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The psychosis high risk state

Rutigliano G, Manalo M, Fusar-Poli P[1]

Affiliation

Department of Psychosis Studies, IoPPN, KCL UK

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[1] Corresponding author Dr. Paolo Fusar-Poli, Department of Psychosis Studies, Institute of Psychiatry PO63, De Crespigny Park, SE58AF London UK. Phone +44(0)2078480900; e-mail: paolo.fusar-poli@kcl.ac.uk

Abstract

The disabling nature and costly impact of mental disorders, such as schizophrenia, can cause significant burden to both person and society. It is also indicated that the negative outcomes associated with psychosis may, in part, be due to the delayed detection and initiation of treatment. Preventative interventions in several arenas of medicine have advanced; however have only come to the fore in psychiatry in the last two decades. It was long-known that a preclinical phase preceded psychosis, now commonly termed as ultra high-risk (UHR) status. The advent of specialized early intervention services provided the cornerstone in taking a preventative and timely endeavor to maximize the chance of positive outcomes in psychosis. Despite the potential, the current state of the UHR concept lacks consensus in how at-risk individuals should be approached. This chapter aims to provide an overview of how preventative medicine can intersect with psychiatry by focusing on the psychosis high risk state. It describes the current criteria and screening procedures used to prospectively detect UHR individuals, as well as discussing the validity of these tools. Whilst advocating the benefits of focused interventions, this chapter also recognizes current challenges and the controversy that leaves the psychosis high risk state on fertile ground for wavering opinions. The chapter concludes with an exploration and discussion that proposes an improved conceptualization of the high risk state and how this can direct intervention, as well as suggesting future lines of research in this area.

Background

Over the past couple of decades, preventative approaches in several medical fields have flourished and developed. In fact, historically in the last century in the industrialized countries, an *epidemiological shift* occurred from infectious to chronic diseases, hence from premature death to years lived with disability, as the main concern for health-related professions[1]. As a consequence, the major goal of health policies became to preserve individuals in full health for the standard life expectancy, by means of preventative interventions.

The Institute of Medicine defines three categories of preventative interventions, according to their target population's level of risk:

1. Universal preventive interventions target "the general population that has not been identified on the basis of individual risk" [2], hence they are usually implemented in schools, whole communities, or workplaces.

2. Selective preventive interventions target "population sub-groups with a significantly higher risk than the wider population" [2]. They aim at preventing the emergence of a given disorder, by addressing biological, psychological, or social risk factors known to be more prominent among high-risk groups.

3. Indicated preventive interventions target "high-risk individuals who are identified as having minimal but detectable signs or symptoms foreshadowing a given disorder" [2]. Interventions focus on the immediate risk and protective factors present in the environments surrounding individuals.

Until two decades ago, the field of psychiatry had remained excluded from preventative approaches, particularly for interventions in schizophrenia. Psychiatric interventions were confined to address the acute phase of illness where positive and negative symptoms were florid, or the more chronic stage where functional decline was evident [3].

However over the past two decades, availability of psychometric instruments to prospectively identify subjects at high clinical risk for psychosis has triggered the development of preventative diagnoses and interventions in psychosis.

Clinical relevance and impact of delayed treatment

Recent surveys into the morbidity burden in Europe reported disorders of the brain and mental disorders as contributing 26.6% of the total cause burden (30.1% in females and 23.4% in males) (Fig.1), as measured by DALYs (Disability-Adjusted Life Years), which is the sum of YLLs (Years of Life Lost due to premature mortality) and YLDs (Years Lived with Disability)[4]. Mental disorders are extremely disabling and costly, as indicated by the amount of work loss days, loss of work productivity, early retirement, and quality of life. Moreover, compared to other chronic diseases, they exert their load mainly on young adult men from 15-39 years of age, who represent the most economically active fraction of the population[5] (Fig.1). Among disorders of the brain, schizophrenia ranks as the 8th cause of DALYs in Europe[4]. Worldwide, a disturbingly high gap exists between the prevalence of those with mental disorders and those who receive treatment, particularly in low middle-income countries. It emerged that only about 35% to 50% of all subjects with mental disorders receive any professional help for their health[6]. Moreover, even once provided, there is often a notable treatment delay. A recent prospective study has estimated that the duration of untreated psychosis (DUP), defined as the time of onset of the first psychotic symptom to the initiation of adequate treatment[7], has a median value of 25.7 weeks, ranging from 2 weeks up to 182 weeks[8]. A significant correlation has been consistently observed between long lapses of DUP and outcome [9]. A long DUP has been found to be associated with more severe positive and negative symptoms [10-12], longer length of first hospitalization[13], poorer remission status and higher risk of relapse and rehospitalisation[8, 11, 13, 14]. Such negative outcomes can lead to further consequences, such as increased burden and expressed emotion in the family[15], reduced compliance to treatment[16, 17], lower treatment response rates [18-22], increased risk of depression, suicide and self-harming behaviour [23-25], higher risk of violence, aggression and delinquent behaviour [26-28] and eventually greater impairment in general functioning, social functioning and quality of life[11, 14, 29, 30].

Early detection and intervention services serve as potential means of the timely recognition and initiation of treatment for psychosis. Indeed evidence has shown that the introduction of such services is consistently followed by a reduction in the DUP, an increase in the proportion of patients treated within 6 months of onset and a significant improvement in short term clinical outcome, in terms of rates of hospitalization and compulsory admission[31, 32].

Delaying treatment to the point where acute and disturbing psychotic symptoms have manifested may potentially place the individual at a vulnerable stage along the continuum of schizophrenia, which is a slippery slope down towards the classically described deterioration syndrome [30].

*** Figure 1 about here ***

Detectable preclinical phase

The existence of early symptoms predating the onset of schizophrenia has been long recognized[33, 34] and were initially named "prodromal" in 1932 by Mayer-Gross[35]. The research field regarding psychotic antecedents was launched in 1989 with the work of Huber and Gross[36], who investigated the chance of those presenting with basic disturbances would transition to full-blown psychosis. Later, the ABC (Age, Begin, and Course) Schizophrenia Study, a representative study on a large group of patients of whom 232 suffered from first-episode psychosis, provided more robust evidence that psychotic symptoms are already present before the first hospitalization for schizophrenia, on average for 1 year and up to 5 years in up to 73% of all patients[37-39]. Earliest signs of a mental disorder in the sense of prodromal symptoms had occurred an average 5-6 years before first hospitalization and 4-5 years before first psychotic symptoms [37-40]

Despite the concept being widely known, the prodromal phase still lacked univocal definition until two decades ago. This was due to the difficulty in unambiguously marking whether or when an individual's experience or behaviour has crossed the boundary from the eccentric or unusual into the psychotic. A further challenge was the blurred and pleiotropic nature of prodromal symptoms, which lay mainly in the domain of depressive mood, negative symptoms and functional impairment[41], rather than in that of the more dramatic positive psychotic symptoms, such as hallucinations and delusions[37, 42] (Fig.2).

*** Figure 2 about here ***

A reliable and accurate detection of the preclinical phase of schizophrenia requires adequate frameworks and instruments. Over the past two decades two major trains of research have been developed for and applied to young help-seeking individuals at specialized services. The former, which had been pioneered by the Melbourne group of the Personal Assessment and Crisis Evaluation (PACE) clinic[43, 44], gave rise to ultra-high risk (UHR)[45], clinical high-

risk[46] or at-risk mental state (ARMS) status[47]; the latter, based on the investigations of Klosterklotter et al. (1996), focused on basic symptoms (BS)[48].

The mentioned preliminary investigations have put forth the operationalized high risk (HR) diagnostic criteria below:

- Attenuated Psychotic Symptoms (APS), which encompasses young people experiencing psychotic symptoms at sub-threshold intensity - not severe enough- or sub-threshold frequency -not occurring often enough to meet a diagnosis of schizophrenia.

- Brief Limited Intermittent Psychotic Symptoms (BLIPS), defined as the presence of a psychotic episode of less than seven days which remit spontaneously with no medication or hospitalization.

- Genetic Risk and Deterioration Syndrome (GRD), which includes young people at-risk of psychosis due to the combination of a trait vulnerability (i.e. family history of psychosis in a first degree relative or schizotypal personality disorder in the identified patient) and a significant deterioration in mental state and/or functioning.

- Cognitive perceptive Basic Symptoms (BS), which identifies at-risk persons on the basis of subtle cognitive and perceptive alterations. Basic symptoms are subjective disturbances of different domains, including perception, thought processing, language and attention that are distinct from classical psychotic symptoms. They are independent of abnormal thought content and reality testing, and insight into the symptoms' psychopathologic nature is intact[49].

The APS criterion is the most prevalent within the ARMS. For example, it resulted in the most represented diagnostic group (70%) followed by APS + GRD (11%) and BLIPS (9%) in a ten-year survey (2001-2011) of the Outreach and support in South London (OASIS) service[50].

The screening procedures

The assessment of young help-seeking subjects is performed via different semi-structured psychometric interviews, which operationalize the above-mentioned criteria. Similar, yet not exactly alike, instruments have been developed and prospectively validated for the UHR/CHR/ARMS state. The first psychometric instrument, the Comprehensive Assessment of At-Risk Mental State (CAARMS), was proposed by Yung et al.[51] on the basis of the work of the Melbourne group of the Personal Assessment and Crisis Evaluation (PACE)[52],

whose goal was to determine the reliability of the prodromal symptoms in first-episode patients.

In the following years, three further semi-structured interviews were developed; the Structured Interview for Prodromal Symptoms (SIPS) (including the companion Scale Of Prodromal Symptoms, SOPS)[53]; the Early Recognition Inventory for the Retrospective Assessment of the Onset of Schizophrenia (ERIraos)[54]; and the Basel Screening Instrument for Psychosis (BSIP)[55]– and a self-rating Prodromal screening Questionnaire (PQ) has been developed and validated[56].

Regarding basic symptoms, they were originally assessed using the Bonn Scale for the Assessment of Basic Symptoms (BSABS)[57] and, more recently, the Schizophrenia Proneness Instrument, Adult version (SPI-A) [58]. Besides a variety of subjective disturbances in affect, drive, stress tolerance, and body perception, these instruments focus on self-perceived cognitive and perceptual changes, ultimately clustered in 2 subsets relating to the COPER criteria (10 cognitive-perceptive BS) and the COGDIS criteria (the 9 cognitive BS that are the most predictive of later psychosis)(compare chapter by Schultze-Lutter in this volume).

Positive predictive value

Although summary results of the diagnostic accuracy of the UHR criteria are still lacking, data from different research groups carrying out psychosis preventative interventions are available and informative. A recent retrospective evaluation in patients with first-episode psychosis found the UHR construct to be highly sensitive. Up to 98.4% of patients reported prodromal symptoms predating the onset of full-blown psychosis[59].

As for positive predictive value, a meta-analysis calculated that on average 29.2% of subjects in a HR state transitioned to a full psychotic episode within 24 months. The transition risk progressively increased over time, ranging from 17.7% at 6 months up to a peak of 35.8% at 36 months[60].

The transition risk following a UHR diagnosis was significantly higher in subjects meeting the criteria compared to help-seeking subjects who screened as negative (30% vs 2%)[61].

Epidemiology of UHR symptoms

In order to have the "attenuated psychotic syndrome" criteria, currently listed in Section III of the DSM-5 [62], included in the DSM-5 main section, its prevalence and clinical significance in the general population need to be elucidated. The epidemiological validity of the UHR state remains a major issue. In fact, the psychosis high-risk criteria achieved validity only in help-seeking subjects. Furthermore, the UHR syndrome did not show epidemiological stability overtime, since a decline in transition rates has been observed over recent years. Different explanations were proposed for the reported trend. Firstly, local communities are becoming more familiar with the HR state, thus referring younger clients at earlier and less severe stages of the prodrome, which could require longer follow-up periods to transition. Secondly, more recent studies recruit subjects who are also offered active treatments and this clinical engagement can potentially impact on the transition risk [60]. In studies conducted in non-help seeking community-based adolescents, UHR criteria, as operationalized by the aforementioned psychometric instruments, were met by 2% to 8% of the participants, without applying the criterion of a 30% drop in functioning in the last year. The latter would decrease the prevalence to 0-0.9% [63, 64]. Similarly, a study found that 0.3% of young adults from the general population (age range 16-40 years) met current "attenuated psychosis syndrome" criteria [62]. However, having excluded the criterion for an onset or worsening of the APS within the past year led to a prevalence of 2.6%, thus avoing to dismiss 2.3% of subjects who experienced and were distressed by APS [65]. It has been proposed that since the APS is to be considered a self-contained, rather than an at-risk syndrome, the onset/worsening criteria originally proposed to capture the progression towards frank psychosis would be better revised to differentiate from schizotypal traits (i.e., to "not always having been present in its current severity") [65]. In the same way, Psychotic-Like Experiences (PLEs) have proven to have very high sensitivity but far too low specificity. Delusion- or hallucination-like experiences are referred with a prevalence rate of 5% and an incidence rate of 3% in the general population [66], but in most cases they are transitory, not associated with any distress and not related to any actual transition risk toward psychosis[63, 65-69].

The epidemiological studies conducted in general population are affected by several limitations. Telephone interviews are generally preferred to face-to-face interviews, because of their assumed larger response rate. However, they may introduce some selection bias given to unequally distributed availability of telephone numbers or language skill exclusion criterion. On the other hand, face-to-face interviews may lead to ascertainment bias, as

persons with family history might be more willing to participate, thus enriching the rates of the condition under study. Besides these caveats, future studies in the general population should compare the prevalence rates using different time and functioning deficit criteria in order to identify an optimal threshold to reliably distinguish between at-risk and non-at-risk persons [63-65].

Focused interventions

The care provided by early intervention services has been shown to reduce the DUP as well as improve short term clinical outcomes, such as the rates of hospitalization and compulsory admission[32].

Although the implementation of early intervention services leads to a great economic burden compared to the costs of standard care in the first years, the apparent economic loss due to direct costs (diagnostic measures, treatment and care)[4] is largely compensated in the following years by a substantial reduction of the disproportionally high indirect cost burden (disability, quality of life) of psychosis. A meta-analysis has further confirmed the cost effectiveness of early detection and early intervention services[70].

Treatment guidelines proposed by different international organizations have been depicted in Table 1. A recent meta-analysis of 11 trials including 1246 participants showed that focused interventions can halve the risk of psychosis onset (RR=0.5) [71]. Treatments that have demonstrated efficacy include cognitive therapy[72], cognitive behavioural therapy (CBT)[73], antipsychotic drugs[74], combined psychological and pharmacological interventions (risperidone plus CBT)[75], nutritional interventions (omega-3 fatty acids)[76], and integrated psychological interventions (cognitive therapy, social skills training, psychoeducation for family, and cognitive remediation)[77]. However, the evidence collected from these trials is not to be considered conclusive but rather preliminary[71]. Moreover, since the treatment is biased toward attenuated positive psychotic symptoms, it is scarcely tailored to negative symptoms and early deficits, which are among the main complaints of HR subjects and best correlate with loss of functioning and worse prognosis[78, 79]. Until better alternative interventions specifically targeting this medical condition are identified, the safest approach is recommended with careful consideration of the risk-benefit ratio of treatment.

*** Table 1 about here ***

Comparison with other preventative approaches in somatic medicine

The goodness of psychosis prevention can be expressed through statistical indexes and so directly compared with other established preventative approaches in somatic medicine. Preventative cognitive behavioural therapies in psychosis are associated with a 0.5 RRR (Relative Risk Reduction) and a NNT (number of subjects who need to be treated to prevent one additional bad outcome) of 14[80, 81]. These values are comparable to those calculated for metformin in the prevention of diabetes (NNT = 14)[82] and even superior to those found for statins in preventing cardiovascular serious events (NNT = 25), although these were computed in the longer term[83] (Tab.2).

*** Table 2 about here ***

Risk syndrome or mental disorder

The preparation of the fifth revision of the Diagnostic and Statistical Manual for Mental Disorders (DSM-5) raised a debate about the inclusion of a risk syndrome for psychosis, which is alike the diagnosis of each grade of cervical dysplasia that are included in ICD-10. The main objections to its inclusion pointed towards the potential stigma associated with a diagnosis of schizophrenia as well as the over-treatment of subjects falsely classified as positive, that is, who will never go on to develop psychosis. Indeed, UHR individuals, by definition, already experience changes in thinking, perception, affect, and behaviour, as well as significant decline in psychosocial functioning and in quality of life. The formal evidence that HR subjects are "probably at risk but certainly ill"[84] derives from a meta-analysis, which demonstrated that HR subjects are as impaired as psychotic patients in quality of life and global functioning at a level that is lower than healthy controls[85]. Moreover, the level of global functioning seems to predict later conversion to psychosis[85]. Therefore, it has been proposed that the currently defined "at-risk state" be conceptualized as an independent disorder in its own right[86]. Consequently, the emphasis would move from prediction and prevention to symptom improvement.

Nonetheless, the observations above only provide support for the conceptual validity of the HR state, i.e. correctly distinguishing between disorder and normality. There is still much to be done in order to fulfill construct validity, i.e. correctly distinguishing between the actual and other disorders, which will be needed in order to bring a new APS syndrome in the DSM-5.1 main text[87]. In particular, the syndrome should additionally demonstrate biological markers, such as laboratory and instrumental correlates; epidemiological validity and socio-demographic consistency; and diagnostic stability, in terms of delineation of one disorder from another and predictability of the course of illness[88]. With regards to diagnostic stability, it should be noted that the UHR is usually an aggregate of comorbid disorders. Since psychopathological boundaries are not so well-defined, patients at-risk for psychosis may fulfill diagnostic criteria for depression, anxiety, substance abuse, personality disorders, and developmental disorders[73]. More importantly, the construct holds the characteristic of pluripotency, in terms of heterogeneity of longitudinal outcomes. Among non-transitioning patients, about 46% appear to remit [89], some persist in ongoing attenuated psychotic symptoms, and others progress to other disorders, mainly bipolar disorder, depression and anxiety[73]. A meta-analysis performed on a database of 2182 HR subjects revealed that the available HR criteria, in particular the BS criteria, are strongly biased toward the identification of early prodromal phases of schizophrenic psychosis (SP) (73%) rather than affective psychosis (AP) (11%)[90]. In conclusion, the pluripotent model of the psychosis high-risk state encompasses different types of cases with attenuated psychotic experiences, each associated with a different evolution. Some of the baseline psychopathology may reflect the emergence of an underlying core psychotic process prodromal for schizophrenia or another psychotic disorder (true prodromal); some may be associated with a non-psychotic clinical condition such as depression (clinical noise); and some may represent normal variation in the general population (incidental psychosis).

Conclusions and future directions

The past two decades have seen a great interest and rise in the importance of the prodromal phase of psychosis. This has been achieved by shifting the traditional negative views of schizophrenia as a disorder with an unpredictable onset and that may be progressive in nature with disabling outcomes (*dementia praecox*) to a disorder that can be delayed, if not prevented, through recognition of those at imminent risk. In this chapter, the evidences

advocating this category as the possible target of focused interventions have been summarized. Moreover, its role as a new diagnosis in its own right in the DSM 5 has been discussed and a shift of the focus from an uncertain future outcome to current psychopathology and needs has been proposed. However, further research is warranted, since many questions remain unanswered. First, it is not clear whether the validity of UHR as used by specialized services can be generalized to general psychiatry/psychology and primary care. It has been argued that the diagnosis of APS in general practice may lead to excessive therapeutics doing more harm than good as well as adding a significant burden, in terms of stigma, to persons experiencing attenuated psychotic symptoms. However, greater attention should be paid to impairments in self, autonomy, personhood, and emotional regulation that people meeting criteria for APS already present. Second, because APS is a broad-based concept, interventions aimed at secondary prevention of psychosis could be tailored on which psychotic disorder vulnerability is present (i.e., schizophrenia spectrum disorder, bipolar disorder, or mood disorder). Third, reliable markers are needed in order to stratify the HR population according to the prediction of outcome; thus, broader and better validated longitudinal studies would be recommended, comparing HR subjects to healthy individuals as well as to people suffering from comorbid diagnoses. Finally, effective interventions should be developed and tested that address the specific needs of at-risk people. Therapeutic discovery should be more focused on functional outcomes or methods for enhancing resiliency or for reducing risk factors such as stress, with less emphasis placed on psychosis prevention. To date, the treatments that have been proven to be effective in frank psychosis have largely focused on positive symptoms, however there is increasing evidence to suggest that negative symptoms as well as cognitive and social functioning meaningfully restrict the prognosis. For example, therapies aimed at ameliorating emotion recognition or exerting a neuroprotective effect may have potential benefits. It is hoped that in the future more knowledge be acquired at developmental stages preceding APS, where prevention strategies have an earlier focus on reducing movement into vulnerability and, in the vulnerable, enhancing resiliency [86]. APS serves as a platform for future research and clinical work.

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Table 1. Treatment guidelines for the psychosis high-risk state	
Organization	**Recommendations**
American Psychiatric Association	"Careful assessment and frequent monitoring"
Canadian Psychiatric Association	"Should be offered monitoring" "May be offered supportive therapy and symptomatic treatment"
International Early Psychosis Association	"Antipsychotic medications not usually indicated" unless "rapid deterioration" or "sever suicidal risk and treatment of depression has proven ineffective" or "aggression and hostility are increasing and pose a risk to others" "If antipsychotics are considered...may be continued" up to 2 years, and then "attempt to withdraw the medication should be made"
Royal Australian and New Zealand College of Psychiatrists	"Antipsychotic medication not normally prescribed" unless "symptoms are directly associated with risk of self-harm or aggression"
Italian National Institute of Health	"Use of antipsychotic medication" is "doubtful"; behavioural cognitive treatment is recommended
German Association for Psychiatry, Psychotherapy, and Neurology	"Continuous care and follow-up. If relevant symptoms reaching disorder level occur, CBT and sociotherapy should be offered. If psychotic symptoms emerge, antipsychotics should be offered"

CBT, cognitive behavioural therapy

Table 2. Psychosis prevention compared to common preventative approaches in clinical medicine

At-risk population	Outcome	Transition risk %	Risk-focused treatment	Risk placebo	RRR	ARR	NNT
Psychosis high-risk state	Psychosis	17%-28% (1 year)[91]	CBT 7% (1 year) [91]	Supportive counselling 14% (1 year) [91]	0.5 (1 year) [91]	0.07 (1 year) [91]	14 (1 year) [91]
			CBT + risperidone 17% (1 year) [91]	CBT + placebo 28% (1 year) [91]	0.39 (1 year) [91]	0.11 (1 year) [91]	9 (1 year) [91]
			Omega 3 FA 7.2% (1 year) [91]	Supportive counselling 40% (1 year) [91]	0.82 (1 year) [91]	0.33 (1 year) [91]	3 (1 year) [91]
Prediabetes	Diabetes	5%-19% (1 year) [92]	Metformin 21.7% (3 years) [82]	Placebo 28.9% (3 years) [82]	0.25 (3 years) [92]	0.07 (3 years) [82]	14 (3 years) [82]
			Lifestyles 14.4% (3 years) [82]	Placebo 28.9% (3 years) [82]	0.5 (3 years) [92]	0.14 (3 years) [82]	7 (3 years) [82]
Cardiovascular high-risk patients[a]	Serious cardiovascular events[b]	1.5% [93]	Antiplatelet therapy 9.9% (2 years) [83]	Placebo 14% (2 years) [83]	0.35 (2 years) [83]	0.04 (2 years) [83]	25 (2 years) [83]

[a] High-risk patients defined as subjects with stable angina
[b] Serious cardiovascular events defined as nonfatal myocardial infarction, nonfatal stroke, or death from a vascular cause
CBT, cognitive behavioural therapy; NS, not significant; FA, fatty acids; RRR, relative risk reduction; ARR, absolute risk reduction; NNT, numbers needed to treat.

Figure 1. Percentage of global Disability-Adjusted Life Years by age, sex, and cause in 2010 worldwide. Distribution of DALYs for male individuals (A) and female individuals (B) [5]. Morbidity burden of disorders of the brain and mental disorders in EU, for male (C) and female (D) individuals [4].
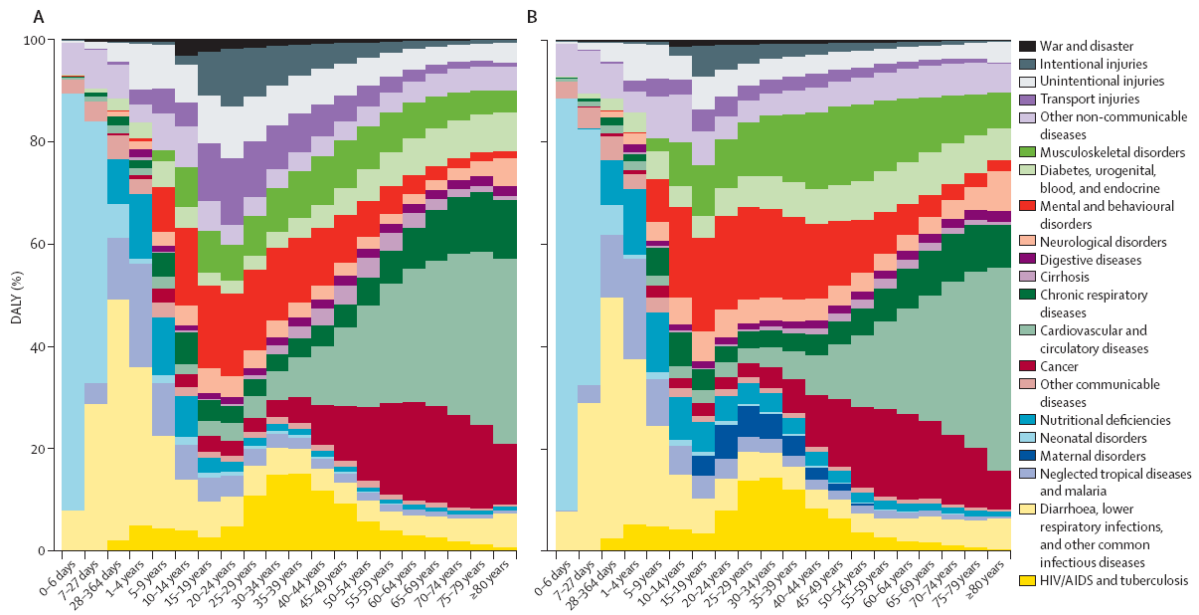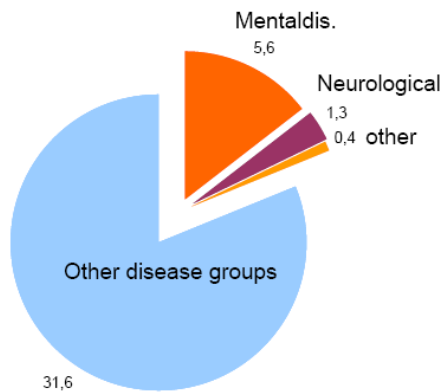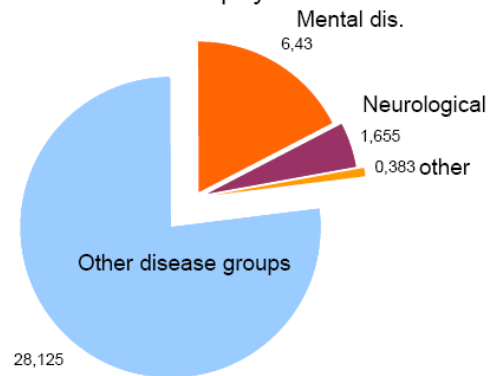
Figure 2. The early stages of schizophrenia from first sign of mental disorder to first admission (ABC first-episode sample N = 232; (108 men, 124 women)) [38]