Prevalence of non-psychotic disorders in ultra-high risk individuals and transition to psychosis: A systematic review

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ARTICLE INFO

Keywords:
Ultra-high risk
Psychosis
Transition rates
Prevalence rates

ABSTRACT

Despite the growing interest in the prodromes of psychosis, the proper identification of those Ultra High Risk (UHR) subjects who will convert to psychosis remains an unresolved issue. It remains to be fully understood whether the risk of transition to psychosis is incremented by the concomitant presence of non-psychotic symptoms. We performed a systematic review in order to estimate: prevalence rates of non-psychotic disorders in UHR individuals and whether any comorbid disorder impacts on the risk of transition to frank psychosis. The review was conducted using the PRISMA guidelines by searching PubMed until August 2017. The inclusion criteria were: studies with appropriate definition of UHR/ ARMS (At Risk Mental States for psychosis); cross-sectional design (for prevalence rates) or longitudinal design (for transition rates to psychosis); adolescents and/or adults; specified instrument/interview for the diagnosis of mental disorder/symptoms. We included 46 English-language articles. We found that non-psychotic symptoms are a prevalent concern in UHR individuals, and this is true for all comorbid disorders examined. None of the mental disorder examined appear to be a marker for transition to psychosis. Our systematic review found that the great majority of UHR individuals actually has a highly prevalent clearly defined, above-the-threshold mental disorder that should constitute the primary focus of intervention.

1. Introduction

Over the past few years there has been a substantial growing interest in the prodromes of psychosis with the hope of identifying individuals at risk for developing the illness before the first psychotic episode. Specific criteria have been developed for selecting subjects who could potentially benefit from preventive interventions. Specific services and/or intervention programs have been created all over the world to treat these subjects in order to prevent the transition to psychosis.

Criteria for identifying subjects considered at risk for transition to psychosis (Ultra-High Risk – UHR; Clinical High Risk - CHR - or At Risk Mental State for psychosis – ARMS) include: a) attenuated psychotic symptoms with sub-threshold positive psychotic symptoms (APS), b) brief limited and intermittent psychotic symptoms (BLIPS - brief psychotic episode of less than 1 week's duration that spontaneously remits without antipsychotic medications), and c) genetic risk (schizotypal personality disorder or a first-degree relative with psychosis) combined with significant decrease in the level of functioning (Yung et al., 2005; Schultze-Lutter et al., 2015; van Os and Guloksuz, 2017).

Subjects presenting with these at-risk conditions may convert to frank psychosis. However, transition risks have been reported to vary extremely; previous studies have reported that over 50% of UHR patients developed a psychosis within the first year (Miller et al., 2002) while more recent studies have found that the majority of UHR individuals did not convert to psychosis (Simon et al., 2011; Fusar-Poli et al., 2012; Nelson et al., 2013) or even did remit from a UHR state (Simon et al., 2013). A recent meta-analysis has estimated a transition risk of 18% after 6 months of follow-up, 22% after 1 year, 29% after 2 years, and 36% after 3 years (Fusar-Poli et al., 2012), independent of the psychometric instruments used.

The proper identification of those UHR subjects who will convert, versus those who will not, remains an unresolved issue, although the clinical significance of such distinction is of utmost importance given that providing early intervention may result in achieving better outcomes.

Among several possible predictors of transition to psychosis, the concomitant presence of non-psychotic symptoms, both at a syndromal

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https://doi.org/10.1016/j.psychres.2018.09.028

level – diagnosis – or at a sub-threshold level – symptoms, has been studied. Growing evidence is indicating that prevalence rates of depressive and anxiety disorders, for example, are higher in UHR individuals than in control subjects; up to 70 to 80% of adolescents and young adults at risk for psychosis have at least one Axis I comorbid diagnosis (Fusar-Poli et al., 2012; Salokangas et al., 2012). A systematic review and meta-analysis has found prevalence rates of 40.7% for depressive disorders and 15.3% for any anxiety disorders in UHR individuals (Fusar-Poli et al., 2014). Obsessive-compulsive disorder (OCD) or syndromes (OCS) are also prevalent among UHR individuals, with prevalence rates higher than expected in the general population (Zink et al., 2014; McAusland et al., 2015).

These abnormally high rates of non-psychotic symptomatologies in UHR individuals have raised several questions: are all non-psychotic disorders/symptoms equally prevalent or are there any specificity (only specific symptomatologies are prevalent among subjects at risk)? Is the risk of transition to frank psychosis greater in UHR individuals with comorbid disorders/symptoms? Again, are there differences in the likelihood of transition to psychosis according to the specific disorder/group of symptoms diagnosed at baseline? For example, it has been traditionally considered that the presence of obsessive-compulsive symptoms might retard the “personality disintegration” associated with schizophrenia, prevent the development of “malignant schizophrenia” and/or herald remission of schizophrenic illness (Stengel, 1945; Rosen, 1957). Obsessions have been viewed as a defense against psychosis, preventing the progression of schizophrenia, rather than constituting a risk of transition to psychosis. It is then possible that different psychopathologies could have a different impact on the risk of transition to frank psychosis in individuals at risk.

Another unresolved issue is whether UHR/ARMS conditions (as they are currently conceptualized) should be considered as risk conditions for transition to psychosis only (observation through the “schizo”-prism as critically discussed by van Os and Guloksuz, 2017) or as a generic marker of vulnerability to several different psychopathologies or even to progression towards a generic deterioration in functioning independent of Axis I disorders. It may be that multidimensional psychopathology at baseline (UHR criteria satisfied – mainly attenuated psychotic symptoms - plus other non-psychotic psychopathologies) in help-seeking young adolescents may predict different trajectories, one of which only is the so-called transition to psychosis (van Os and Guloksuz, 2017).

Returning to the first questions, it remains also to be fully understood whether the risk of transition to psychosis is incremented by the baseline presence of other non-psychotic symptoms; meta-regression analyses revealed no significant impact of anxiety or depressive disorders on the longitudinal risk of transition to psychosis (Fusar-Poli et al., 2014). However, this meta-analysis did not specifically examine individual mental disorders, did not consider disorders other than anxiety or depressive ones, such as OCD and/or eating disorders, and several recently published reports appeared that are of course not included.

Within this framework, we aimed at systematically review the available literature in order to estimate: (1) prevalence rates of non-psychotic disorders in UHR individuals (anxiety disorders, obsessive-compulsive disorder, depressive and bipolar disorders, eating disorders) and (2) whether any comorbid psychopathology impacts on the risk of transition to frank psychosis.

2. Methods

2.1. Search strategy

The systematic review was conducted using the PRISMA guidelines (Moher et al., 2009, 2010) by searching PubMed from the date of the first available article to August 2017. The search terms [At Risk Mental States for Psychosis (ARMS)] OR [Ultra High Risk (UHR)] OR [Attenuated Psychotic Symptoms (APS)] OR [Brief Limited Intermittent Psychotic Symptoms (BLIPS)] were combined with the followings: 1) [anxiety] OR [anxiety disorder] OR [anxiety symptoms] OR [panic] OR [panic disorder] OR [panic attack] OR [panic symptoms] OR [phobia] OR [social phobia] OR [agoraphobia] OR [phobic symptoms] OR [PTSD]; 2) [OCD] OR [OC syndrome] OR [obsessive-compulsive symptoms]; 3) [depression] OR [major depression] OR [depressive episode] OR [depressive symptoms] OR [mania] OR [bipolar disorder] OR [manic episode] OR [manic symptoms]; 4) [eating disorders] OR [anorexia nervosa] OR [bulimia nervosa] OR [binge eating].

2.2. Article selection and review strategy

Articles were identified and assessed for eligibility by two independent reviewers (UA and SaT), who independently decided which identified articles to include according to clinical importance and eligibility criteria. In case of disagreement, a third author (SiT) was consulted to mediate consensual decisions. Duplicate studies were excluded. Cross-references from the articles identified were also examined. Unpublished studies, conference abstracts or poster presentations were not included. The database search was restricted to English language papers.

2.3. Eligibility criteria

The inclusion criteria for the studies were the following: 1) studies with appropriate definition of UHR/ARMS (specific structured interview, established international criteria); 2) cross-sectional design (for prevalence rates) or longitudinal design (for transition rates to psychosis); 3) adolescents and/or adults; 4) specified instrument/interview for the diagnosis of psychiatric disorder/symptoms with the possibility to calculate lifetime and/or current prevalence rates for specific/sub-threshold diagnoses and/or transition rates to psychosis.

The definition of the Ultra-High Risk (UHR) condition included: a) attenuated psychotic symptoms with sub-threshold positive psychotic symptoms (APS), b) brief limited and intermittent psychotic symptoms (BLIPS - brief psychotic episode of less than 1 week's duration that spontaneously remits without antipsychotic medications), and c) genetic risk (schizotypal personality disorder or a first-degree relative with psychosis) combined with significant decrease in the level of functioning (Yung et al., 2005; Schultze-Lutter et al., 2015; van Os and Guloksuz, 2017).

Studies that used self-report measures of psychopathology without providing prevalence rates (such as the SCL-90, which gives mean scores) were deliberately excluded from the qualitative synthesis.

In reporting prevalence rates of non-psychotic disorders in UHR individuals (anxiety disorders, obsessive-compulsive disorder, depressive and bipolar disorders, eating disorders), each diagnostic category was examined as a whole, e.g. at least one anxiety disorder, and as rates of each of its components e.g. panic disorder etc.

3. Results

3.1. Search results

The flowchart of studies selected and included in the systematic review is provided in Fig. 1. We retrieved 784 records (772 from PubMed research and 12 cross-references from the articles identified). Sixty-nine full-text articles were assessed for eligibility; of them, 20 did not report prevalence rates of non-psychotic disorders in UHR individuals, nor reported transition rates and 3 additional articles did not clearly define UHR subjects, and then were excluded from the qualitative analysis. As a result, studies included in our systematic review were 46.

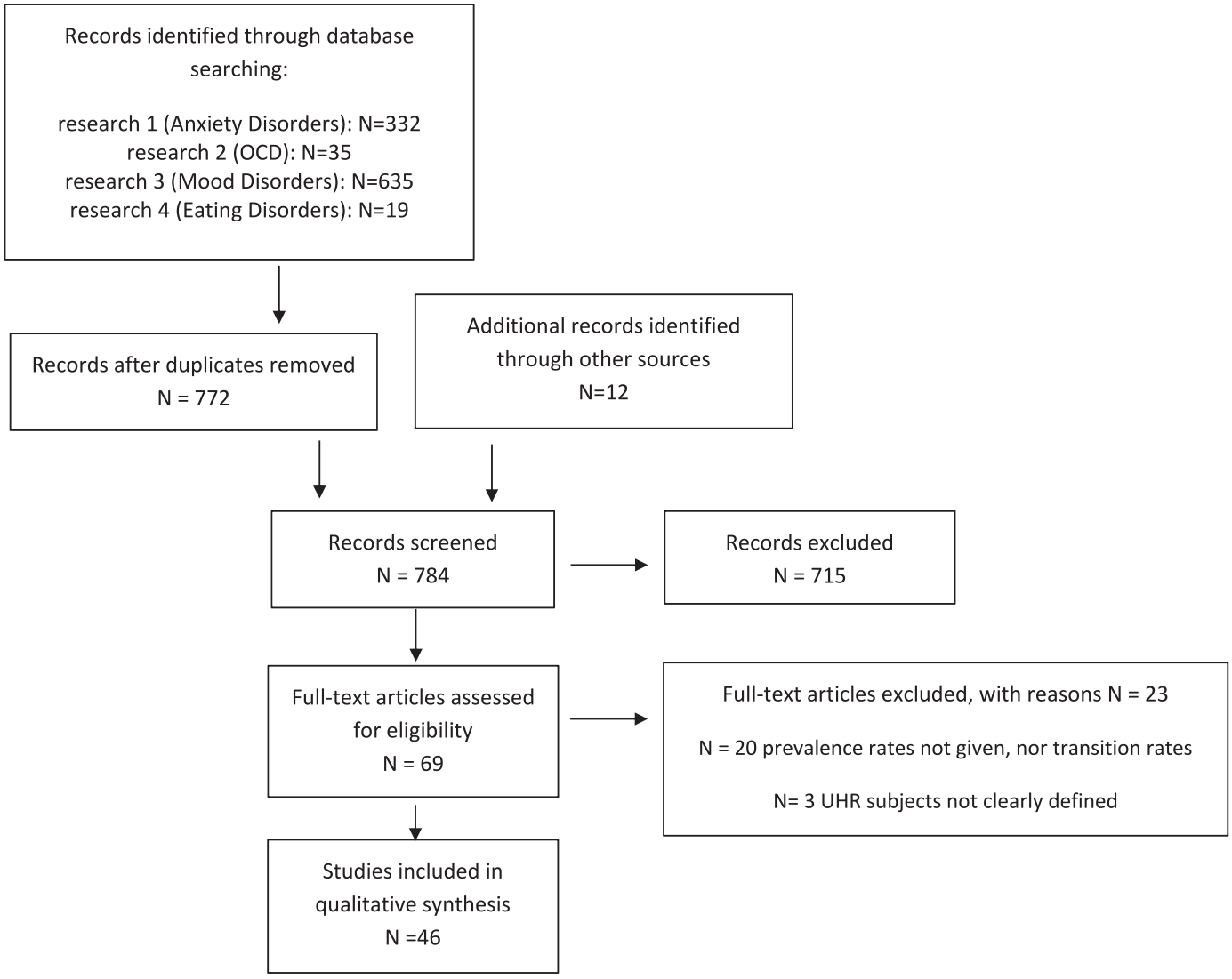

Fig. 1. Flow Chart showing the selection of studies.

3.2. Anxiety disorders

Prevalence rates of baseline Anxiety Disorders in UHR individuals are reported in Table 1. Thirty-one studies (three more studies reported duplicate results) contributed to the evaluation of prevalence rates, which vary widely: at least one DSM-IV anxiety disorder is present (current prevalence) in 2.8–50.9% of UHR individuals, while lifetime prevalence rates are comprised between 28.0 and 74.0%. Among the individual anxiety disorders, social phobia (SP) is by far the most prevalent (current prevalence rate: 5.0–19.4% according to DSM-IV criteria; 42.3% when defined according to the Social Interaction Anxiety Scale –SIAS- score > 36), followed by generalized anxiety disorder (GAD), panic disorder (PD) and post-traumatic stress disorder (PTSD). Table 2 reports results of longitudinal studies that examined whether baseline anxiety disorders influence transition rates to frank psychosis over the follow-up: taken together, the seven studies examined showed that anxiety does not appear to be a marker for transition to psychosis. One additional study (Rutigliano et al., 2016), performed in 154 UHR individuals (74 of whom assessed at follow-up), found that incidence, persistence or recurrence of comorbid mood and/or anxiety disorders were not significantly associated with risk of transition to psychosis, or with persistence of attenuated psychotic symptoms over the 6-year follow-up. Persistence or recurrence of non-psychotic mental disorders was related to lower functional levels at 6-year follow-up (Rutigliano et al., 2016).

Only one study (Salokangas et al., 2012) found that UHR individuals with baseline current anxiety disorders have a lower risk than UHR subjects in general of sliding into full-blown psychosis.

3.3. OCD/OCS

Prevalence rates of obsessive-compulsive disorder (OCD) and obsessive-compulsive syndrome (OCS) in UHR subjects are reported in Table 3. Nineteen studies reported rates of DSM-IV current OCD ranging from 2.0 to 12.3% and lifetime OCD from 4.0 to 15.0%. Hui et al. (2013) also found that the mean Yale-Brown Obsessive-Compulsive Scale (Y-BOCS) total score was significantly higher in UHR individuals than in healthy volunteers (20.1 ± 5.8 vs. 5.3 ± 1.5; $p < 0.001$). OCS appears even more prevalent among UHR individuals, although prevalence rates are not comparable given the different criteria used to define OCS (Hui et al., 2013).

Only 4 studies provided information on the longitudinal risk of transition to psychosis in UHR individuals with versus without OCD/OCS at baseline; results are summarized in Table 4. Results are congruent and show that baseline OCD/OCS does not increase nor decrease the risk of transition to frank psychosis.

Table 1
Investigation of Anxiety Disorders prevalence rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients.

Authors	Definition of UHR/ ARMS	*N*	Design	Any Anxiety Disorder (%)		Individual Anxiety Disorders (%)		Diagnosis (criteria)
				current	lifetime	current	lifetime	
Lencz et al. (2004)	SIPS/SOPS	82	Cross-sectional	–	–	–	SoP: 17.1	K-SADS-E
Meyer et al. (2005)	SIPS/SOPS CAPPS	24	Cross-sectional	81%[b]	–	SoP: 17 SP:4 GAD: 8 PD: 4 PTSD: 4 Anxiety NOS: 17	–	SCID (DSM-IV)
Rosen et al. (2006)	SIPS/SOPS	29	Cross-sectional	24	28	SoP: 7 Ago: 4 GAD: 7 PD: 4 PTSD: 4	SoP: 10 Ago: 4 GAD: 7 PD: 4 PTSD: 7	SCID (DSM-IV)
Thompson et al. (2007)	CAARMS	23 PACE Clinic	Cross-sectional	–	–	SoP: 17.4 GAD: 8.7 PD: 4.3 PTSD: 8.7	–	SCID (DSM-IV)
Woods et al. (2009)	SIPS	297 NAPLS	Cross-sectional	–	38.5	–	SoP: 13.2 SP: 3.5 Ago: 1.0 GAD: 6.8 PD: 7.6 PTSD: 3.4	SCID (DSM-IV)
Bechdolf et al. (2010)	CAARMS	92 PACE Clinic	Cross-sectional Longitudinal	8.7	–	PTSD: 15.2	–	ICD-10
Chung et al. (2010)	CAARMS	38	Cross-sectional	–	–	SoP: 5.3 PTSD: 2.6 Anxiety NOS: 7.9	–	DSM-IV
Sabb et al. (2010)[a]	SIPS	40	Cross-sectional	–	–	SoP: 5 Anxiety NOS: 12.5	–	SCID (DSM-IV)
Simon and Umbricht (2010)	SIPS/SOPS	72	Cross-sectional Longitudinal	2.8	–	–	–	DSM-IV
Addington et al. (2011) Marshall et al. (2012)	SIPS/SOPS PRIME Clinic	51	Cross-sectional Longitudinal	35.3	–	–	–	SCID (DSM-IV)
Bechdolf et al. (2011)	SIPS/SOPS PREVENT	156	Cross-sectional	–	–	SoP: 12.1 Ago: 1.2 Phobias: 10.8 PD: 6.3 PTSD: 2.5	–	SCID (DSM-IV)
Kim et al. (2012)	CAARMS	78	Cross-sectional	17	–	–	–	SCID (DSM-IV)
Salokangas et al. (2012)	SIPS EPOS	245	Cross-sectional Longitudinal	39.2	49	–	–	SCID (DSM-IV)
Schlosser et al. (2012)	SIPS CAPPS	84	Cross-sectional Longitudinal	47.6	–	–	–	SCID (DSM-IV)
Hui et al. (2013) Morcillo et al. (2015) Russo et al. (2017)	CAARMS	60	Cross-sectional Controlled	–	–	SoP: 12.7 GAD: 12.7 PD: 1.8 PTSD: 1.8	–	MINI (DSM-IV)
Korkeila et al. (2013)	SIPS EPOS	238	Cross-sectional	–	–	PD: 11.3	PD: 24.4	SCID (DSM-IV)
Rietdijk et al. (2013)	CAARMS EDIE-NL	201	Cross-sectional	–	–	SoP: 42.3	–	SIAS > 36
Conrad et al. (2014)	CAARMS PAS	191	Cross-sectional	42.9	–	–	–	not specified
Fusar-Poli et al. (2014)	CAARMS	509	Cross-sectional Longitudinal	21.6	–	–	–	SCID (DSM-IV)
Falkenberg et al. (2015)	CAARMS	221	Cross-sectional	14.5	–	–	–	SCID (DSM-IV)
Lim et al. (2015)	CAARMS	163	Cross-sectional LYRIKS Longitudinal	27.6	34.4	SoP: 6.1 Ago: 2.5 GAD: 7.4 PD: 1.8 PTSD: 0.6	SoP: 7.4 Ago: 3.1 GAD: 7.4 PD: 3.7 PTSD: 3.1	SCID (DSM-IV)
Lin et al. (2015)	CAARMS PACE Clinic	203	Cross-sectional Longitudinal	39.9	–	–	–	SCID (DSM-IV)
McAusland et al. (2015)	SIPS/SOPS	765	Cross-sectional Controlled Longitudinal	50.9	–	SoP: 14.4 SP: 10.1 GAD: 11.6 PD + Ago: 4.7 PD: 6.1 PTSD: 2.2		SCID (DSM-IV)
Rapado-Castro et al. (2015)	CAARMS	73	Cross-sectional	12.3	–	–	–	Clinical Interview
Tay et al. (2015)	CAARMS SWAP	155	Cross-sectional	20	–	–	–	SCID (DSM-IV)

(*continued on next page*)

Table 1 (*continued*)

Authors	Definition of UHR/ ARMS	*N*	Design	Any Anxiety Disorder (%)		Individual Anxiety Disorders (%)		Diagnosis (criteria)
				current	lifetime	current	lifetime	
Webb et al. (2015)	SIPS	160 NAPLS-1 111 PREDICT	Cross-sectional Controlled Longitudinal	43.1 41.4	–	–	–	SCID (DSM-IV)
Kotlicka-Antczak et al. (2016)	CAARMS	99	Cross-sectional	19.2	–	–	–	SCID (DSM-IV)
Rutigliano et al. (2016)	CAARMS	74	Cross-sectional Longitudinal	16.2	–	–	–	SCID (DSM-IV)
Kraan et al. (2017)	CAARMS	259 EU-GEI	Cross-sectional Longitudinal	–	–	SoP: 19.4 PD: 18.6 PTSD: 10.1	–	SCID (DSM-IV)
Lee et al. (2017)	SIPS	63	Cross-sectional Controlled	22.2	–	SoP: 14.3	–	SCID (DSM-IV)
Madsen et al. (2017)	CAARMS	42	Cross-sectional	–	74	–	SoP: 33.3 SP: 14.3 GAD: 11.9 PD: 38.1 PTSD: 16.7	SCID (DSM-IV)

SIPS: structured interview for prodromal symptoms; SOPS: scale of prodromal symptomatology; CAARMS: comprehensive assessment of at-risk mental states; MINI: Mini International Neuropsychiatric Interview for DSM-IV psychiatric disorders; SCID: Structured Clinical Interview for DSM-IV Axis I Disorders; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version; SIAS: Social Interaction Anxiety Scale.
CAPPS: UCLA center for the Assessment and Prevention of Prodromal States; PACE: Personal Assessment and Crisis Evaluation Clinic; EPOS: European Prediction of Psychosis Study; EDIE-NL: Dutch Early Detection Intervention Evaluation Trial; PAS: Psychological Assistance Service; LYRIKS: Longitudinal Youth at Risk Study; SWAP: Support for Wellness Achievement Programme; NAPLS-1: North American Prodromal Longitudinal Study; EU-GEI: European network of national schizophrenia networks studying Gene-Environment Interactions.
SoP: Social Phobia; SP: Specific Phobia; GAD: Generalized Anxiety Disorder; PD: Panic Disorder; Ago: Agoraphobia; PTSD: Post-Traumatic Stress Disorder.
[a] Includes patients from the study of Meyer et al. (2005).
[b] Anxiety Problems as from the DSM-IV Child Behavior CheckList.

3.4. Mood disorders (depressive and bipolar disorders)

Prevalence rates of major depressive disorder (MDD) and bipolar disorder (BD) in UHR/ARMS individuals are reported in Table 5. Thirty-five studies assessed rates of MDD and BP, as defined by the DSM-IV criteria, in UHR individuals and found prevalence ranging from 10.0 to 66.7% for current major depressive disorder and from 0.0 to 8.7 for current bipolar disorder (both type I and II). Moreover, lifetime MDD was shown in 31.7–79.0% of UHR/ARMS subjects and lifetime BD in 1.2–7.1% of individuals at risk. Current and lifetime prevalence rates of at least one DSM-IV Mood Disorder vary widely from 28.0 to 71.4% and from 55.0 to 59.0%, respectively.

Six studies only provided information on the longitudinal risk of transition to psychosis in UHR individuals with versus without MDD/

Table 2
Transition rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients with or without Anxiety Disorders at baseline.

Authors	Definition of UHR/ ARMS	*N*	Anxiety Disorders + (%)	Follow-up	Prevalence rates (%) of Anxiety Disorders in:			*p*
					Baseline	Converters	Non-converters	
Bechdolf et al. (2010)	CAARMS	92	8.7	1.7 years	Anxiety Disorders	15.0	6.9	n.s.
Schlosser et al. (2012)	SIPS	84	47.6	2 years	Anxiety Disorders	48.1	47.4	n.s.
Lim et al. (2015)	CAARMS	163	–	1 year	*Current*			
					Anxiety or	63.6	31.0	n.s.
					Depression	0	14.8	n.s.
					Anxiety &	72.7	47.2	n.s.
					Depression	27.3	27.2	n.s.
					lifetime			
					Anxiety or Depression			
					Anxiety & Depression			
McAusland et al. (2015)	SIPS/SOPS	321	50.9	2 years	Anxiety Disorders	50.5	50.9	n.s.
					transition rates (%) to psychosis			
Salokangas et al. (2012)	SIPS	245	39.2	1.5 year	All subjects	15.1		.045
					Anxiety Disorder (current)	9.5		HR: 0.464 (CI 0.219–0.984)
Fusar-Poli et al. (2014)	CAARMS	509	21.6 Anxiety alone: 7.7 Anxiety & Depression: 13.9	3.7 years	No Anxiety Anxiety alone Anxiety & Depression	14.2 15.4 12.7		n.s.
Webb et al. (2015)	SIPS	160[a] 111#	43.1 41.4	2.5 years 4 years	All patients Included Anxiety excluded	19.6 23.1		n.s.

SIPS: structured interview for prodromal symptoms; SOPS: scale of prodromal symptomatology; CAARMS: comprehensive assessment of at-risk mental states.
[a] NAPLS-1: North American Prodromal Longitudinal Study; # PREDICT Study.

Table 3
Investigation of OCD/OCS prevalence rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients.

Authors	Definition of UHR/ARMS	*N*	Design	OCD (%)		OCS (%)	Diagnosis (criteria)
				Current	Lifetime		
Lencz et al. (2004)	SIPS/SOPS	82	Cross-sectional	–	11	–	K-SADS-E
Meyer et al. (2005)	SIPS/SOPS	24	Cross-sectional	4	15	21 (current)	SCID (DSM-IV)
Rosen et al. (2006)	SIPS/SOPS	29	Cross-sectional	4	4	–	SCID (DSM-IV)
Niendam et al. (2009)[a]	SIPS/SOPS	64	Cross-sectional, controlled, longitudinal		14	20.3[b]	SCID (DSM-IV)
Woods et al. (2009)	SIPS	297	Cross-sectional	–	5.2	–	SCID (DSM-IV)
Chung et al. (2010)	CAARMS	38	Cross-sectional	7.9	–	–	DSM-IV
Sabb et al. (2010)[a]	SIPS	40	Cross-sectional	5.0	–	–	SCID (DSM-IV)
Bechdolf et al. (2011)	SIPS/SOPS	156	Cross-sectional	3.8	–	–	SCID (DSM-IV)
Fontenelle et al. (2011)	CAARMS	396	Cross-sectional Longitudinal	8.1	–	–	SCID (DSM-IV)
Sterk et al. (2011)	SIPS, CASH	29	Cross-sectional	3.4	–	20.7[b] (current)	SCID (DSM-III-R)
Hur et al. (2012)	CAARMS	65	Cross-sectional Longitudinal	12.3	–	36.9[b] (current) (YBOCS ≥ 8)	SCID (DSM-IV)
De Vylder et al. (2012)	SIPS/SOPS	20	Cross-sectional	30	–	60 (current) (YBOCS)[c]	YBOCS/DIGS
Hui et al. (2013)	CAARMS	60	Cross-sectional, controlled	9.1	–	–	MINI (DSM-IV)
Fusar-Poli et al. (2014)	CAARMS	509	Cross-sectional	2	–	–	SCID (DSM-IV)
Zink et al. (2014)	SIPS/SOPS	233	Cross-sectional	5.2	7.7	11.2[b] (lifetime)	SCID (DSM-IV)
Lim et al. (2015)	CAARMS	163	Cross-sectional Longitudinal	9.2	11.0		SCID (DSM-IV)
McAusland et al., (2015)	SIPS/SOPS	765	Cross-sectional, controlled, longitudinal	6.9	–	–	SCID (DSM-IV)
Kraan et al. (2017)	CAARMS	259	Cross-sectional Controlled Longitudinal	8.5	–	–	SCID (DSM-IV)
Madsen et al. (2017)	CAARMS	42	Cross-sectional	–	4.8	–	SCID (DSM-IV)

SIPS: structured interview for prodromal symptoms; SOPS: scale of prodromal symptomatology; CAARMS: comprehensive assessment of at-risk mental states; CASH: comprehensive assessment of symptoms and history.
SCID: Structured Clinical Interview for DSM-IV Axis I Disorders; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version; MINI: Mini International Neuropsychiatric Interview for DSM-IV psychiatric disorders; YBOCS: Yale-Brown Obsessive-Compulsive Scale; DIGS: Diagnostic Interview for Genetic Studies.
Note: Niendam et al. (2009): not specified whether current or lifetime diagnoses.
[a] Includes patients from the study of Meyer et al. (2005).
[b] Includes full-threshold OCD.
[c] At least 1 symptom on the YBOCS.

BD at baseline; results are shown in Table 6. Taken together, the studies examined showed that depression does not appear to be a marker for transition to psychosis. Only one study (Salokangas et al., 2012) found that UHR individuals with baseline current bipolar disorder have a 3.7 higher risk than UHR subjects in general of sliding into full-blown psychosis at the 1.5-year follow-up.

3.5. Eating disorders

Prevalence rates of eating disorders (ED) in UHR/ARMS subjects are shown in table 7. Eleven studies reported current and lifetime prevalence rates for any DSM-IV ED, ranging from 1.0 to 4.0% and 2.9 to 26.1%, respectively. Bulimia nervosa might be more prevalent than Anorexia Nervosa, although only few of the studies reported prevalence rates of the individual disorders.

We found only one study providing information on the longitudinal risk of transition to psychosis in UHR individuals with ED at baseline versus those without: none of the subjects with current ED at baseline (1.6%) converted after 1.5 years compared to a conversion rate of 15.1% in the whole sample (this difference was statistically not significant) (Salokangas et al., 2012).

4. Discussion

Our systematic review was conceptualized in order to answer two major questions: a) Are non-psychotic comorbid disorders prevalent among UHR individuals? All non-psychotic disorders are equally prevalent or are there any specificity? b) Is risk of transition to frank

Table 4
Transition rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients with or without OCD/OCS at baseline.

Authors	Definition of UHR/ARMS	*N*	OCS + (Including OCD)	Follow-up	Transition rates (%)		
					OCS +	OCS-	*p*
Niendam et al. (2009)	SIPS/SOPS	64	20.3%	11 months	0	22	n.s. (0.06)
Fontenelle et al. (2011)	CAARMS	312	8.1% (OCD +)	7.4 years	Any Psychosis: 19.2 Schizophrenia: 15.4	22 12.1	n.s. n.s.
Hur et al. (2012)	CAARMS	53	33.9	1 year	16.7	20	n.s.
McAusland et al. (2015)	SIPS/SOPS	321	n.a.	2 years	Baseline OCD in those who transitioned: 9.7% in those who did not: 6.5%		

SIPS: structured interview for prodromal symptoms; SOPS: scale of prodromal symptomatology; CAARMS: comprehensive assessment of at-risk mental states.

Table 5
Investigation of Mood Disorders prevalence rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients.

Authors	Definition of UHR/ ARMS	*N*	Design	Any mood disorder (%)		MDD (%)		BD (%)		Diagnosis (criteria)
				Current	Lifetime	Current	Lifetime	Current	Lifetime	
Lencz et al. (2004)	SIPS/SOPS	82	Cross-sectional	–	–	–	31.7	–	–	K -SADS-E
Meyer et al. (2005)	SIPS/SOPS	24	Cross-sectional	–	–	50.0 (8.0 depression NOS)	–	5.0	–	SCID (DSM-IV)
Rosen et al. (2006)	SIPS/SOPS	29	Cross-sectional	28.0	59.0	17.0 (4.0 dysthymia 7.0 depression NOS)	48.0 (4.0 dysthymia 10.0 depression NOS)	–	–	SCID (DSM- IV)
Thompson et al. (2007)	CAARMS	23 PACE	Cross-sectional	–	–	13.0 (4.3 dysthymia)	–	8.7	–	SCID (DSM- IV)
Woods et al. (2009)	SOPS/SIPS	297	Longitudinal	–	55.2	–	42.0 (4.9 dysthymia, 8.4 any other)	–	2.4	SCID (DSM-IV)
Bechdolf et al. (2010)	CAARMS	92 PACE	Longitudinal	–	–	52.2	–	–	–	ICD-10
Chung et al. (2010)	CAARMS	38	Cross-sectional	–	–	10.0 (7.9 dysthymia 18.4 depression NOS)	–	–	–	DSM-IV
Sabb et al. (2010)	SIPS	43	Longitudinal	–	–	41.8 (6.9 other)	–	2.3	–	SCID (DSM- IV)
Simon and Umbricht (2010)	SOPS/SIPS	72	Cross-sectional	50.0	–	–	–	–	–	DSM-IV
Addington et al. (2011)	SIPS/SOPS	51	Cross-sectional	50.9	–	–	–	–	–	SCID (DSM-IV)
Bechdolf et al. (2011)	SIPS/SOPS	156 PREVENT	Cross-sectional	–	–	38.9 (9.6 dysthymia 1.9 depression NOS)	–	–	–	SCID (DSM- IV)
Addington et al. (2012)	COPS/SIPS	360	Cross-sectional	–	–	41.1	35.1 longitudinal	–	–	SCID (DSM- IV)
Kim et al. (2012)	CAARMS	78	Cross-sectional	61.0	–	–	–	–	–	SCID (DSM- IV)
Salokangas et al. (2012)	SIPS	245 EPOS	Cross-sectional Longitudinal	–	–	34.3 (any unipolar)	52.2 (any unipolar)	4.1	6.9	SCID (DSM- IV)
Schlosser et al. (2012)	SIPS	84 CAPPS	Cross-sectional Longitudinal	44.0	–	–	–	–	–	SCID (DSM- IV
Fusar-Poli et al. (2013)	CAARMS	209	Longitudinal	–	–	21	–	–	–	SCID (DSM- IV)
Hui et al. (2013)	CAARMS	55	Cross-sectional	–	–	47.3	–	3.6 (BDII)	–	MINI (DSM-IV)
Rietdijk et al. (2013)	CAARMS	201	Cross-sectional	–	–	58.2	–	–		BDI > 19
Addington et al. (2014)	SIPS/SOPS	155	Longitudinal	37.3	–	25.4 (2.6 dysthymia 3.3 depression NOS)	–	–	–	SCID (DSM-IV)
Conrad et al. (2014)	CAARMS	191	Cross-sectional	62.3	–	–	–	–	–	ICD-10
Fusar-Poli et al. (2014)	CAARMS	509	Longitudinal	–	–	40.3	–	–	–	SCID (DSM-IV)
Leopold et al. (2014)	SIPS	29[a]	Cross-sectional	–	–	55.0	–	–	–	SCID (DSM-IV)
Falkenberg et al. (2015)	CAARMS	221	Longitudinal	–	–	35.3 depression and/or anxiety	–	–	–	SCID (DSM-IV)
Ohmuro et al. (2015)	CAARMS	50	Cross-sectional	–	–	16.0	–	2 (BDII)	–	SCID (DSM-IV)
Lim et al. (2015)	CAARMS	163 LYRIKS	Cross-sectional Longitudinal			23.3 (8.0 dysthymia 0.6 depression NOS)	58.9 MDD (8.0 dysthymia 3.1 depression NOS)	0.6	1.2	SCID (DSM-IV)
Lin et al. (2015)	CAARMS	203 PACE Clinic	Cross-sectional Longitudinal	71.4	–	–	–	–	–	SCID (DSM-IV)
Rapado-Castro et al. (2015)	CAARMS	73	Cross-sectional	72.6	–	–	–	–	–	Clinical Interview
Tay et al. (2015)	CAARMS	155	Cross-sectional	–	–	34.8	–	7.1	–	SCID (DSM-IV)
Webb et al. (2015)	SIPS	160 NAPLS-1 111 PREDICT	Longitudinal	–	–	57.5 48.6	–	2.5 0.0	–	SCID (DSM-IV)

(*continued on next page*)

Table 5 (*continued*)

Authors	Definition of UHR/ ARMS	*N*	Design	Any mood disorder (%)		MDD (%)		BD (%)		Diagnosis (criteria)
				Current	Lifetime	Current	Lifetime	Current	Lifetime	
Kotlicka-Antczak et al. (2016)	CAARMS	99	Cross-sectional	–	–	35.3	–	2.0	–	SCID (DSM-IV)
Rutigliano et al. (2016)	CAARMS	74	Cross-sectional Longitudinal	41.9	–	–	–	–	–	SCID (DSM-IV)
Zeni-Graiff et al. (2016)	CAARMS	12	Cross-sectional	–	–	66.7	–	8.3	–	SCID (DSM-IV)
Kraan et al. (2017)	CAARMS	259 EU-GEI	Cross-sectional Longitudinal	–	–	30.4	–	–	–	SCID (DSM-IV)
Lee et al. (2017)	SIPS	63	Cross-sectional	–	–	36.5	–	1.6	–	SCID (DSM-IV)
Madsen et al. (2017)	CAARMS	42	Cross-sectional	–	–	–	79	–	7.1 (DBII)	SCID (DSM-IV)

MDD: Major Depressive Disorder; BD: Bipolar Disorder.
SIPS: structured interview for prodromal symptoms; SOPS: scale of prodromal symptomatology; CAARMS: comprehensive assessment of at-risk mental states; MINI: Mini International Neuropsychiatric Interview for DSM-IV psychiatric disorders; SCID: Structured Clinical Interview for DSM-IV Axis I Disorders; K-SADS-E: Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiologic Version;
PACE: Personal Assessment and Crisis Evaluation Clinic; LYRIKS: Longitudinal Youth at Risk Study; NAPLS-1: North American Prodromal Longitudinal Study;
[a] At-risk state (only 5 UHR).

psychosis greater in UHR individuals with comorbid disorders? Again, are there differences in the likelihood of transition to psychosis according to the specific disorder/group of symptoms?

We then selected all relevant studies with appropriate definitions of UHR/ARMS (specific structured interview, established international criteria) that provided current and/or lifetime prevalence rates of anxiety disorders, obsessive–compulsive disorder, depressive and bipolar disorders, and eating disorders.

Despite the huge variability in prevalence rates found in different studies, due to the heterogeneity of individuals included in each of the study, which in turns reflects the differences in help-seeking behaviors and access to first episode services in different areas of the world, our main result is that non-psychotic symptoms are a prevalent concern in UHR/ARMS individuals, and this is true for all comorbid disorders examined in the present systematic review.

Anxiety disorders are more prevalent in UHR/ARMS individuals than expected given their prevalence rates in the general population (for example, 12-month prevalence rate in Europe estimated to be 14.0%) (Wittchen et al., 2011). Individual anxiety disorders appear also to be abnormally more represented in this population than in the general population (for example, Social Phobia, the most prevalent individual anxiety disorder, has a current prevalence rate of 5.0–19.4% in UHR individuals as compared to an estimated 12-month prevalence of 2.3% in Europe) (Wittchen et al., 2011).

Obsessive-Compulsive Disorder prevalence rates in UHR individuals (current: 2.0–12.3%, lifetime: 4.0–15.0%) are higher than expected in the general population, if we refer to a 12-month OCD prevalence rate of 0.7% in the general population in Europe (Wittchen et al., 2011), and to 12-month and lifetime prevalence rates of 1.2% and 2.3%, respectively, in the National Comorbidity Survey-Replication in USA (Ruscio et al., 2010).

Mood disorders are also extremely prevalent among UHR individuals: 28-to-72% of help-seeking subjects who satisfy UHR/ARMS criteria have a current DSM-IV mood disorder (both MDD and BD are abnormally prevalent, with current rates of 10.0–67.0% and 0.6–8.7% respectively). Lifetime prevalence rates are even higher, confirming that the vast majority of subjects who seek help in specific services for the prodromes of psychoses do satisfy criteria for DSM-IV mood disorders. Even dysthymia appears to be highly prevalent among those subjects.

We have to conclude, then, as pointed out by Fusar-Poli et al. (2014), that symptoms of both anxiety and depressive disorders and functional disability are often of more concern to UHR individuals than their sub-threshold psychotic symptoms, triggering help-seeking behaviours. It may then be that offering them psychological interventions to improve anxiety and depressive symptoms (Rietdijk et al., 2013) or to reduce the distress experienced in response to life events (or to other environmental stressors) (Kelleher and Cannon, 2011), maladaptive metacognitions and unusual perceptual experiences may help to prevent some people from developing full psychosis (Barkus et al., 2010). Indeed, a paper (Chudleigh et al., 2011) found that depressive symptoms were related to interpersonal social functioning outcome in a group of at risk subjects, indicating the significance of depressive symptoms on social functioning in those with sub-threshold psychotic symptoms. Depression should be targeted early in order to ameliorate social dysfunction in ARMS, due the predictive value of marked impairment in psychosocial functioning on the transition to psychosis.

Regarding eating disorders, their prevalence rates in UHR subjects are higher than expected considering the estimated 0.2–0.5% 12-month prevalence rate for anorexia nervosa, and 0.1–0.9% prevalence rate for bulimia nervosa in the general population in Europe (Wittchen et al., 2011).

The relatively high prevalence of anxiety disorders, OCD/OCS, depressive syndromes and eating disorders in UHR subjects, possibly prodromal to First Episode Psychosis (FEP), suggests that these

Table 6
Transition rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients with or without Mood Disorders.

Authors	Definition of UHR/ ARMS	*N*	Mood Disorders + (%)	Follow-up	Prevalence rates (%) of Mood Disorders in:			*p*
					baseline	converters	non-converters	
Bechdolf et al. (2010)	CAARMS	92	52.2 (MDD)	1.7 years	current MDD	50.0	58.3	n.s.
Schlosser et al. (2012)	SIPS	84	44.0 (current)	2 years	Current Mood Disorders	40.7	45.6	n.s.
Hui et al. (2013)	CAARMS	60	43.7 (MDD lifetime)	1 year	lifetime MDD	80.0	–	–
Lim et al. (2015)	CAARMS	163	23.3 MDD (current)	1 year	*current*			
			58.9 MDD (lifetime)		Anxiety or	63.6	31.0	n.s.
					Depression	0	14.8	n.s.
					Anxiety &	72.7	47.2	n.s.
					Depression	27.3	27.2	n.s.
					lifetime			
					Anxiety or Depression			
					Anxiety & Depression			
						transition rates (%) to psychosis		
Salokangas et al. (2012)	SIPS	245	34.3 (current UDD)	1.5 year	All subjects	15.1		
			4.1 (current BD)		UDD (current)	17.9		n.s
					BD (current)	40.1		.014 HR: 3.691 (CI 1.307–10.429)
Fusar-Poli et al. (2014)	CAARMS	509	MDD 40.0	3.7 years	No depression	14.2	n.s.	
					depression alone	12.7		
					Anxiety & Depression	12.7		

MDD: Major Depressive Disorder; BD: Bipolar Disorder; UD: Unipolar Depressive Disorder
CAARMS: comprehensive assessment of at-risk mental states; SIPS: structured interview for prodromal symptoms

disorders/syndromes in adolescence/early adulthood might be part of the prodromal phase of FEP. If we assume that UHR subjects are really a population at greater risk for the transition to psychosis, then individuals with multidimensional psychopathologies could be at even greater risk of converting to psychosis. Another alternative hypothesis is that UHR individuals (as they are currently defined according to Yung's criteria, predominantly on the basis of the presence of attenuated psychotic symptoms) are actually a heterogeneous group made of subjects at greater risk of developing several different disorders, not only psychosis, where only longitudinal course will clarify the trajectories of evolution of the psychopathologies in each subject (Fusar-Poli et al., 2014). The presence of OCD, anxiety and mood disorders in adolescents with attenuated psychotic symptoms would not mean that this symptomatology is part of the prodromes of schizophrenia/psychosis; thus, subjects with comorbid disorders would not be at greater risk of converting to psychosis than individuals without comorbid psychopathologies.

Indeed, our review clearly found that the vast majority of individuals considered at risk for developing psychosis actually has a clearly defined, above-the-threshold mental disorder that should constitute the primary focus of intervention; subjects with OCD and attenuated psychotic symptoms, to give an example, should receive adequate treatments for their OCD independently (and as a priority) from the presence of attenuated psychotic symptoms.

The second aim of our review was to establish whether the risk of transition to frank psychosis is greater in UHR individuals with comorbid disorders. Moreover, we aimed to examine, through a systematic review of longitudinal studies, the independent predictive

Table 7
Investigation of ED prevalence rates in UHR (Ultra-High Risk) - ARMS (At Risk Mental State) patients.

Authors	Definition of UHR/ARMS	*N*	Design	Any ED (%)	AN (%)	BN (%)	Diagnosis (criteria)
Meyer et al. (2005)	SIPS/SOPS	24	Cross-sectional	1.0 (current)	–	–	SCID (DSM-IV)
Thompson et al. (2007)	CAARMS	23 PACE	Cross-sectional	–	–	4.3 (current)	SCID (DSM-IV)
Woods et al. (2009)	SIPS/SOPS	297	Cross-sectional Longitudinal	2.9 (lifetime)	–	–	SCID (DSM-IV)
Sabb et al. (2010)	SIPS	43	Cross-sectional Longitudinal	2.3 (current)	–	–	SCID (DSM-IV)
Bechdolf et al. (2011)	SIPS/SOPS	156 PREVENT	Cross-sectional	–	–	0.6 (current) (2.5 current Binge Eating Disorder)	SCID (DSM- IV)
Salokangas et al. (2012)	SIPS	245 EPOS	Cross-sectional Longitudinal	1.6 (current) 3.3 (lifetime)	–	–	SCID (DSM-IV)
Ohmuro et al. (2015)	CAARMS	50	Cross-sectional	4.0 (current)	–	–	SCID (DSM-IV)
Lim et al. (2015)	CAARMS	163 LYRIKS	Cross-sectional Longitudinal	–	0.6 (current) 0.6 (lifetime)	–	SCID (DSM-IV)
Rapado-Castro et al. (2015)	CAARMS	73	Cross-sectional	2.7 (current)	–	–	Clinical Interview
Lee et al. (2017)	SIPS	63	Cross-sectional	1.6 (current)	–	–	SCID (DSM-IV)
Madsen et al. (2017)	CAARMS	42	Cross-sectional	26.2 (lifetime)	–	–	SCID (DSM-IV)

ED: Eating Disorders; AN: Anorexia Nervosa; BN: Bulimia Nervosa.
SIPS: structured interview for prodromal symptoms; CAARMS: comprehensive assessment of at-risk mental states; SCID: Structured Clinical Interview for DSM-IV Axis I Disorders.
LYRIKS: Longitudinal Youth at Risk Study.

validity of psychopathologies other than psychotic ones for transition to psychosis in UHR/ARMS subjects.

At this regard, several limitations should be noticed; first of all, we could retrieve relatively few longitudinal studies specifically investigating whether baseline comorbid disorders increase the risk of transition to psychosis. Moreover, they differ in the duration of follow-up (e.g. length of follow-up extremely variable in studies which considered OCD, from 11 months to 7.5 years and MDD from 1 year to 3.6 years), definition of UHR individuals (SIPS/SOPS versus CAARMS; the SIPS excludes symptoms "better explained by another Axis I disorder" thus potentially altering comorbidity rates), inclusion/exclusion criteria (e.g. substance-induced psychotic states). However, we only included studies that used clearly defined criteria for recruiting UHR individuals and used structured clinical interview (SCID or MINI) for the detection of baseline comorbid disorders.

Notwithstanding these limitations, we can conclude that anxiety does not appear to be a marker for transition to psychosis; baseline comorbid anxiety disorders did not predict a greater transition rate to psychosis in the longitudinal studies that examined this issue (Bechdolf et al., 2010; Schlosser et al., 2012; Fusar-Poli et al., 2014; Lim et al., 2015; McAusland et al., 2015; Webb et al., 2015). On the contrary, the EPOS group (Salokangas et al., 2012) found that UHR individuals with current anxiety disorders have a lower risk (HR 0.464) than UHR individuals in general of sliding into full-blown psychosis over the 18-month follow-up. Alternative to the hypothesis that anxiety protects or delays the conversion to psychosis is the idea that subjects with anxiety disorders and brief psychotic experiences are vulnerable subjects for severe anxiety disorders with low social functioning over the follow-up.

Not even OCD/OCS, although abnormally prevalent among UHR/ARMS individuals, predicts transition to psychosis: none of the four studies found an increased likelihood of transition among UHR subjects with baseline OCD/OCS (Niendam et al., 2009; Fontenelle et al., 2011; Hur et al., 2012; McAusland et al., 2015). On the contrary, in one study (Niendam et al., 2009) baseline OCD was associated with a statistical trend towards lower rates of conversion to psychosis over the follow-up period. This may even suggest that obsessive-compulsive symptoms may protect or delay the conversion, as suggested by some Authors in the psychoanalytic arena (Stengel, 1945; Rosen, 1957).

Comorbid mood disorders (mainly comorbid major depressive disorder or unipolar disorders) had no effect on the risk of transition to frank psychotic illness, and this is clearly documented in the six studies that examined this issue (Bechdolf et al., 2010; Salokangas et al., 2012; Schlosser et al., 2012; Hui et al., 2013; Fusar-Poli et al., 2014; Lim et al., 2015). This confirms results of the meta-regression analyses performed by Fusar-Poli and colleagues that revealed no significant impact of anxiety or depressive disorders on the longitudinal risk of transition to psychosis (Fusar-Poli et al., 2014). Our review adds to existing literature in confirming that MDD does not constitute a marker of greater transition while it may be that BD is associated with such greater risk (Salokangas et al., 2012). This also raises the question of the boundaries between psychotic BD and non-affective psychoses.

Regarding comorbid eating disorder, we found only one longitudinal study on the transition to psychosis (Salokangas et al., 2012), indicating that baseline ED does not impact on this risk.

The evidence that multidimensional psychopathology in UHR individuals, although highly prevalent, does not identify subjects at greater risk for transition to frank psychosis questions the current paradigm that considers these UHR subjects (individuals who are help-seeking and fulfill Yung's criteria for UHR) really at risk for transition to psychosis. It may be that the current focus of attention to attenuated psychotic symptoms (the vast majority of individuals recruited in the longitudinal preventive studies as UHR presented APS) as the "core" psychopathology of these individuals should move towards multidimensional psychopathologies where brief psychotic experiences are viewed as common to several disorders other than schizophrenia (van Os and Guloksuz, 2017). Indeed, our systematic review found that the great majority of UHR individuals actually has a clearly defined, above-the-threshold mental disorder that should constitute the primary focus of intervention; all psychopathologies examined in the present review (DSM-IV anxiety disorders, OCD specifically, depressive and bipolar disorders, eating disorders) appear to be over-represented in this group of help-seeking subjects at risk for developing frank psychosis (as per Yung's criteria). The presence of a mental disorder (any of the disorders examined in our review) in UHR individuals is not associated with a greater rate of conversion to frank psychosis over the follow-up as compared to UHR subjects without such "comorbidities"; thus, non-psychotic so-called "comorbid" disorders (although the term comorbid should only be used when two above-the-threshold disorders are present, and this is not the case) should not be viewed as a marker of greater risk of transition and could not constitute an help in identifying those patients that should be the focus of preventive treatments. Indeed, being affected by a clearly above-the-threshold non-psychotic disorders, these individuals should be treated accordingly and independently from the presence of attenuated psychotic symptoms. The true question to be answered is then whether these young individuals with a non-psychotic disorder (e.g. OCD) at risk for psychosis as per Yung's criteria are at greater risk of conversion to frank psychosis as compared to young individuals with the same non-psychotic disorder (e.g. OCD) without an at-risk condition.

The picture is more complicated, as other factors may play a significant role in determining the conversion to frank psychosis, among which personality (e.g. borderline personality pathology) (Ryan et al., 2017) and temperamental traits (e.g. interpersonal sensitivity, harm avoidance) (Fresàn et al., 2015; Masillo et al., 2016), as well as environmental and genetic factors (Fusar-Poli et al., 2017). In the present systematic review, we focused our attention on some non-psychotic Axis I disorders, but we are well aware that several contributing factors may interact in determining the transition to frank psychosis. Among non-psychotic disorders, moreover, we limited our review to anxiety disorders, OCD, affective disorders and eating disorders; we did not examine the role of comorbid substance use disorders, which are very common in UHR individuals and may also contribute to the conversion to psychosis (Valmaggia et al., 2014; Carrà et al., 2016; Carney et al., 2017). Comorbid substance use disorders have a profound negative impact on the prognosis of first-episode psychosis (Colizzi et al., 2016), and future studies should examine the specific contribution of substances other than cannabis on the transition to psychosis in UHR individuals.

Another aspect of potential interest not examined in the present review but worth to be discussed is the possible role of suicidal ideation or suicide attempts as markers for recognizing transition to psychosis in UHR individuals. Each disorder hypothesized to be a condition for subsequent transition to psychosis (anxiety disorders, OCD, affective disorders, eating disorders) has indeed higher suicide risk compared to the general population. It is then possible that only UHR individuals with the comorbid disorder (e.g. OCD) *and* suicidal ideation/attempts are at higher risk for transition to psychosis, and that suicide risk more than the presence of a non-psychotic disorder in UHR individuals could constitute a marker of future transition to psychosis. Although the literature on the topic is scant, suicide risk in the early phases of schizophrenia (first-episode individuals but also UHR subjects) is higher than expected in the general population (Pompili et al., 2011; Bang et al., 2017) and suicidal ideation in schizophrenia is related to the severity of positive symptoms and social cognition impairments (Comparelli et al., 2018). As UHR subjects are mainly individuals with attenuated psychotic (positive) symptoms and/or subjects with a decrease in functioning (including impairments in social cognition), one may assume that UHR individuals are at greater risk for suicide and that UHR individuals who attempt suicide and/or have suicidal ideation are at greater risk for transition to frank psychosis. Indeed, a recent systematic review and meta-analysis (Taylor et al., 2015) found that self-harm and suicidality are highly prevalent in the UHR population and

that co-morbid psychiatric problems, mood variability and a family history of psychiatric problems were among the factors associated with self-harm and suicide risk. It remains to be demonstrated whether these UHR individuals with high suicide risk and comorbid non-psychotic disorders are those with the higher risk for transition to psychosis; the answer to this question is of highly clinical relevance in clinical practice as suicide risk could be easily investigated.

Role of funding source

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.psychres.2018.09.028.

References

Addington, J., Cadenhead, K.S., Cornblatt, B.A., Mathalon, D.H., McGlashan, T.H., Perkins, D.O., et al., 2012. North American prodrome longitudinal study (NAPLS 2): overview and recruitment. Schizophr. Res. 142 (1-3), 77–82.

Addington, J., Epstein, I., Liu, L., French, P., Boydell, K.M., Zipursky, R.B., 2011. A randomized controlled trial of cognitive behavioral therapy for individuals at clinical high risk of psychosis. Schizophr. Res. 125 (1), 54–61.

Addington, J., Shah, H., Liu, L., Addington, D., 2014. Reliability and validity of the calgary depression scale for schizophrenia (CDSS) in youth at clinical high risk for psychosis. Schizophr. Res. 153 (1-3), 64–67.

Bang, M., Park, J.Y., Kim, K.R., Lee, S.Y., Song, Y.Y., Kang, J.I., et al., 2017. Suicidal ideation in individuals at ultra-high risk for psychosis and its association with suspiciousness independent of depression. Early Interv. Psychiatry. https://doi.org/10.1111/eip.12517. Nov 22[Epub ahead of print].

Barkus, E., Stirling, J., French, P., Morrison, A., Bentall, R., Lewis, S., 2010. Distress and metacognition in psychosis prone individuals: comparing high schizotypy to the at-risk mental state. J. Nerv. Ment. Dis. 198 (2), 99–104.

Bechdolf, A., Müller, H., Stützer, H., Wagner, M., Maier, W., Lautenschlager, M., et al., 2011. PREVENT study group. Rationale and baseline characteristics of PREVENT: a second-generation intervention trial in subjects at-risk (prodromal) of developing first-episode psychosis evaluating cognitive behavior therapy, aripiprazole, and placebo for the prevention of psychosis. Schizophr. Bull 37 (Suppl 2), S111–S121.

Bechdolf, A., Thompson, A., Nelson, B., Cotton, S., Simmons, M.B., Amminger, G.P., et al., 2010. Experience of trauma and conversion to psychosis in an ultra-high-risk (prodromal) group. Acta Psychiatr. Scand. 121, 377–384.

Carney, R., Cotter, J., Firth, J., Bradshaw, T., Yung, A.R., 2017. Cannabis use and symptom severity in individuals at ultra high risk for psychosis: a meta-analysis. Acta Psychiatr. Scand. 136 (1), 5–15.

Carrà, G., Johnson, S., Crocamo, C., Angermeyer, M.C., Brugha, T., Azorin, J.M., et al., 2016. Psychosocial functioning, quality of life and clinical correlates of comorbid alcohol and drug dependence syndromes in people with schizophrenia across Europe. Psychiatry Res. 239, 301–307.

Chudleigh, C., Naismith, S.L., Blaszczynski, A., Hermens, D.F., Hodge, M.A., Hickie, I.B., 2011. How does social functioning in the early stages of psychosis relate to depression and social anxiety? Early Interv. Psychiatry 5 (3), 224–232.

Chung, Y.C., Jung, H.Y., Kim, S.W., Lee, S.H., Shin, S.E., Shin, Y.M., et al., 2010. What factors are related to delayed treatment in individuals at high risk for psychosis? Early Interv. Psychiatry 4 (2), 124–131.

Colizzi, M., Carra, E., Fraietta, S., Lally, J., Quattrone, D., Bonaccorso, S., et al., 2016. Substance use, medication adherence and outcome one year following a first episode of psychosis. Schizophr. Res. 170 (2-3), 311–317.

Comparelli, A., Corigliano, V., Lamis, D.A., De Carolis, A., Stampatore, L., De Pisa, E., et al., 2018. Positive symptoms and social cognition impairment affect severity of suicidal ideation in schizophrenia. Schizophr Res. 193, 470–471.

Conrad, A.M., Lewin, T.J., Sly, K.A., Schall, U., Halpin, S.A., Hunter, M., et al., 2014. Ten-year audit of clients presenting to a specialised service for young people experiencing or at increased risk for psychosis. BMC Psychiatry 18 (14), 318.

DeVylder, J.E., Oh, A.J., Ben-David, S., Azimov, N., Harkavy-Friedman, J.M., Corcoran, C.M., 2012. Obsessive compulsive symptoms in individuals at clinical risk for psychosis: association with depressive symptoms and suicidal ideation. Schizophr. Res. 140 (1-3), 110–113.

Falkenberg, I., Valmaggia, L., Byrnes, M., Frascarelli, M., Jones, C., Rocchetti, M., et al., 2015. Why are help-seeking subjects at ultra-high risk for psychosis help-seeking? Psychiatry Res. 228 (3), 808–815.

Fontenelle, L.F., Lin, A., Pantelis, C., Wood, S.J., Nelson, B., Yung, A.R., 2011. A longitudinal study of obsessive-compulsive disorder in individuals at ultra-high risk for psychosis. J. Psychiatr. Res. 45 (9), 1140–1145.

Fresán, A., León-Ortiz, P., Robles-García, R., Azcárraga, M., Guizar, D., Reyes-Madrigal, F., et al., 2015. Personality features in ultra-high risk for psychosis: a comparative study with schizophrenia and control subjects using the temperament and character inventory-revised (TCI-R). J. Psychiatr. Res. 61, 168–173.

Fusar-Poli, P., Bonoldi, I., Yung, A.R., Borgwardt, S., Kempton, M.J., Valmaggia, L., et al., 2012. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch. Gen. Psychiatry 69 (3), 220–229.

Fusar-Poli, P., Byrne, M., Badger, S., Valmaggia, L.R., McGuire, P.K., 2013. Outreach and support in south London (OASIS), 2001-2011: ten years of early diagnosis and treatment for young individuals at high clinical risk for psychosis. Eur. Psychiatry 28 (5), 315–326.

Fusar-Poli, P., Nelson, B., Valmaggia, L., Yung, A.R., McGuire, P.K., 2014. Comorbid depressive and anxiety disorders in 509 individuals with an at-risk mental state: impact on psychopathology and transition to psychosis. Schizophr. Bull. 40 (1), 120–131.

Fusar-Poli, P., Tantardini, M., De Simone, S., Ramella-Cravaro, V., Oliver, D., Kingdon, J., et al., 2017. Deconstructing vulnerability for psychosis: meta-analysis of environmental risk factors for psychosis in subjects at ultra high-risk. Eur. Psychiatry 40, 65–75.

Hui, C., Morcillo, C., Russo, D.A., Stochl, J., Shelley, G.F., Painter, M., et al., 2013. Psychiatric morbidity, functioning and quality of life in young people at clinical high risk for psychosis. Schizophr. Res. 148 (1-3), 175–180.

Hur, J.W., Shin, N.Y., Jang, J.H., Shim, G., Park, H.Y., Hwang, J.Y., et al., 2012. Clinical and neurocognitive profiles of subjects at high risk for psychosis with and without obsessive-compulsive symptoms. Aust. N. Z. J. Psychiatry 46 (2), 161–169.

Kelleher, I., Cannon, M., 2011. Psychotic-like experiences in the general population: characterizing a high-risk group for psychosis. Psychol. Med. 41 (1), 1–6.

Kim, E., Jang, J.H., Park, H.Y., Shim, G., Hwang, J.Y., Kim, S.N., et al., 2012. Pharmacotherapy and clinical characteristics of ultra-high-risk for psychosis according to conversion status: a naturalistic observational study. Early Interv. Psychiatry 6 (1), 30–37.

Korkeila, J., Salokangas, R.K., Heinimaaa, M., Svirskis, T., Laine, T., Ruhrmann, S., et al., EPOS Group, 2013. Physical illnesses, developmental risk factors and psychiatric diagnoses among subjects at risk of psychosis. Eur. Psychiatry 28 (3), 135–140.

Kotlicka-Antczak, M., Pawelczyk, T., Podgorski, M., Zurner, N., Karbownik, M.S., Pawelczyk, A., 2016. Polish individuals with an at-risk mental state: demographic and clinical characteristics. Early Interv. Psychiatry(April). https://doi.org/10.1111/eip.12333. [Epub ahead of print].

Kraan, T.C., Velthorst, E., Themmen, M., Valmaggia, L., Kempton, M.J., McGuire, P., et al., EU-GEI High Risk Study, 2017. Child Maltreatment and clinical outcome in individuals at ultra-high risk for psychosis in the EU-GEI high risk study. Schizophr. Bull.(June). https://doi.org/10.1093/schbul/sbw162. [Epub ahead of print].

Lee, S.J., Kim, K.R., Lee, S.Y., An, S.K., 2017. Impaired social and role function in ultra-high risk for psychosis and first-episode schizophrenia: its relations with negative symptoms. Psychiatry Investig. 14 (2), 186–192.

Lencz, T., Smith, C.W., Auther, A., Correll, C.U., Cornblatt, B., 2004. Nonspecific and attenuated negative symptoms in patients at clinical high-risk for schizophrenia. Schizophr. Res. 68 (1), 37–48.

Leopold, K., Ratzer, S., Correll, C.U., Rottmann-Wolf, M., Pfeiffer, S., Ritter, P., et al., 2014. Characteristics, symptomatology and naturalistic treatment in individuals at-risk for bipolar disorders: baseline results in the first 180 help-seeking individuals assessed at the Dresden high-risk project. J. Affect. Disord. 152–154, 427–433.

Lim, J., Rekhi, G., Rapisarda, A., Lam, M., Kraus, M., Keefe, R.S., et al., 2015. Impact of psychiatric comorbidity in individuals at ultra high risk of psychosis – findings from the longitudinal youth at risk study (LYRIKS). Schizophr. Res. 164 (1–3), 8–14.

Lin, A., Wood, S.J., Nelson, B., Beavan, A., McGorry, P., Yung, A.R., 2015. Outcomes of nontransitioned cases in a sample at ultra-high risk for psychosis. Am. J. Psychiatry 172 (3), 249–258.

Madsen, H.K., Nordholm, D., Krakauer, K., Randers, L., Nordentoft, M., 2017. Psychopathology and social functioning of 42 subjects from a Danish ultra high-risk cohort. Early Interv. Psychiatry(April). https://doi.org/10.1111/eip.12438. [Epub ahead of print].

Marshall, C., Addington, J., Epstein, I., Liu, L., Deighton, S., Zipursky, R.B., 2012. Treating young individuals at clinical high risk for psychosis. Early Interv. Psychiatry 6 (1), 60–68.

Masillo, A., Valmaggia, L.R., Saba, R., Brandizzi, M., Lindau, J.F., Solfanelli, A., et al., 2016. Interpersonal sensitivity and functioning impairment in youth at ultra-high risk for psychosis. Eur. Child. Adolesc. Psychiatry 25 (1), 7–16.

McAusland, L., Buchy, L., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Heinssen, R., et al., 2015. Anxiety in youth at clinical high risk for psychosis. Early Interv. Psychiatry(October). https://doi.org/10.1111/eip.12274. [Epub ahead of print].

Meyer, S.E., Bearden, C.E., Lux, S.R., Gordon, J.L., Johnson, J.K., O'Brien, M.P., et al., 2005. The psychosis prodrome in adolescent patients viewed through the lens of DSM-IV. J. Child. Adolesc. Psychopharmacol. 15 (3), 434–451.

Miller, T.J., McGlashan, T.H., Rosen, J.L., Somjee, L., Markovich, P.J., Stein, K., et al., 2002. Prospective diagnosis of the initial prodrome for schizophrenia based on the Structured Interview for Prodromal Syndromes: preliminary evidence of interrater reliability and predictive validity. Am. J. Psychiatry 159 (5), 863–865.

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., Group, Prisma, 2009. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 6 (7).

Moher, D., Liberati, A., Tetzlaff, J., Altman, D.G., PRISMA Group, 2010. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int. J. Surg. 8 (5), 336–341.

Morcillo, C., Stochl, J., Russo, D.A., Zambrana, A., Ratnayake, N., Jones, P.B., et al., 2015. First-rank symptoms and premorbid adjustment in young individuals at increased risk of developing psychosis. Psychopathology. 48 (2), 120–126.

Nelson, B., Yuen, H.P., Wood, S.J., Lin, A., Spiliotacopoulos, D., Bruxner, A., et al., 2013. Long-term follow-up of a group at ultra high risk ("prodromal") for psychosis: the PACE 400 study. JAMA Psychiatry 70 (8), 793–802.

Niendam, T.A., Berzak, J., Cannon, T.D., Bearden, C.E., 2009. Obsessive compulsive symptoms in the psychosis prodrome: correlates of clinical and functional outcome. Schizophr. Res. 108 (1–3), 170–175.
Ohmuro, N., Matsumoto, K., Katsura, M., Obara, C., Kikuchi, T., Hamaie, Y., et al., 2015. The association between cognitive deficits and depressive symptoms in at-risk mental state: a comparison with first-episode psychosis. Schizophr. Res. 162 (1–3), 67–73.
Pompili, M., Serafini, G., Innamorati, M., Lester, D., Shrivastava, A., Girardi, P., et al., 2011. Suicide risk in first episode psychosis: a selective review of the current literature. Schizophr. Res. 129 (1), 1–11.
Rapado-Castro, M., McGorry, P.D., Yung, A., Calvo, A., Nelson, B., 2015. Sources of clinical distress in young people at ultra high risk of psychosis. Schizophr. Res. 165 (1), 15–21.
Rietdijk, J., Ising, H.K., Dragt, S., Klaassen, R., Nieman, D., Wunderink, L., et al., 2013. Depression and social anxiety in help-seeking patients with an ultra-high risk for developing psychosis. Psychiatry Res. 209 (3), 309–313.
Rosen, I., 1957. The clinical significance of obsessions in schizophrenia. J. Ment. Sci. 103 (433), 773–785.
Rosen, J.L., Miller, T.J., D'Andrea, J.T., McGlashan, T.H., Woods, S.W., 2006. Comorbid diagnoses in patients meeting criteria for the schizophrenia prodrome. Schizophr. Res. 85 (1–3), 124–131.
Ruscio, A.M., Stein, D.J., Chiu, W.T., Kessler, R.C., 2010. The epidemiology of obsessive-compulsive disorder in the national comorbidity survey replication. Mol. Psychiatry 15 (1), 53–63.
Russo, D.A., Stochl, J., Hodgekins, J., Iglesias-Gonzalez, M., Chipps, P., Painter, M., et al., 2017. Attachment styles and clinical correlates in people at ultra-high risk for psychosis. Br. J. Psychol.(April). https://doi.org/10.1111/bjop.12249. [Epub ahead of print].
Rutigliano, G., Valmaggia, L., Landi, P., Frascarelli, M., Cappucciati, M., Sear, V., et al., 2016. Persistence or recurrence of non-psychotic comorbid mental disorders associated with 6-year poor functional outcomes in patients at ultra high risk for psychosis. J. Affect. Disord. 203, 101–110.
Ryan, J., Graham, A., Nelson, B., Yung, A., 2017. Borderline personality pathology in young people at ultra high risk of developing a psychotic disorder. Early Interv. Psychiatry 11 (3), 208–214.
Sabb, F.W., van Erp, T.G.M., Hardt, M.E., Dapretto, M., Caplan, R., Cannon, T.D., et al., 2010. Language network dysfunction as a predictor of outcome in youth at clinical high risk for psychosis. Schizophr. Res. 116, 173–183.
Salokangas, R.K., Ruhrmann, S., von Reventlow, H.G., Heinimaa, M., Svirskis, T., From, T., et al., EPOS group, 2012. Axis I diagnoses and transition to psychosis in clinical high-risk patients EPOS project: prospective follow-up of 245 clinical high-risk outpatients in four countries. Schizophr. Res. 138 (2–3), 192–197.
Schlosser, D.A., Jacobson, S., Chen, Q., Sugar, C.A., Niendam, T.A., Li, G., et al., 2012. Recovery from an at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. Schizophr. Bull. 38 (6), 1225–1233.
Schultze-Lutter, F., Michel, C., Schmidt, S.J., Schimmelmann, B.G., Maric, N.P., Salokangas, R.K., et al., 2015. EPA guidance on the early detection of clinical high risk states of psychoses. Eur. Psychiatry 30 (3), 405–416.
Simon, A.E., Borgwardt, S., Riecher-Rössler, A., Velthorst, E., de Haan, L., Fusar-Poli, P., 2013. Moving beyond transition outcomes: meta-analysis of remission rates in individuals at high clinical risk for psychosis. Psychiatry Res. 209 (3), 266–272.
Simon, A.E., Umbricht, D., 2010. High remission rates from an initial ultra-high risk state for psychosis. Schizophr. Res. 116 (2–3), 168–172.
Simon, A.E., Velthorst, E., Nieman, D.H., Linszen, D., Umbricht, D., de Haan, L., 2011. Ultra high-risk state for psychosis and non-transition: a systematic review. Schizophr. Res. 132 (1), 8–17.
Stengel, E., 1945. A study on some clinical aspects of the relationship between obsessional neurosis and psychotic reaction types. J. Ment. Sci. 91, 166–187.
Sterk, B., Lankreijer, K., Linszen, D.H., de Haan, L., 2011. Obsessive-compulsive symptoms in first episode psychosis and in subjects at ultra high risk for developing psychosis; onset and relationship to psychotic symptoms. Aust. N. Z. J. Psychiatry 45 (5), 400–406.
Tay, S.A., Yuen, S., Lim, L.K., Pariyasami, S., Rao, S., Poon, L.Y., et al., 2015. Support for wellness achievement programme (SWAP): clinical and demographic characteristics of young people with at-risk mental state in Singapore. Early Interv. Psychiatry 9 (6), 516–522.
Taylor, P.J., Hutton, P., Wood, L., 2015. Are people at risk of psychosis also at risk of suicide and self-harm? A systematic review and meta-analysis. Psychol Med 45 (5), 911–926.
Thompson, K.N., Phillips, L.J., Komesaroff, P., Yuen, H.P., Wood, S.J., Pantelis, C., et al., 2007. Stress and HPA-axis functioning in young people at ultra high risk for psychosis. J Psychiatr. Res. 41 (7), 561–569.
Valmaggia, L.R., Day, F.L., Jones, C., Bissoli, S., Pugh, C., Hall, D., et al., 2014. Cannabis use and transition to psychosis in people at ultra-high risk. Psychol. Med. 44 (12), 2503–2512.
van Os, J., Guloksuz, S., 2017. A critique of the ``ultra-high risk" and ``transition" paradigm. World Psychiatry 16 (2), 200–206.
Webb, J.R., Addington, J., Perkins, D.O., Bearden, C.E., Cadenhead, K.S., Cannon, T.D., et al., 2015. Specificity of incident diagnostic outcomes in patients at clinical high risk for psychosis. Schizophr. Bull. 41 (5), 1066–1075.
Wittchen, H.U., Jacobi, F., Rehm, J., Gustavsson, A., Svensson, M., Jönsson, B., et al., 2011. The size and burden of mental disorders and other disorders of the brain in Europe 2010. Eur. Neuropsychopharmacol 21 (9), 655–679.
Woods, S.W., Addington, J., Cadenhead, K.S., Cannon, T.D., Cornblatt, B.A., Heinssen, R., et al., 2009. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophr. Bull. 35 (5), 894–908.
Yung, A.R., Yuen, H.P., McGorry, P.D., Phillips, L.J., Kelly, D., Dell'Olio, M., et al., 2005. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust. N. Z. J. Psychiatry 39 (11–12), 964–971.
Zeni-Graiff, M., Rizzo, L.B., Mansur, R.B., Maurya, P.K., Sethi, S., Cunha, G.R., et al., 2016. Peripheral immuno-inflammatory abnormalities in ultra-high risk of developing psychosis. Schizophr. Res. 176 (2–3), 191–195.
Zink, M., Schirmbeck, F., Rausch, F., Eifler, S., Elkin, H., Solojenkina, X., et al., 2014. Obsessive-compulsive symptoms in at-risk mental states for psychosis: associations with clinical impairment and cognitive function. Acta Psychiatr. Scand. 130 (3), 214–226.