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Review

Deconstructing vulnerability for psychosis: Meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk

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ABSTRACT

Background: Subjects at ultra high-risk (UHR) for psychosis have an enhanced vulnerability to develop the disorder but the risk factors accounting for this accrued risk are undetermined.
Method: Systematic review of associations between genetic or environmental risk factors for psychosis that are widely established in the literature and UHR state, based on comparisons to controls.
Results: Forty-four studies encompassing 170 independent datasets and 54 risk factors were included. There were no studies on association between genetic or epigenetic risk factors and the UHR state that met the inclusion criteria. UHR subjects were more likely to show obstetric complications, tobacco use, physical inactivity, childhood trauma/emotional abuse/physical neglect, high perceived stress, childhood and adolescent low functioning, affective comorbidities, male gender, single status, unemployment and low educational level as compared to controls.
Conclusions: The increased vulnerability of UHR subjects can be related to environmental risk factors like childhood trauma, adverse life events and affective dysfunction. The role of genetic and epigenetic risk factors awaits clarification.

1. Introduction

Since its inception two decades ago (in 1996, [1]), the ultra high-risk (hereafter UHR) state for psychosis quickly became increasingly influential in the field of psychiatry. The UHR state is defined on the basis of three inclusion criteria which have been validated internationally [2]: attenuated psychotic symptoms (APS), brief and limited intermittent psychotic symptoms (BLIPS) and genetic risk and deterioration syndrome (GRD) [3]. This has led to specialist UHR care provision being recognized as an important component of clinical services for early psychosis intervention [4,5] (e.g. NICE guidelines [6]; recent NHS England Access and Waiting Time [AWT] standard [4], DSM-5 diagnostic manual) [7]. Accumulating evidence has confirmed that help-seeking individuals meeting UHR criteria have an enhanced risk of developing psychotic disorders – mostly schizophrenia spectrum disorders [8] – within a relatively short period of time. The transition to psychosis in UHR individuals is most likely to occur within the first 2 years after presentation to clinical services, with 25% of transitions occurring by 106 days and 50% by 240 days [9,10]. The risk of transition to psychosis accumulates to 29% (95% CI, 23–36) at 2 years [11]. After this phase, the speed of psychosis progression tends to plateau from the third year, reaching approximately 35% after 10 years [11]. This risk is significantly higher than the risk of psychosis of 0.0317 per 100 person-years

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(95% CI: 0.025–0.041) [12] observed in the general population. Consequently, UHR individuals have a 2-year relative risk (RR) for developing psychosis of 460, as compared to the general population (29%/0.063%). The risk is higher even when restricting the comparison to UHR subjects meeting only attenuated psychosis symptoms (APS) criteria, which have a 2-year risk of transition of 0.16 (95% CI 0.13–0.19 [3], RR = 254). There is also converging evidence suggesting that the APS and the BLIPS subgroups of the UHR show an increased risk of psychosis as compared to subjects seeking help at clinical services but not meeting UHR criteria (i.e. UHR−) [3]. Conversely, there is no evidence indicating that UHR individuals are at risk of developing other non-psychotic disorders. Although a substantial proportion those not developing psychosis would present with persistent symptoms or associated comorbid disorders [13], the vast majority of these problems had already been present at baseline [14,15]. Furthermore, understanding whether the UHR status delineates specific risk for developing non-psychotic mental disorders necessarily relies upon the comparing of incident rates of non-psychotic mental disorders in UHR versus a control group not at risk for psychosis. The only available study confirmed that, compared to a control group, UHR individuals are not at higher risk of developing non-psychotic mental disorders [16].

The risk factors accounting for such substantial risk accumulation (RR = 460) are undetermined. The most validated model to understand the aetiology of psychosis is based on genetic and environmental risk factors and their interaction [17], likely involving epigenetic mechanisms [18]. Because UHR individuals are at enhanced risk of psychosis but not of non-psychotic disorders, the current review focus on risk factors for psychosis that have been widely established in the available literature. According to these premises, UHR individuals are likely to show a heightened vulnerability because of accumulating genetic and/or environmental risk factors for psychosis. Indeed, several original studies have investigated the association of established risk factors for psychosis and the UHR state. However, the findings are sparse and often conflicting. For example, some studies showed that UHR individuals have been more exposed to traumatic events than controls [19,20], while others found no differences [21].

To address these inconsistencies and to improve current knowledge of risk enrichment in the UHR state, this systematic review investigates the association of established genetic and environmental risk factors for psychosis and the UHR state. We first test the hypothesis that these risk factors are more likely to affect UHR individuals, compared to control groups, accounting for increased vulnerability to psychosis observed in these samples, compared to controls (RR = 460). We then investigate the specific impact of each risk factor by providing a quantitative analysis of the strength of the association between specific risk factors for psychosis and the UHR state.

2. Materials and methods

2.1. Search strategy

Two independent investigators (SDS, MT) conducted two-step literature searches. First, the Web of Knowledge℠ database was searched, incorporating both the Web of Science℠ and Medline®. The search was extended until 1st of June 2016, including English language abstracts only. The electronic database searches used several combinations of the search terms "UHR", "psychosis risk", "ultra high risk", "at risk mental state", "subclinic* psychosis", "earl* psychosis", "prodrom* psychosis", "psychosis onset", with specific keywords relating to the type of the diverse risk factors of interest (eTable 1), and refined by the topic "research" in the Web of Knowledge℠ database. Second, a manual search of the reference lists of retrieved articles was performed. The abstracts of the articles identified through these two steps were then screened in relation to the selection criteria. The full text of the remaining articles were then assessed for eligibility, following the MOOSE checklist (eTable 2) [22].

2.2. Selection criteria

Studies were eligible for inclusion when the following criteria were fulfilled:

- an original article, written in English;
- inclusion of UHR individuals, defined according to established international criteria (i.e. Comprehensive Assessment of At Risk Mental State [CAARMS]; Brief Psychiatric Rating Scale [BPRS]; Structured Interview for Psychosis-Risk Syndrome [SIPS]; Basel Screening Instrument for Psychosis [BSIP]) [23–25];
- inclusion of a comparison group of controls (healthy or UHR− or local general population);
- cohort studies and case-control studies (in line with previous meta-analyses of risk factors [26]) investigating risk factors in UHR individuals as part of the primary or secondary study's aims;
- reported sufficient meta-analytical data to perform the statistical analyses. When data were not available, the corresponding author was contacted and invited to send additional information.

Exclusion criteria were:

- abstracts, pilot datasets and manuscripts in languages other than English;
- studies that did not employ internationally validated definitions for UHR;
- studies acknowledging that their datasets were completely included in other larger samples;
- Randomized Controlled Trials;
- studies that did not investigate risk factors in UHR samples as part of the primary or secondary study's aims;
- studies that could not provide meta-analytical data;
- studies addressing biomarkers of psychosis.

The literature search was summarized according to the PRISMA guidelines [27].

2.3. Definition of risk factors

Because the ARMS predicts psychosis but not non-psychotic disorders [16], we focused only on the association between risk factors for psychosis and the ARMS, compared to controls. According to the WHO, a risk factor is any attribute, characteristic or exposure of an individual that increases the likelihood of developing a disease or injury [28]. Therefore, in our case, a risk factor for psychosis should increase the likelihood of developing psychosis. Accordingly, the risk factors for psychosis considered in the present manuscript were identified on the basis of previous published evidence showing a significant association with established psychotic disorders (i.e. the 95% CIs of association measures should not include 1). A qualitative summary table of association measures for each risk factor considered in the current review was produced for descriptive purposes. Two additional methodological considerations relate to the nature and exposure to risk factors in UHR individuals. First, although risk factors can be either causal or correlational, pathophysiology of psychosis is unknown and there are no causal risk factors as such. Consequently, all the included risk