenia [2], with a median incidence of schizophrenia of 15.2 per 100,000 and rates ranging from 7.7 to 43.0 per 100,000 [3].

The lifetime prevalence of schizophrenia is often assumed to be approximately 1%. However, a recent Finnish general population survey of 8028 persons found a lower lifetime prevalence of schizophrenia (0.87%) and higher rates (3.06%) of all psychotic disorders [4].

Genetic risk factors

The fact that schizophrenia has a hereditary component is well established [5]. Heritability is estimated to be between 66 and 85% [6]. The classic evidence for genetic predisposition has come from three main sources: family studies such as the Roscommon Family Study [7] have shown that the closer the genetic relationship, the higher the risk for schizophrenia; twin studies have shown that the monozygotic co-twins of individuals with schizophrenia are more likely to also be schizophrenic than the dizygotic co-twins of individuals with schizophrenia (e.g., Cardno and coworkers) [6]; and adoption studies such as that carried out in Finland by Tienari and coworkers have shown that liability to schizophrenia is transmitted by biological rather than adoptive parents [8].

Genetic linkage and association studies have identified a number of putative susceptibility genes such as *NRG1*, *DTNBPI*, *COMT*, *DISC 1*, *DRD2*, *GRM3* and zinc finger protein. However, each of these has very small effects and it is likely that very many such genes contribute to the occurrence of schizophrenia [9]. Recently,

copy-number variants (CNVs) have been found to be in excess in schizophrenia, but although they have a larger effect size than common variants, they are probably responsible for only a small proportion of cases [10,11]. A better understanding of gene–environment interactions and correlations will hopefully integrate the vast amount of genetic and epidemiological data in the field, pointing more clearly towards the pathogenic mechanisms involved in schizophrenia.

Pregnancy & birth complications

Patients with schizophrenia more frequently have a history of obstetric complications (OCs) than normal subjects [12]. Geddes and coworkers performed an individual patient meta-analysis of 12 studies on 700 schizophrenia subjects and 835 controls [13]. Premature rupture of membranes, gestational ages shorter than 37 weeks and use of resuscitation or incubators were identified as significant risk factors for the subsequent development of schizophrenia [13].

In a meta-analysis of population-based studies, Cannon and coworkers found significant associations with schizophrenia for three groups of complications: complications of pregnancy (e.g., bleeding, diabetes, rhesus incompatibility or pre-eclampsia); abnormal fetal growth and development (e.g., low birth weight, congenital malformations or reduced head circumference); complications of delivery (e.g., uterine atony, asphyxia or emergency cesarean section) [14].

Obstetric complications associated with hypoxia have been associated with greater structural brain abnormalities among patients with schizophrenia [14,15]. Of course, only a few of those individuals exposed to obstetric complications develop schizophrenia. Therefore it is likely that obstetric complications contribute to the causation of schizophrenia only in combination with other risk factors, particularly susceptibility genes [16], perhaps by increasing vulnerability to neuromaturational events and stressors later in life (i.e., adolescence) [17].

Many studies have claimed that environmental hazards in pregnancy increase risk of schizophrenia. These include marked prenatal nutritional deprivation [18,19], hypovitaminosis D [20] and elevated third-trimester homocysteine levels [21]. One of the most consistently replicated findings in schizophrenia is the significant excess of winter–spring births found in the northern hemisphere (~7–10%), although patterns in the southern hemisphere are less clear [22,23]. One

possible explanation is that the mother is passing through the second trimester of her pregnancy in the height of the winter and the fetus is more exposed to nutritional deficiencies or maternal infections. Prenatal infections such as influenza [24], rubella [25] and *Toxoplasma gondii* [26] have been postulated to play a role, as may herpes simplex virus type 2 [27,28]. Infection with viruses such as rubella could explain at least part of the acknowledged association between early hearing impairment and later psychosis [29].

According to van Lieshout and coworkers, offspring of mothers who experienced diabetes mellitus during their pregnancies are seven-times more likely to develop schizophrenia compared with offspring who were not so exposed. Three mechanisms could potentially explain why diabetes mellitus during pregnancy could predispose an individual to schizophrenia in adult life: hypoxia, oxidative stress and increased inflammation [30].

Paternal age

Recent data support the suggestion of Edward Hare [31] of an association between increased paternal age and schizophrenia in offspring [32,33]. Malaspina and coworkers investigated a population-based birth cohort of 87,907 individuals born in Jerusalem from 1964 to 1976. The relative risk of schizophrenia reached 2.02 (95% CI; 1.17–3.51) and 2.96 (95% CI; 1.60–5.47) in offspring of men aged 45–49 and 50 years or more, respectively [32]. This association is claimed to be present particularly in those with no family history of the disorder, but not in those with a positive family history. However, a recent meta-analysis of ten studies by Torrey and coworkers found a population-attributable risk due to advanced paternal age to be relatively small, with a mean paternal age for cases slightly, but not significantly, higher than matched controls [34]. An attractive theory implicates the possibility that accumulation of *de novo* mutations [35] in paternal sperm with aging contributes to the risk [36]. However, this is discounted by a comprehensive study from Denmark that suggests instead personality attributes in fathers leading to late marriage [37].

Substance abuse

■ Psychostimulants

Epidemiological studies have reported an association between substance misuse and psychosis [38,39]. The rates of substance misuse are

consistently higher in first-episode psychosis (FEP) patients compared with the general population, but vary significantly between studies and countries [40]. Not all addictive drugs appear to be able to induce psychotic symptoms [41], but particular attention has focused on stimulants and cannabis.

Chen and coworkers observed that methamphetamine users with psychosis presented a clinical picture that mimicked the positive symptoms of schizophrenia [42]. The likely mechanism is that repeated use of stimulants may induce sensitization of the dopamine system [43], to a point that it becomes dysregulated and results in disordered salience and ultimately psychosis [44]. A strong dose–response relationship between the prevalence of psychotic symptoms and severity of cocaine and amphetamine use confirms this hypothesis [45].

■ Cannabis

The use of cannabis in the general population is associated with increased levels of psychotic symptoms [46]. Moreover, patients suffering from a psychotic disorder use more cannabis than the general population. Both sets of findings are compatible with the idea that cannabis use is a risk factor for psychotic illnesses such as schizophrenia. Indeed, several meta-analyses have reported that cannabis use increases by twofold the risk of developing later psychotic symptoms or psychotic disorders independently of individual psychosis susceptibility [47,48], other known sociodemographic risk factors and use of other drugs. Neuroimaging studies have also described structural changes in both gray and white matter associated with heavy cannabis use in both healthy subjects and FEP patients [49–51].

However, only a minority of cannabis users develop psychosis. This might be explained by differences in patterns of use [52] and age at first use. Converging evidence suggests that adolescence is a particularly vulnerable period for a person to be exposed to cannabis. In the Dunedin birth cohort study, those starting to use cannabis at the age of 15 years or earlier were at greater risk of developing schizophreniform disorder at 26 years of age than those who started by 18 years of age [53]. This finding has been widely replicated, and a recent meta-analysis has shown that the age of psychosis onset in those who used cannabis is almost 3 years earlier than in nonusers [54].

Another explanation as to why only a minority of cannabis users develop psychosis is that some individuals may be especially genetically

vulnerable to its effect [55]. A positive family history for psychosis has been described to interact with cannabis use to further increase the risk of developing a psychotic disorder [56]. Other studies have indicated specific genetic variants as moderators of the psychotogenic effect of cannabis, indicating a mechanism of gene–environment interaction [57–60].

Urbanicity

Urban birth, urban upbringing and urban residence increase the risk of psychosis [61,62]. As long ago as 1939, Faris and Dunham demonstrated variation in the prevalence of schizophrenia across the city of Chicago, and suggested that social isolation in disorganized parts of the city could increase the risk of schizophrenia [63].

The Aetiology and Ethnicity of Schizophrenia and Other Psychoses (AESOP) study indicated significantly lower incidence rates for all psychoses in Nottingham and Bristol, (25 per 100,000 person years and 22 per 100,000 person years, respectively), compared with south-east London (55 per 100,000 person years) [64,65]. Even within London, there were wide variations on the rates [66], the highest being found in the areas with least social cohesion [67].

The larger the town and the longer the individual has lived in the city, the greater the risk [68,69]. Zammit and coworkers examined whether the association between urbanicity and psychosis was explained by individual, school or area characteristics; social fragmentation was found to be most important [70].

As many people live in urban areas but only a tiny minority of these will develop schizophrenia, it is likely that the urban exposure is conditional on some other factor [71]. Place of birth could be a proxy marker for some other factor. However, because most people who are born in metropolitan areas are also brought up there, it is difficult to disentangle pre- and peri-natal effects from those operating later in childhood [36].

Migration

There is a high incidence of schizophrenia among migrant and ethnic minority groups, with a mean weighted relative risk among first-generation migrants of 2.7 (95% CI: 2.3–3.2) [72]. The association between migration and schizophrenia was noted by Odegard (1932) in Norwegian migrants to the USA [73]. He suggested selective migration of people who are genetically predisposed to develop the disorder. However, this

hypothesis has found little support, as it cannot explain the increased risk for schizophrenia found among second-generation migrants.

A high risk of psychosis has been demonstrated among Surinamese migrants in The Netherlands [74], African refugees in Sweden [75], Greek migrants to Belgium [76] and Scandinavian migrants to Denmark [77]. However, most attention has been directed towards the high incidence among the African–Caribbean population in UK [78,79].

The AESOP study discussed earlier indicated a ninefold increase in incidence among African–Caribbean individuals, mostly living in London, compared with white Britons [80]. This excess of psychosis cannot be explained exclusively in genetic terms or by the selective migration [81] or by misdiagnosis by British psychiatrists [82]. Social adversities, racial discrimination, family break-up and unemployment have all been proposed as contributing factors. Ethnic minority populations are at less risk in situations where they become majority populations [83,84]. Thus, Boydell and coworkers found that the incidence of schizophrenia in London among people from nonwhite ethnic minorities increased significantly as the proportion of nonwhite ethnic minorities in the local population fell [85].

United Kingdom black populations have also reported a higher prevalence of psychotic-like experiences compared with white British populations [86]. The association with a number of indicators of social disadvantage in the black Caribbean group is suggestive of a social contribution to the etiology [87]. However, it is only partly mediated by perceptions of disadvantage [88] and only partly explained by socioeconomic disadvantage [89].

Adversity in childhood & adulthood

■ Parental separation or loss

Agid and coworkers found that permanent separation from, or death of, one or both parents were associated with a more than threefold increased risk of schizophrenia [90]. Morgan and coworkers, using data from the AESOP study, observed that cases were approximately three-times more likely than controls to have experienced a long-term separation from one or both parents or to have had a parent die before the age of 16 years [91]. Furthermore, in their general population sample, separation was associated with increased odds of psychotic-like

experiences [86]. Of course, parental separation and loss are associated with a range of adverse early experiences, including family conflict, socioeconomic disadvantage and neglect and abuse [92]. Consequently, the debate has centered on the question of whether the separation or loss event itself is important or whether these are merely markers for family discord and disadvantage both before and after separation or loss.

Child abuse & victimization

There is renewed interest in the relationship between early childhood trauma and risk of psychosis [93]. Retrospective data from the second British National Survey of Psychiatric Morbidity showed a marked excess of victimizing experiences, especially during childhood, in people with psychosis [94]. Studies of specific psychotic symptoms have related hallucinations to childhood abuse and neglect [95]. Husted and coworkers found that the association between early trauma and schizophrenia remained significant after adjusting for paternal or maternal history of schizophrenia [96]. The mechanism by which childhood trauma leads to psychosis is still unclear, but it has been suggested that traumatic experiences may result in changes in the function of the hypothalamus–pituitary–adrenal axis, which is involved in the stress response [95].

Social exclusion

There is an association between social exclusion and psychosis [97,98]. Individuals with longstanding psychotic mental disorders often live alone [99], fail to establish long-term relationships [100] and have high rates of unemployment [101]. Agerbo and coworkers found that up to 19 years before the first hospitalization, the odds of being single and unemployed were higher for people with schizophrenia than for controls [102].

Social exclusion may be related to absence of social cohesion or support [103]. Morgan and coworkers reported that all current and long-term indicators (e.g., unemployment, living alone and/or social housing) were associated with an increased odds of psychosis in the AESOP study [98].

There remains uncertainty as to whether the association between social disadvantage and psychosis is a consequence of the disorder itself, leading to a drift down the social class scale (social drift hypothesis) and increasing isolation,

or an etiological factor increasing the risk of developing schizophrenia and other psychoses (social causation hypothesis) [104].

Stress

In rats, prolonged social defeat results in long-term changes of biochemical, physiological and behavioral parameters, such as hyperactivity of hypothalamic–pituitary–adrenal axis and the consequent increase in serum corticosterone levels, decrease of both hippocampal volume and hippocampal cell proliferation and depression-like symptoms [105].

In humans, the dysregulation of the hypothalamic–pituitary–adrenal axis that has been consistently reported in depression [106] has also been described in schizophrenia [107]. In a recent paper, Mondelli and coworkers found increased salivary cortisol in FEP patients, which was associated with smaller left hippocampal volume [108]. Other studies have supported the hypothesis that chronic experience of social defeat is associated with changes in the dopamine system [109,110].

Dopaminergic abnormalities in schizophrenia have been well replicated. Together with the evidence that dopamine D2 receptor antagonists are antipsychotic, this has given rise to the dopamine hypothesis. An integrative hypothesis suggests that dopamine dysregulation may be the final common consequence of the interaction between early developmental factors, environmental and social pressures (**Figure 1**) [111–113]. Other studies have shown abnormalities in NMDA receptors, suggesting a glutamatergic dysfunction [114], and deficits in the GABAergic system [115] in schizophrenia. Of course, there are close interactions between the dopamine, GABA and glutamate systems.

Conclusion & future perspective

We know a lot about the causal risk factors for schizophrenia. However, none of the risk factors we have discussed appear likely to ‘cause’ psychosis by itself. Elucidating gene–environment interactions may shed further light [116]. However, the history of medicine shows that there have been some spectacular applications of primary prevention based on incomplete knowledge [117]. Although understanding genetic susceptibility is crucial to elucidating the etiology of psychosis, environmental risk factors may be easier to modify. Kirkbride and coworkers investigated the proportion of psychotic illnesses that could be prevented if we could identify and remove all factors associated with ethnic

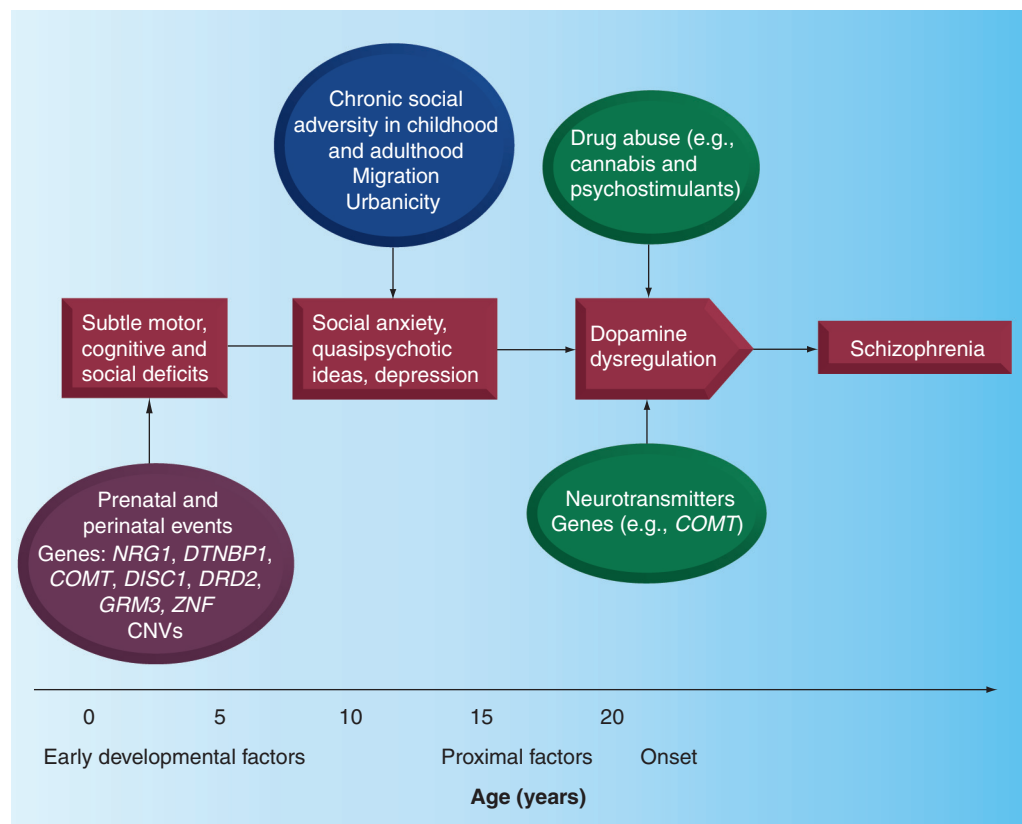


Figure 1. Developmental cascade towards schizophrenia.

CNV: Copy-number variation. Adapted with permission from [111].

minority status and urbanicity [118]. They calculated that up to 46.9% of all psychoses within the study regions could be prevented if exposures associated with the increased incidence in ethnic minority populations could be removed.

The evidence that obstetric and other early hazards to the fetus increase risk of schizophrenia has implications for prevention. In particular, it points to the importance of women with schizophrenia being given the best possible obstetric care. If prenatal infection turns out to be important, routine vaccination of women of reproductive age might prevent a proportion of cases.

Early indicators may include delays in childhood development, motor or cognitive impairment, difficulties on social adjustment, schizotypal personality traits as well than minor physical anomalies and neurological soft signs. A recent development that holds promise comes from studies that examined the significance of minor psychotic symptoms in late childhood and adolescence. Poulton and coworkers analyzed a cohort of 761 children and showed that self-reported psychotic symptoms 11 years of age predicted a very high risk of a

schizophreniform diagnosis at 26 years of age (odds ratio: 16.4; 95% CI: 3.9–67.8) [119]. Subsequent studies have shown that some of the same risk factors associated with adult schizophrenia are also associated with minor psychotic symptoms in late childhood and adolescence. Thus, Zammit found that obstetric events increase the risk of such symptoms [120]. Arseneault *et al.* showed that the risk of developing psychotic symptoms was associated with maltreatment by an adult and bullying by peers in a UK cohort of young twins [121]. In the same sample, psychotic symptoms were associated with earlier cognitive impairments and behavioral, emotional and educational problems [122].

Interventions could be beneficially aimed at adolescents with such minor psychotic symptoms, particularly if they are associated with earlier risk factors.

An obvious preventive strategy is to attempt to persuade young people to decrease their use of illicit drugs, particularly cannabis. However, such a strategy demands more courage and resources than most governments seem prepared to show.

These strategies are, in the main, universal preventive strategies, which are possibly too difficult to be applied to the population in general. At present, the main attempt at prevention is by early detection of those at high risk of schizophrenia; so-called prodromal cases. A variety of approaches from medication and psychosocial interventions to cognitive-behavioral therapy are being used in such prodromal cases in an attempt to prevent the onset of full-blown psychosis.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

Bibliography

Papers of special note have been highlighted as:

■ of interest

■ ■ of considerable interest

- 1 Jablensky A. The 100-year epidemiology of schizophrenia. *Schizophr. Res.* 28, 111–125 (1997).
- 2 McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med.* 2, 13 (2004).
- Systematically reviews the wealth of data available regarding the incidence of schizophrenia and the significant impact of sex, urbanicity and migrant status on the distribution.
- 3 McGrath JJ. Myths and plain truths about schizophrenia epidemiology – the NAPE lecture 2004. *Acta Psychiatr. Scand.* 111, 4–11 (2005).
- 4 Perala J, Suvisaari J, Saarni S *et al.* Lifetime prevalence of psychotic and bipolar I disorders in a general population. *Arch. Gen. Psychiatr.* 64, 19–28 (2007).
- 5 Tsuang M. Schizophrenia. genes and environment. *Biol. Psychiatr.* 47, 210–220 (2000).
- 6 Cardno AG, Marshall EJ, Coid B *et al.* Heritability estimates for psychotic disorders: the Maudsley twin psychosis series. *Arch. Gen. Psychiatr.* 56, 162–168 (1999).
- 7 Kendler KS, McGuire M, Gruenberg AM, O'Hare A, Spellman M, Walsh D. The roscommon family study. I. Methods, diagnosis of probands, and risk of schizophrenia in relatives. *Arch. Gen. Psychiatr.* 50, 527–540 (1993).
- 8 Tienari P. Interaction between genetic vulnerability and family environment: the Finnish adoptive family study of schizophrenia. *Acta Psychiatr. Scand.* 84, 460–465 (1991).
- 9 Owen MJ, Craddock N, O'Donovan MC. Suggestion of roles for both common and rare risk variants in genome-wide studies of schizophrenia. *Arch. Gen. Psychiatr.* 67, 667–673 (2010).
- Reviews the most recent genome-wide association studies of schizophrenia and considers future research directions by suggesting the need for large-scale studies.
- 10 Feuk L, Carson AR, Scherer SW. Structural variation in the human genome. *Nat. Rev. Genet.* 7, 85–97 (2006).
- 11 Stefansson H, Rujescu D, Cichon S *et al.* Large recurrent microdeletions associated with schizophrenia. *Nature* 455, 232–236 (2008).
- 12 Murray RM, Lewis SW. Is schizophrenia a neurodevelopmental disorder? *Br. Med. J. (Clin. Res. Ed.)* 295, 681–682 (1987).
- 13 Geddes JR, Verdoux H, Takei N *et al.* Schizophrenia and complications of pregnancy and labor an individual patient data meta-analysis. *Schizophr. Bull.* 25, 413–423 (1999).
- 14 Cannon TD, van Erp TG, Rosso IM *et al.* Fetal hypoxia and structural brain abnormalities in schizophrenic patients, their siblings, and controls. *Arch. Gen. Psychiatr.* 59, 35–41 (2002).
- 15 Stefanis N, Frangou S, Yakeley J *et al.* Hippocampal volume reduction in schizophrenia: effects of genetic risk and pregnancy and birth complications. *Biol. Psychiatr.* 46, 697–702 (1999).
- 16 Nicodemus KK, Marengo S, Batten AJ *et al.* Serious obstetric complications interact with hypoxia-regulated/vascular-expression genes to influence schizophrenia risk. *Mol. Psychiatr.* 13, 873–877 (2008).
- 17 Mittal VA, Ellman LM, Cannon TD. Gene-environment interaction and covariation in schizophrenia: the role of obstetric complications. *Schizophr. Bull.* 34, 1083–1094 (2008).
- Extensively discusses mechanisms by which the most well-documented environmental indicators of risk for schizophrenia may interact with susceptibility genes to trigger psychosis.
- 18 Susser ES, Lin SP. Schizophrenia after prenatal exposure to the Dutch hunger winter of 1944–1945. *Arch. Gen. Psychiatr.* 49, 983–988 (1992).
- 19 St Clair D, Xu M, Wang P *et al.* Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959–1961. *JAMA* 294, 557–562 (2005).
- 20 McGrath J, Saari K, Hakko H *et al.* Vitamin D supplementation during the first year of life and risk of schizophrenia: a Finnish birth cohort study. *Schizophr. Res.* 67, 237–245 (2004).
- 21 Brown AS, Bottiglieri T, Schaefer CA *et al.* Elevated prenatal homocysteine levels as a risk factor for schizophrenia. *Arch. Gen. Psychiatr.* 64, 31–39 (2007).
- 22 McGrath JJ, Welham JL. Season of birth and schizophrenia: a systematic review and meta-analysis of data from the southern hemisphere. *Schizophr. Res.* 35, 237–242 (1999).
- 23 Torrey EF, Miller J, Rawlings R, Yolken RH. Seasonality of births in schizophrenia and bipolar disorder: a review of the literature. *Schizophr. Res.* 28, 1–38 (1997).
- 24 Brown AS, Begg MD, Gravenstein S *et al.* Serologic evidence of prenatal influenza in the etiology of schizophrenia. *Arch. Gen. Psychiatr.* 61, 774–780 (2004).
- 25 Brown AS, Cohen P, Greenwald S, Susser E. Nonaffective psychosis after prenatal exposure to rubella. *Am. J. Psychiatr.* 157, 438–443 (2000).
- 26 Mortensen PB, Norgaard-Pedersen B, Waltoft BL, Sorensen TL, Hougaard D, Yolken RH. Early infections of *Toxoplasma gondii* and the later development of schizophrenia. *Schizophr. Bull.* 33, 741–744 (2007).

- 27 Buka SL, Tsuang MT, Torrey EF, Klebanoff MA, Bernstein D, Yolken RH. Maternal infections and subsequent psychosis among offspring. *Arch. Gen. Psychiatr.* 58, 1032–1037 (2001).
- 28 Brown AS, Schaefer CA, Quesenberry CP Jr, Shen L, Susser ES. No evidence of relation between maternal exposure to herpes simplex virus type 2 and risk of schizophrenia? *Am. J. Psychiatr.* 163, 2178–2180 (2006).
- 29 van der Werf M, Thewissen V, Dominguez MD, Lieb R, Wittchen H, van Os J. Adolescent development of psychosis as an outcome of hearing impairment: a 10-year longitudinal study. *Psychol. Med.* 41, 477–485 (2011).
- 30 Van Lieshout RJ, Voruganti LP. Diabetes mellitus during pregnancy and increased risk of schizophrenia in offspring: a review of the evidence and putative mechanisms. *J. Psychiatr. Neurosci.* 33, 395–404 (2008).
- 31 Hare EH, Moran PA. Raised parental age in psychiatric patients: evidence for the constitutional hypothesis. *Br. J. Psychiatry* 134, 169–177 (1979).
- 32 Malaspina D, Harlap S, Fennig S *et al.* Advancing paternal age and the risk of schizophrenia. *Arch. Gen. Psychiatr.* 58, 361–367 (2001).
- Shows a strong effect of advancing paternal age on the incidence of schizophrenia, supported by a large sample size.
- 33 Sipos A, Rasmussen F, Harrison G *et al.* Paternal age and schizophrenia: a population based cohort study. *BMJ* 329, 1070 (2004).
- 34 Torrey EF, Buka S, Cannon TD *et al.* Paternal age as a risk factor for schizophrenia: how important is it? *Schizophr. Res.* 114, 1–5 (2009).
- 35 Byrne M, Agerbo E, Ewald H, Eaton WW, Mortensen PB. Parental age and risk of schizophrenia: a case–control study. *Arch. Gen. Psychiatr.* 60, 673–678 (2003).
- 36 McGrath JJ, Susser ES. New directions in the epidemiology of schizophrenia. *Med. J. Aust.* 1(Suppl. 90), S7–S9 (2009).
- 37 Petersen L, Mortensen PB, Pedersen CB. Paternal age at birth of first child and risk of schizophrenia. *Am. J. Psychiatr.* 168, 82–88 (2011).
- 38 Murray RM, Sham P, Van Os J, Zanelli J, Cannon M, McDonald C. A developmental model for similarities and dissimilarities between schizophrenia and bipolar disorder. *Schizophr. Res.* 71, 405–416 (2004).
- 39 Curran C, Byrappa N, McBride A. Stimulant psychosis: systematic review. *Br. J. Psychiatr.* 185, 196–204 (2004).
- 40 Mazzoncini R, Donoghue K, Hart J *et al.* Illicit substance use and its correlates in first episode psychosis. *Acta Psychiatr. Scand.* 121, 351–358 (2010).
- 41 Paparelli A, Di Forti M, Morrison PD, Murray RM. Drug-induced psychosis: how to avoid star gazing in schizophrenia research by looking at more obvious sources of light. *Front. Behav. Neurosci.* 5, 1 (2011).
- 42 Chen CK, Lin SK, Sham PC *et al.* Pre-morbid characteristics and co-morbidity of methamphetamine users with and without psychosis. *Psychol. Med.* 33, 1407–1414 (2003).
- 43 Boileau I, Dagher A, Leyton M *et al.* Modeling sensitization to stimulants in humans: an [¹¹C]raclopride/positron emission tomography study in healthy men. *Arch. Gen. Psychiatr.* 63, 1386–1395 (2006).
- 44 Murray RM, Forti MD, Howes O. Integrating the epidemiology and pathogenesis of schizophrenia from the street to the striatum: integrating the epidemiology and pathogenesis of schizophrenia. *Adv. Schizophr. Res.* 5, 357–366 (2010).
- Comprehensive review of the field under investigation. This article attempts to integrate epidemiology and the major pathogenic theories of schizophrenia (the dopamine hypothesis and the neurodevelopmental hypothesis).
- 45 Smith MJ, Thirthalli J, Abdallah AB, Murray RM, Cottler LB. Prevalence of psychotic symptoms in substance users: a comparison across substances. *Compr. Psychiatr.* 50, 245–250 (2009).
- 46 van Os J, Bak M, Hanssen M, Bijl RV, de Graaf R, Verdoux H. Cannabis use and psychosis: a longitudinal population-based study. *Am. J. Epidemiol.* 156, 319–327 (2002).
- 47 Henquet C, Murray R, Linszen D, van Os J. The environment and schizophrenia: the role of cannabis use. *Schizophr. Bull.* 31, 608–612 (2005).
- 48 Moore TH, Zammit S, Lingford-Hughes A *et al.* Cannabis use and risk of psychotic or affective mental health outcomes: a systematic review. *Lancet* 370, 319–328 (2007).
- 49 Yucel M, Zalesky A, Takagi MJ *et al.* White-matter abnormalities in adolescents with long-term inhalant and cannabis use: a diffusion magnetic resonance imaging study. *J. Psychiatr. Neurosci.* 35, 409–412 (2010).
- 50 Rais M, Cahn W, Van Haren N *et al.* Excessive brain volume loss over time in cannabis-using first-episode schizophrenia patients. *Am. J. Psychiatr.* 165, 490–496 (2008).
- 51 Yucel M, Solowij N, Respondek C *et al.* Regional brain abnormalities associated with long-term heavy cannabis use. *Arch. Gen. Psychiatr.* 65, 694–701 (2008).
- 52 Di Forti M, Morgan C, Dazzan P *et al.* High-potency cannabis and the risk of psychosis. *Br. J. Psychiatr.* 195, 488–491 (2009).
- First study to collect detailed information on the patterns of use and potency of cannabis and their effects on increasing the risk of psychosis.
- 53 Arseneault L, Cannon M, Poulton R, Murray R, Caspi A, Moffitt TE. Cannabis use in adolescence and risk for adult psychosis: longitudinal prospective study. *BMJ* 325, 1212–1213 (2002).
- 54 Large M, Sharma S, Compton MT, Slade T, Nielssen O. Cannabis use and earlier onset of psychosis: a systematic meta-analysis. *Arch. Gen. Psychiatr.* 68(6), 555–61 (2011).
- 55 Henquet C, Di Forti M, Morrison P, Kuepper R, Murray RM. Gene–environment interplay between cannabis and psychosis. *Schizophr. Bull.* 34, 1111–1121 (2008).
- 56 McGuire PK, Jones P, Harvey I, Williams M, McGuffin P, Murray RM. Morbid risk of schizophrenia for relatives of patients with cannabis-associated psychosis. *Schizophr. Res.* 15, 277–281 (1995).
- 57 Caspi A, Moffitt TE, Cannon M *et al.* Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyltransferase gene: longitudinal evidence of a gene X environment interaction. *Biol. Psychiatr.* 57, 1117–1127 (2005).
- 58 Henquet C, Rosa A, Krabbendam L *et al.* An experimental study of catechol-O-methyltransferase Val158Met moderation of δ -9-tetrahydrocannabinol-induced effects on psychosis and cognition. *Neuropsychopharmacology* 31, 2748–2757 (2006).
- 59 Zammit S, Spurlock G, Williams H *et al.* Genotype effects of *CHRNA7*, *CNR1* and *COMT* in schizophrenia: interactions with tobacco and cannabis use. *Br. J. Psychiatr.* 191, 402–407 (2007).
- 60 van Winkel R. Family-based analysis of genetic variation underlying psychosis-inducing effects of cannabis: sibling analysis and proband follow-up. *Arch. Gen. Psychiatr.* 68, 148–157 (2011).
- 61 Lewis G, David A, Andreasson S, Allebeck P. Schizophrenia and city life. *Lancet* 340, 137–140 (1992).

- 62 Kelly BD, O'Callaghan E, Waddington JL *et al.* Schizophrenia and the city: a review of literature and prospective study of psychosis and urbanicity in Ireland. *Schizophr. Res.* 116, 75–89 (2010).
- 63 Faris REL, Durham HW. *Mental disorders in urban areas: an ecological study of schizophrenia and other psychoses.* The University of Chicago press, Chicago, IL, USA, 270 (1939).
- 64 Morgan C, Dazzan P, Morgan K *et al.* First episode psychosis and ethnicity: initial findings from the AESOP study. *World Psychiatr.* 5, 40–46 (2006).
- 65 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. Psychiatr.* 63, 250–258 (2006).
- **Highlights the variation in incidence of schizophrenia in terms of age, sex, ethnic group and place, as well as the importance of the environmental effects in its etiology.**
- 66 Kirkbride JB, Fearon P, Morgan C *et al.* Neighbourhood variation in the incidence of psychotic disorders in southeast London. *Soc. Psychiatr. Psychiatr. Epidemiol.* 42, 438–445 (2007).
- 67 Kirkbride JB, Morgan C, Fearon P, Dazzan P, Murray RM, Jones PB. Neighbourhood-level effects on psychoses: re-examining the role of context. *Psychol. Med.* 37, 1413–1425 (2007).
- 68 Pedersen CB, Mortensen PB. Evidence of a dose–response relationship between urbanicity during upbringing and schizophrenia risk. *Arch. Gen. Psychiatr.* 58, 1039–1046 (2001).
- 69 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.* 340, 603–608 (1999).
- 70 Zammit S, Lewis G, Rasbash J, Dalman C, Gustafsson JE, Allebeck P. Individuals, schools, and neighborhood: a multilevel longitudinal study of variation in incidence of psychotic disorders. *Arch. Gen. Psychiatr.* 67, 914–922 (2010).
- 71 Krabbendam L, van Os J. Schizophrenia and urbanicity: a major environmental influence – conditional on genetic risk. *Schizophr. Bull.* 31, 795–799 (2005).
- 72 Cantor-Graae E, Selten JP. Schizophrenia and migration: a meta-analysis and review. *Am. J. Psychiatr.* 162, 12–24 (2005).
- 73 Odegaard O. Emigration and insanity: a study of mental disease among Norwegian born population in Minnesota. *Acta Psychiatr. Neurol. Scand.* 4(Suppl.), 1206 (1932).
- 74 Selten JP, Slaets JP, Kahn RS. Schizophrenia in Surinamese and Dutch Antillean immigrants to The Netherlands: evidence of an increased incidence. *Psychol. Med.* 27, 807–811 (1997).
- 75 Johansson LM, Sundquist J, Johansson SE, Bergman B. Immigration, moving house and psychiatric admissions. *Acta Psychiatr. Scand.* 98, 105–111 (1998).
- 76 Charalabaki E, Bauwens F, Stefanos G, Madianos M, Mendlewicz J. Immigration and psychopathology: a clinical study. *Eur. Psychiatr.* 10, 237–244 (1995).
- 77 Mortensen PB, Cantor-Graae E, McNeil TF. Increased rates of schizophrenia among immigrants: some methodological concerns raised by Danish findings. *Psychol. Med.* 27, 813–820 (1997).
- 78 Bebbington P, Hurry J, Tennant C, Sturt E, Wing JK. Epidemiology of mental disorders in Camberwell. *Psychol. Med.* 11, 561–579 (1981).
- 79 Castle D, Wessely S, Der G, Murray RM. The incidence of operationally defined schizophrenia in Camberwell, 1965–84. *Br. J. Psychiatr.* 159, 790–794 (1991).
- 80 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.* 36, 1541–1550 (2006).
- **Largest incidence study of psychosis in England. It shows that ethnic minority groups, especially African–Caribbeans and black Africans, are at increased risk of psychosis.**
- 81 Sharpley M, Hutchinson G, McKenzie K, Murray RM. Understanding the excess of psychosis among the African–Caribbean population in England. Review of current hypotheses. *Br. J. Psychiatr. Suppl.* 40, S60–S68 (2001).
- 82 Lewis G, Croft-Jeffreys C, David A. Are British psychiatrists racist? *Br. J. Psychiatr.* 157, 410–415 (1990).
- 83 Bhugra D, Hilwig M, Hossein B *et al.* First-contact incidence rates of schizophrenia in Trinidad and one-year follow-up. *Br. J. Psychiatr.* 169, 587–592 (1996).
- 84 Hickling FW, Rodgers-Johnson P. The incidence of first contact schizophrenia in Jamaica. *Br. J. Psychiatr.* 167, 193–196 (1995).
- 85 Boydell J, van Os J, McKenzie K *et al.* Incidence of schizophrenia in ethnic minorities in London: ecological study into interactions with environment. *BMJ* 323, 1336–1338 (2001).
- 86 Morgan C, Fisher H, Hutchinson G *et al.* Ethnicity, social disadvantage and psychotic-like experiences in a healthy population based sample. *Acta Psychiatr. Scand.* 119, 226–235 (2009).
- 87 Fearon P, Morgan C. Environmental factors in schizophrenia: the role of migrant studies. *Schizophr. Bull.* 32, 405–408 (2006).
- 88 Cooper C, Morgan C, Byrne M *et al.* Perceptions of disadvantage, ethnicity and psychosis. *Br. J. Psychiatr.* 192, 185–190 (2008).
- 89 Brugha T, Jenkins R, Bebbington P, Meltzer H, Lewis G, Farrell M. Risk factors and the prevalence of neurosis and psychosis in ethnic groups in Great Britain. *Soc. Psychiatr. Psychiatr. Epidemiol.* 39, 939–946 (2004).
- 90 Agid O, Shapira B, Zislin J *et al.* Environment and vulnerability to major psychiatric illness: a case control study of early parental loss in major depression, bipolar disorder and schizophrenia. *Mol. Psychiatr.* 4, 163–172 (1999).
- 91 Morgan C, Kirkbride J, Leff J *et al.* Parental separation, loss and psychosis in different ethnic groups: a case–control study. *Psychol. Med.* 37, 495–503 (2007).
- 92 Rutter M. *Genes and Behaviour: Nature–Nurture Interplay explained.* Blackwell Publishing, Oxford, UK (2006).
- 93 Morgan C, Fisher H. Environment and schizophrenia: environmental factors in schizophrenia: childhood trauma – a critical review. *Schizophr. Bull.* 33, 3–10 (2007).
- 94 Bebbington PE, Bhugra D, Brugha T *et al.* Psychosis, victimisation and childhood disadvantage: evidence from the second British National Survey of Psychiatric Morbidity. *Br. J. Psychiatr.* 185, 220–226 (2004).
- **Analyzes data from the second British National Survey of Psychiatric Morbidity and demonstrates associations between psychosis and a number of early victimization experiences.**
- 95 Read J, van Os J, Morrison AP, Ross CA. Childhood trauma, psychosis and schizophrenia: a literature review with theoretical and clinical implications. *Acta Psychiatr. Scand.* 112, 330–350 (2005).
- 96 Husted JA, Ahmed R, Chow EW, Brzustowicz LM, Bassett AS. Childhood trauma and genetic factors in familial schizophrenia associated with the *NOS1AP* gene. *Schizophr. Res.* 121, 187–192 (2010).

- 97 Boydell J, van Os J, McKenzie K, Murray RM. The association of inequality with the incidence of schizophrenia – an ecological study. *Soc. Psychiatry Psychiatr. Epidemiol.* 39, 597–599 (2004).
- 98 Morgan C, Kirkbride J, Hutchinson G *et al.* Cumulative social disadvantage, ethnicity and first-episode psychosis: a case–control study. *Psychol. Med.* 38, 1701–1715 (2008).
- **Demonstrates a strong association between indicators of disadvantage and psychosis.**
- 99 Harvey CA, Pantelis C, Taylor J *et al.* The Camden schizophrenia surveys. II. High prevalence of schizophrenia in an inner London borough and its relationship to socio–demographic factors. *Br. J. Psychiatr.* 168, 418–426 (1996).
- 100 Walsh E, Leese M, Taylor P *et al.* Psychosis in high-security and general psychiatric services: report from the UK700 and special hospitals’ treatment resistant schizophrenia groups. *Br. J. Psychiatr.* 180, 351–357 (2002).
- 101 Thornicroft G, Strathdee G, Phelan M *et al.* Rationale and design. PRISM Psychosis Study I. *Br. J. Psychiatr.* 173, 363–370 (1998).
- 102 Agerbo E, Byrne M, Eaton WW, Mortensen PB. Marital and labor market status in the long run in schizophrenia. *Arch. Gen. Psychiatr.* 61, 28–33 (2004).
- 103 Allardyce J, Boydell J. Review: the wider social environment and schizophrenia. *Schizophr. Bull.* 32, 592–598 (2006).
- 104 Freeman H. Schizophrenia and city residence. *Br. J. Psychiatr. Suppl.* 23, 39–50 (1994).
- 105 Becker C, Zeau B, Rivat C, Blugeot A, Hamon M, Benoliel JJ. Repeated social defeat-induced depression-like behavioral and biological alterations in rats: involvement of cholecystinin. *Mol. Psychiatr.* 13, 1079–1092 (2008).
- 106 Kunugi H, Ida I, Ohashi T *et al.* Assessment of the dexamethasone/CRH test as a state-dependent marker for hypothalamic–pituitary–adrenal (HPA) axis abnormalities in major depressive episode: a Multicenter Study. *Neuropsychopharmacology* 31, 212–220 (2006).
- 107 Tandon R, Mazzara C, DeQuardo J *et al.* Dexamethasone suppression test in schizophrenia: relationship to symptomatology, ventricular enlargement, and outcome. *Biol. Psychiatr.* 29, 953–964 (1991).
- 108 Mondelli V, Pariante CM, Navari S *et al.* Higher cortisol levels are associated with smaller left hippocampal volume in first-episode psychosis. *Schizophr. Res.* 119, 75–78 (2010).
- **By investigating the relationship between cortisol secretion and hippocampal volume, this study suggests that stress-related processes contribute to the small hippocampal volume observed in schizophrenia.**
- 109 Hall FS, Wilkinson LS, Humby T *et al.* Isolation rearing in rats: pre- and postsynaptic changes in striatal dopaminergic systems. *Pharmacol. Biochem. Behav.* 59, 859–872 (1998).
- 110 Lodge DJ, Grace AA. Developmental pathology, dopamine, stress and schizophrenia. *Int. J. Dev. Neurosci.* 29(3), 207–213 (2011).
- 111 Di Forti M, Lappin JM, Murray RM. Risk factors for schizophrenia – all roads lead to dopamine. *Eur. Neuropsychopharmacol.* 1S–101S 7(Suppl. 2), 10–17 (2007).
- **Integrates contradictory results and emphasizes the role of dopamine dysregulation as the final common pathway underlying psychotic symptoms.**
- 112 Murray RM, Lappin J, Di Forti M. Schizophrenia: from developmental deviance to dopamine dysregulation. *Eur. Neuropsychopharmacol.* 18(Suppl. 3), S129–S134 (2008).
- 113 Stilo SA, Murray RM. The epidemiology of schizophrenia: replacing dogma with knowledge. *Dialogues Clin. Neurosci.* 12, 305–315 (2010).
- 114 Moghaddam B. Bringing order to the glutamate chaos in schizophrenia. *Neuron* 40, 881–884 (2003).
- 115 Jarskog LF, Miyamoto S, Lieberman JA. Schizophrenia: new pathological insights and therapies. *Annu. Rev. Med.* 58, 49–61 (2007).
- 116 van Os J, Rutten BP, Poulton R. Gene–environment interactions in schizophrenia: review of epidemiological findings and future directions. *Schizophr. Bull.* 34, 1066–1082 (2008).
- **Excellent review of state-of-the-art and future directions of gene–environmental interactions in schizophrenia research.**
- 117 Brown AS, McGrath JJ. The prevention of schizophrenia. *Schizophr. Bull.* 37(2), 257–261 (2011).
- 118 Kirkbride J, Coid JW, Morgan C *et al.* Translating the epidemiology of psychosis into public mental health: evidence, challenges and future prospects. *J. Public Ment. Health* 9, 4–14 (2010).
- 119 Poulton R, Caspi A, Moffitt TE, Cannon M, Murray R, Harrington H. Children’s self-reported psychotic symptoms and adult schizophreniform disorder: a 15-year longitudinal study. *Arch. Gen. Psychiatr.* 57, 1053–1058 (2000).
- 120 Zammit S, Odd D, Horwood J *et al.* Investigating whether adverse prenatal and perinatal events are associated with non-clinical psychotic symptoms at age 12 years in the ALSPAC birth cohort. *Psychol. Med.* 39, 1457–1467 (2009).
- 121 Arseneault L, Cannon M, Fisher HL, Polanczyk G, Moffitt TE, Caspi A. Childhood trauma and children’s emerging psychotic symptoms: a genetically sensitive longitudinal cohort study. *Am. J. Psychiatr.* 168, 65–72 (2011).
- 122 Polanczyk G, Moffitt TE, Arseneault L *et al.* Etiological and clinical features of childhood psychotic symptoms: results from a birth cohort. *Arch. Gen. Psychiatr.* 67, 328–338 (2010).