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PERSISTENCE OR RECURRENCE OF NON-PSYCHOTIC COMORBID MENTAL DISORDERS ASSOCIATED WITH 6-YEAR POOR FUNCTIONAL OUTCOMES IN PATIENTS AT ULTRA HIGH RISK FOR PSYCHOSIS

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Abstract

Background: Patients at ultra-high risk for psychosis (UHR) are a highly heterogeneous group in terms of clinical and functional outcomes. Several non-psychotic mental disorders co-occur together with the UHR state. Little is known about the impact of non-psychotic comorbid mental disorders on clinical and functional outcomes of UHR patients.

Methods: The sample included 154 UHR help-seeking patients (identified with the CAARMS, Comprehensive Assessment of the At-Risk Mental State), evaluated at baseline on the Ham-D, Ham-A (Hamilton Depression/Anxiety Rating Scale), and PANSS (Positive and Negative Syndrome Scale). 74 patients completed the 6-year follow-up assessment (mean=6.19, SD=1.87). Comorbid disorders at follow-up were assessed with the SCID I and II. Global functioning was rated on the Global Assessment of Functioning (GAF) scale.

Results: In the present sample, 6-year risk of psychosis transition was 28.4%. Among non-transitioned UHR patients, 28.3% reported Attenuated Psychotic Symptoms (APS) and 45.3% remained functionally impaired at follow-up (Global Assessment of Functioning, GAF < 60). 56.8% patients were affected by at least one comorbid disorder at follow-up. Among UHR patients who presented with some comorbid disorder at baseline, 61.5% had persistent or recurrent course. Incident comorbid disorders emerged in 45.4% of baseline UHR patients. The persistence or recurrence of non-psychotic comorbid mental disorders was associated with poorer global functional outcomes at follow-up.

Limitations: A substantial proportion of the initial sample was not available for follow-up interviews and some groups in the analyses had small sample size. Predictors of longitudinal outcomes were not explored.

Conclusions: Among UHR patients, persistence or recurrence of non-psychotic comorbid mental disorders, mostly affective disorders, is associated with 6-year poor functional outcomes.

Keywords: UHR; comorbid; global functioning; remission; outcomes.

Introduction

Preventative strategies in psychosis have received growing attention since the introduction of psychometric criteria for identifying patients at ultra-high risk for psychosis (UHR) (McGlashan et al., 2010; Yung et al., 2005). Current psychometric instruments allow the preventative identification of subjects with an enhanced 36% risk of developing psychosis after 3 years (Fusar-Poli et al., 2012a), a risk which peaks within the first two years since initial assessment (Kempton et al., 2015). However, since most of those initially deemed at risk will not actually transition to full-blown psychosis, and given that the transition risk appears to be declining over the recent years (Fusar-Poli et al., 2015d), it is crucial to address the clinical and functional outcomes of UHR patients beyond transition to psychosis.

The UHR state tends to co-occur with other non-psychotic mental disorders (Fusar-Poli et al., 2013a; Salokangas et al., 2012; Svirskis et al., 2005). Our previous multicentre study found that at presentation about 73% of UHR patients had at least one comorbid Axis I diagnosis in addition to the UHR, with the most common one being of depressive and/or anxiety disorders (Fusar-Poli et al., 2014a). These comorbid disorders were impacting the baseline functional level of UHR patients, with an accumulating effect of concurrent anxiety and depressive disorders (Fusar-Poli et al., 2014a). These results suggest that UHR patients suffer from mental difficulties which are distressing and disabling *per se*, regardless of the development of a psychotic disorder. Indeed, the presence of psychopathological symptoms other than Attenuated Psychotic Symptoms (APS) is the most common subjective complaint triggering help-seeking behaviours in this population (Addington et al., 2002; Falkenberg et al., 2015; Stowkowy et al., 2013).

Despite the above findings exploring the impact of non-psychotic comorbid mental disorders on baseline UHR presentation, less is known about their impact on the long-term outcomes. Only a few papers have addressed the impact of comorbid disorders on longitudinal outcomes at 12mo (Lim et al., 2015; Niendam et al., 2009; Ryan et al., 2015; Van Dael et al., 2011), 24mo (Thompson et al., 2012; Van Dael et al., 2011), 44mo (Fusar-Poli et al., 2014a), and 84mo (de Wit et al., 2014; Fontenelle et al., 2011, 2012; Lin et al., 2015). These studies confirmed high percentages of co-occurrence of the UHR state with non-psychotic comorbid mental disorders at baseline, with meta-analytical prevalences of 40.7% (95% CI 32.5%-49.4%) for depressive disorders and 15.3% (95% CI 8.9%-25%) for anxiety disorders (Fusar-Poli et al., 2014a).

Other non-psychotic mental disorders consistently observed in UHR samples were obsessive-compulsive disorders, pervasive developmental disorders, substance use disorders, and borderline personality disorders, with baseline prevalence prevalence of up to 14% (Niendam et al., 2009), 38.6% (de Wit et al., 2014), 8% (Fusar-Poli et al., 2014a), and 25% (Ryan et al., 2015), respectively. High comorbidity rates were also found over follow-up assessments. For example, Lin, et al. found that 68.1% of their initial UHR patients presented at least one non-psychotic comorbid mental disorder over 7-year follow-up, the more frequent being mood disorders (48.7%), anxiety disorders (34.5%), and substance use disorders (29.2%) (Lin et al., 2015). In their UHR sample, non-psychotic comorbid mental disorders tended to persist or recur (51.6% persistent/recurring course vs 26.0% remittent course). Incident non-psychotic comorbid mental disorders developed in 37.5% UHR patients, leaving only 7.3% of the baseline UHR patients with no experience of any comobid disorders (Lin et al., 2015) over follow-up time. Overall, these studies showed that baseline non-psychotic comorbid mental disorders were not predicting subsequent transition to psychosis (Fontenelle et al., 2011; Fusar-Poli et al., 2014a; Lim et al., 2015; Niendam et al., 2009; Ryan et al., 2015; Thompson et al., 2012), whereas their presence during follow-up was associated with lower GAF scores at one-year follow-up(Lim et al., 2015).

However, it is not known how non-psychotic comorbid mental disorders might impact outcomes other than psychosis onset. For example, recent studies have shown that a substantial proportion of the UHR patients - up to 50% - continue suffering from APS over the follow-up period (Lee et al., 2014; Lemos-Giraldez et al., 2009; Velthorst et al., 2011), but the impact of affective anxiety or depressive disorders on APS persistence is underinvestigated. Because of the persistence of conjoint APS and non-psychotic comorbid mental disorders, functional level in UHR may be impaired (Addington et al., 2011). Indeed, there is recent meta-analytical evidence indicating the UHR, as a whole group, is characterized by baseline functional impairments and quality of life deficits that are comparable to other mental disorders (Fusar-Poli et al., 2015c).

The current study followed the methodological approach described in previous analyses (Lin et al., 2015) to investigate the long-term impact of non-psychotic comorbid mental disorders on several clinical outcomes in UHR patients. Our primary aim was to describe the broader spectrum of long term clinical outcomes of UHR patients. This included transition to psychosis, persistence of APS, prevalence and type of non-psychotic comorbid disorders, persistence of functional impairment as well as complete clinical remission. Our

secondary aim was then to address the longitudinal course of non-psychotic comorbid disorders and their association with clinical and functional outcomes in UHR patients.

Methods

Setting and study participants

OASIS is a specialist clinic for patients at UHR for psychosis. Currently it covers a wide urban area of about 1.18 million citizens in South London in three different boroughs (Lewisham, Lambeth, Southwark) (Fusar-Poli et al., 2013b). It is known that South London has very high psychosis rates (Kirkbride et al., 2006).

The service is aimed at 14-35 help seeking UHR patients meeting the Comprehensive Assessment of the At-Risk Mental State (CAARMS) criteria (Yung et al., 2006) for: (1) Genetic risk and deterioration syndrome (GRD, schizotypal personality disorder or history of psychosis in a first degree relative); (2) APS (symptoms which do not reach threshold levels for psychosis due to sub-threshold intensity or frequency); (3) Brief Limited Intermittent Psychotic Symptoms (BLIPS, recent history of frank psychotic symptoms that resolved spontaneously within one week). In addition participants have to experience a decline in functioning sustained for at least one month in the past year or a low level of functioning sustained over the past year (Yung et al., 2006). All the subjects assessed at the OASIS clinic (Fusar-Poli et al., 2013b) in the period 2001-2012 and deemed to endorse a UHR state were considered eligible for this study.

All patients signed an informed consent to use data about clinical measures and treatment.

Baseline Assessment

UHR patients were identified according to the CAARMS criteria (Yung et al., 2005). The CAARMS composite score was computed by weighting intensity (I) of symptoms by their frequency (F) within the three domains of Positive Symptoms measured by CAARMS: Disorders of Thought Content (DTC), Perceptual Abnormalities (PA) and Disorganized Speech (DS), according to the formula (I-DTC*F-DTC) + (I-PA*F-PA) + (I-DS*F-DS) (Morrison et al., 2012). Higher scores indicated more severe APS.

Comorbid lifetime and current non-psychotic mental disorders were established using the CAARMS and the Hamilton Depression and Anxiety Scales (Ham-D, Ham-A) (Hamilton, 1959, 1960). In this study, comorbidity was defined as fulfilling the criteria for both UHR and at least one non-psychotic mental disorder.

Psychopathology was also investigated quantitatively at baseline with Ham-D, Ham-A (Hamilton, 1959, 1960) and Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987).

Global functioning in the past week was rated on the Global Assessment of Functioning (GAF) scale (Hall, 1995). We used the GAF scale, which encompasses both psychopathology and social and role functioning, because the majority of our sample was recruited before the introduction of the Social and Occupational Functioning Assessment Scale (SOFAS) as part of the CAARMS 12/2006 assessment (Yung et al., 2005).

Additionally, there is consistent evidence showing a stringent relationship between the SOFAS and GAF scores (Samara et al., 2014).

Follow-up assessment

Non-psychotic comorbid mental disorders at follow-up were assessed with the Structured Clinical Interview for DSM-IV TR Axis I and Axis II Disorders (SCID-I and SCID-II) (First et al., 1997, 2008). The CAARMS criteria were used to assess the presence of APS and to define the transition to psychosis. Functional outcome at follow-up was assessed with the GAF scale. Type and course of comorbid diagnoses was further described: UHR were grouped according to the course of comorbid disorders, as previously indicated (Lin et al., 2015). In patients without comorbid disorders at baseline, those who still had no comorbid disorders over follow-up were classed as “Never”, whereas those who developed one as “Incident”. Amongst patients presenting with comorbid disorders at baseline, “Persistent/Recurrent” was used if the disorder was still present at follow-up, while “Remittent” if not (Lin et al., 2015).

Primary outcome

The primary aim was to describe the broader spectrum of clinical outcomes of UHR patients. Clinical outcomes of UHR patients at follow-up included: (i) transition to psychosis, (ii) persistence of APS, (iii) prevalence and type of non-psychotic comorbid mental disorders, (iv) persistence of functional impairment,

and (v) complete clinical remission. Persistence of APS was defined as presenting APS above the threshold for meeting the APS subgroup on the CAARMS. Persistence of functional impairment was defined as having GAF score < 60 (Lee et al., 2014). We chose this cut-off because subjects scoring in the 60-70 range "generally function pretty well, have some meaningful interpersonal relationships" despite "some difficulty in social and occupational functioning", whereas scores lower than 60 correspond to "moderate to severe impairment", as previously suggested (Hall, 1995). Complete clinical remission was defined as: absence of non-psychotic comorbid mental disorder, no longer presenting with APS meeting the CAARMS threshold, and absence of functional impairment (GAF > 60).

Secondary outcome

The secondary aim was then to address the longitudinal course of comorbid disorders and their association with clinical and functional outcomes in UHR patients: (i) transition to psychosis, (ii) persistence of APS, and (iii) persistence of functional impairment, defined as above here.

Statistical analyses

The primary outcome (clinical outcomes at follow-up) was analyzed with descriptive frequency of each class: (i) transition to psychosis, (ii) persistence of APS, (iii) prevalence and type of non-psychotic comorbid mental disorders , (iv) persistence of functional impairment, and (v) complete clinical remission.

The secondary outcome addressed the longitudinal courses of non-psychotic comorbid mental disorders and their association with clinical and functional outcomes: (i) transition to psychosis, (ii) persistence of APS, and (iii) persistence of functional impairment. Due to the size of our sample, we were not able to perform separate analyses for different comorbid disorders. Binary logistic regression analyses were employed to ascertain the effects of the course (incidence and persistence/recurrence) of comorbid disorders on the probability of: (i) transition to psychosis, (ii) persistence of APS, and (iii) persistence of functional impairment. We controlled our analyses for covariates selected a priori on the basis of their clinical relevance: age at baseline (Fusar-Poli et al., 2012b); gender (Willhite et al., 2008); follow-up time (Nelson et al., 2013); CAARMS intake group (Nelson et al., 2011); CAARMS composite scores (Yung et al., 2005). Supplementary analyses are appended online as eMethods.

All statistical analyses were performed on SPSS 22.0 (IBM, 2013).

Results

Sample characteristics

The current sample included a total of 154 UHR patients. Out of the 154 patients assessed at baseline, 20 (13.0%) refused to come for a face to face assessment but agreed to answer a brief phone questionnaire, and limited follow-up data was provided from the general practitioners of another 22 patients (14.3%), 36 (23.4%) were no longer available at follow-up and 2 (1.3%) had deceased. Therefore, follow-up interviews were completed by 74 (48.0%) patients, 21 of whom (28.4%) had transitioned to psychosis and 53 (%) had not. The clinical follow-up of UHR patients is pictured in Figure 1.

Figure 1 about here

We checked whether people who dropped out had different characteristics then those who did not, respect to socio demographic and clinical characteristics as well as if there were statistically significant differences in GAF and prevalence of non-psychotic comorbid mental disorders at baseline. No significant between group differences were found, with the exception of gender. The dropouts tended to be male (70% male $\chi 2=6.43$; $p<0.05$) (Table 1).

Table 1 about here

Follow-up length was between 4 and 10 years (mean=6.19, SD=1.87, median =6). Patients who were available for the follow-up assessment were aged on average 23.20 (SD=4.90) at baseline and 29.39 (SD=5.64) at follow-up. 50% of patients were female. All our patients but one met the APS group criteria.

Of them, 11 (14.9%) fulfilled also the BLIPS criteria, 8 (10.8%) met also the GRD criteria, and 1 (1.4%) fulfilled all three. The only patient who did not present APS at baseline met the BLIPS subgroup. Along with case-management, 38 (51.4%) of the participants engaged in up to 24 sessions of cognitive behavioural therapy (CBT) by trained clinical psychologists, 3 (4.1%) were commenced on low-dose antipsychotics, 19 (25.7%) received both CBT and low-dose antipsychotics; specific details of focused interventions provided in this sample have been described elsewhere (Fusar-Poli et al., 2015b).

Primary outcome

Transition to psychosis at 6-year follow-up

At 6-year follow-up, 21 (28.4%) UHR patients had transitioned to any psychotic disorder (Figure 2). No significant differences in transition were found between treated and untreated patients.

Persistence of APS at 6-year follow-up

Among non-transitioned patients (n = 53), about one third, 28.3% (n = 15) continued meeting the APS subgroup on the CAARMS. Patients who had received any intervention did not report significantly lower APS rates at follow-up compared to those who had not ($\chi^2 = 1.76$, df = 1, p = 0.18).

Prevalence and type of non-psychotic comorbid mental disorders at follow-up

Among the whole sample assessed at follow-up (%), 42 (56.8%) patients were affected by at least one non-psychotic comorbid mental disorder. Among non-transitioned cases, APS and non-psychotic comorbid mental disorders co-occurred in 10 (13.5%) patients at 6-year follow-up (Figure 2). We found no significant differences in comorbid disorders prevalence at follow-up between treated and untreated patients.

The prevalence of specific types of non-psychotic disorders at follow-up is showed in table 2. Among the patients reporting at least one current comorbid mental disorder at follow-up, the most common were affective (n = 25, 33.8%) and anxiety (n = 16, 21.6%) disorders, which co-occurred in 6.8% of the whole sample. In particular, major depressive disorders and panic disorder accounted for most of the affective and anxiety disorders, respectively.

Table 2 about here

Persistence of functional impairment ay 6-year follow-up

Among non-transitioned UHR, 45.3% (n = 24) remained functionally impaired at follow-up (GAF < 60).

Complete clinical remission at 6-year follow-up

Of those who had not transitioned, only 11 (14.9%) UHR patients achieved a complete clinical remission.

***Figure 2 about here ***

Secondary outcome

Longitudinal course of non-psychotic comorbid mental disorders

The longitudinal course of non-psychotic comorbid mental disorders is displayed in table 3. Of the UHR patients who presented with a comorbid disorder at baseline (n = 52, 70.3%), 61.5% (n = 32) had persistent or recurrent course. Moreover, 45.4% (n = 10) of those without comorbid disorders at baseline (n = 22, 29.7%) developed a new disorder over the follow-up period. Only 16.5% (n = 12) of the entire sample never experienced any comorbid disorder (Figure 3).

Figure 3 about here

Most of the patients with affective comorbid disorders at baseline (n = 27, 36.5%) had remittent course (n = 16, 59.3%). An incident affective disorder emerged in 29.8% (n = 14) of those without affective disorders at baseline (n = 47, 63.5%). Overall, 44.6% (n = 33) never reported any affective disorder. Half of anxiety disorders present at baseline (n = 8, 10.8%) had persistent or recurrent course (n = 4, 50.0%) and 18.2% (n = 12) of those not reporting anxiety at baseline (n = 66, 89.2%) developed an anxiety disorder over follow-up. 70.3% (n = 52) of UHR patients never experienced any anxiety disorder.

Table 3 about here

There were no significant differences in the use of medication between groups of patients with distinct course of comorbid disorders (respectively, F = 2.44, p = 0.29 and F = 1.98, p = 0.37).

Association between course of non-psychotic comorbid mental disorders and transition to psychosis

There was no association between incident comorbid disorders over the follow-up and transition to psychosis. The statistical significance of the overall model, χ^2 (2) = 7.99, p = 0.02 was driven by the type of the CAARMS intake group, in that patients in the BLIPS group resulted at higher risk of transition as compared to the other two groups (OR = 22.42, 95% CI for OR = 1.45-347.16, p = 0.03). The model explained 42.7% (Nagelkerke R^2) of the variance in transition rates. No association was found between persistence or recurrence of comorbid disorders and transition to psychosis (p = 0.10).

Association between course of non-psychotic comorbid mental disorders and persistence of APS at 6-year follow up

Incidence of comorbid disorders over the follow-up was not significantly associated with persistence of APS, though the overall model was statistically significant, χ^2 (2) = 6.58, p = 0.04 because of the significant effect of follow-up length on the likelihood of APS persistence at follow-up (OR = 2.53, 95% CI for OR = 1.03-6.25, p = 0.04). The model explained 37.5% (Nagelkerke R^2) of the variance in APS persistence.

The association between persistence or recurrence of comorbid disorders and the probability of persistence of APS at follow-up was not significant. Nonetheless, the overall model was statistically significant, χ^2 (2) = 9.02, p = 0.01, again because of the effects of covariates such as follow-up length. The model explained 23.1% (Nagelkerke R^2) of the variance in APS persistence.

Association between course of non-psychotic comorbid mental disorders and persistence of functional impairment at 6-year follow-up

We found no association between incidence of comorbid disorders over the follow-up and persistence of functional impairment (e.g. having GAF scores lower than 60). Viceversa, persistence or recurrence of comorbid disorders was associated with an increased chance of functional impairment at 6-year follow-up

(OR = 5.05, 95% CI for OR = 1.16-21.96, p = 0.03). The model explained 42.0% (Nagelkerke R^2) of the variance in persistence of functional impairment.

Discussion

The current study investigated the broad clinical outcomes of UHR patients at 6-year follow-up, and the longitudinal impact of non-psychotic comorbid mental disorders. About one third of the baseline sample (28%) had transitioned to psychosis. Among those who did not transition, only 11 (14.9%) achieved complete clinical remission. The majority of UHR patients (56.8%) presented at least one non-psychotic comorbid mental disorder at follow-up. About 61.5% of the patients had persistent or recurrent course of non-psychotic comorbid mental disorders, while incident non-psychotic comorbid mental disorders emerged in 45.4% of patients. The persistence or recurrence of non-psychotic comorbid mental disorders was associated with poorer global functional outcomes at 6-year follow-up.

Our first aim was to fully describe transition to psychosis, persistence of APS, prevalence and type of non-psychotic comorbid mental disorders, persistence of functional impairment, and complete clinical remission at 6-year follow-up. The transition risk observed in our patients over a 6-year follow-up period was of 28.4%, which is in line with recent meta-analytical reports (Fusar-Poli et al., 2012b; Fusar-Poli et al., 2015d). Even though we observed a substantial symptomatic improvement of UHR symptoms, in terms of reduced severity (see supplementary material) and frequency of APS, about a third (28.3%) of non-transitioned patients continued to experience significant symptoms meeting the APS intake criterion on the CAARMS at follow-up assessment. Furthermore, about half (45.3%) of non-transitioned patients remained significantly functionally impaired. Overall, the proportion of the non-transitioned UHR patients showing complete clinical remission at 6-year follow-up was of 14.9%. In our sample, 6-year probability of persistence of APS was around 17% lower than persistence of functional impairment (45.3%). This finding is consistent with a large study showing that global functioning in UHR remains poor even after significant improvement of APS, suggesting that initial UHR categorization is associated with persistent disability (Addington et al., 2011). Moreover, our supplementary analyses showed that the functional level was almost virtually indistinguishable between patients who transitioned to psychosis and those who did not transition but with persistent attenuated psychotic symptoms. This finding is corroborated by additional meta-analytical

evidence indicating that the functional level of UHR patients is significantly worse than matched healthy comparisons, but comparable to those observed in other mental disorders, beyond their risk of transitioning to psychosis (Fusar-Poli et al., 2015c). The observed outcomes may have been influenced by the treatment received. Indeed, our remission rates are similar to previous UHR patients exposed to either pharmacotherapy or psychotherapy (Lee et al., 2014; Simon and Umbricht, 2010). In the current study, 81.1% of the baseline sample had received some type of focused intervention. We have fully reported on the impact of different types of focused interventions on risk of psychosis transition in a separate study (Fusar-Poli et al., 2015b). We observe here that, despite the majority of our sample was treated, complete clinical remission was achieved in a minority of them only. There may be limitations in the effectiveness of available treatments with respect to functional remission and quality of life outcomes.

With respect to prevalence of non-psychotic comorbid mental disorders, they affected 56.8% of our sample at 6-year follow-up, in line with converging findings from other UHR cohorts (Hui et al., 2013; Kwon et al., 2012; Lim et al., 2015; Lin et al., 2015; Rosen et al., 2006; Salokangas et al., 2012; Svirskis et al., 2005; Woods et al., 2009). Of interest, prevalence of comorbid disorders in UHR samples are higher than prevalence rates of non-psychotic disorders in epidemiological studies of the general population (Charlson et al., 2013; Costello et al., 2003; Ferrari et al., 2013; Kessler et al., 2005a), suggesting a close concurrence of APS and comorbid disorders in UHR samples. With respect to the specific type of non-psychotic comorbid disorders, major depression was the most frequent diagnosis among mood disorders, while panic disorder was the most frequent diagnosis among anxiety disorders, as previously reported in different populations (Hui et al., 2013; Lim et al., 2015; Svirskis et al., 2005).

The clinical significance of non-psychotic comorbid disorders in UHR patients is not completely clear. Highly prevalent affective comorbid disorders are frequently observed in other mental disorders, and they occur in up to 50% of subjects with a psychiatric diagnosis (Demyttenaere et al., 2004; Kessler et al., 2005b). In particular, several epidemiological studies reported non-psychotic comorbid mental disorder prevalences as high as 58% among patients with schizophrenia spectrum disorders (Cassano et al., 1998; Cutler and Siris, 1991; Kendler et al., 1996; Strakowski et al., 1993; Sutliff et al., 2015). Retrospective studies have shown that depression and anxiety are the most frequent symptoms in the prodromal phase of a first psychotic episode (Hafner et al., 2005). It has been proposed that such extensive overlay and continuity between the

psychotic and affective syndromes may be explained with a network theory of psychiatric disorders, where clusters of strongly interacting symptoms may communicate through individual “bridge” symptoms (Goekoop and Goekoop, 2014). Results from these network analyses showed “depression” and “anxiety” as the most influential clusters (Goekoop and Goekoop, 2014), in line with phenomenological, cognitive and neurobiological models of affective dysregulation as a crucial factor in the emergence and maintenance of UHR symptoms (Mishara and Fusar-Poli, 2013).

Our secondary aim was to address the longitudinal course of non-psychotic comorbid mental disorders and their impacts on transition to psychosis, persistence of APS, and persistence of functional impairment. Among UHR patients who presented with some comorbid disorder at baseline, 61.5% had persistent or recurrent course. In addition, incident comorbid disorders emerged in 45.4% of patients without comorbid disorders at baseline. Such figures are consistent with the results of a recent long-term follow-up study (Lin et al., 2015). The authors of this study argued that the UHR criteria might be also useful for predicting a broader risk for chronic and emerging mental disorders [(Lin et al., 2015), page 256]. However, they could not identify any strong predictors of the course of non-psychotic disorders, in contrast with the good diagnostic accuracy of several clinical, cognitive, biological, and environmental discriminative predictors of psychosis onset (Koutsouleris et al., 2015; Michel et al., 2014; Nieman et al., 2013).

Incidence, persistence or recurrence of comorbid disorders were not significantly associated with risk of psychosis transition, or of persistence of APS over the follow-up. Viceversa, persistent or recurrent course of comorbid disorders (mostly affective) was associated with probability of persistent functional impairment at 6-year follow-up. We specifically found that persistence or recurrence of non-psychotic comorbid mental disorders related to lower functional levels at 6-years follow-up. This finding was corrected for age at baseline, gender, follow-up time, CAARMS intake group and CAARMS composite scores.

To our best knowledge this is the first study to have investigated the impact of persistence/recurrence of affective comorbid disorders on the long-term longitudinal functional status of UHR patients. The finding of an association between persistent or recurrent course of non-psychotic comorbid mental disorders and poor functional outcome in the long term may have some clinical relevance. First, it suggests extending the National Institute for Health and Care Excellence (NICE) guidelines, number 1.3.3.3, recommending a

routinely comprehensive assessment of comorbid non-psychotic mental disorders during early psychosis, to UHR patients at several timepoints over the follow-up periods. Moreover, our finding supports the NICE guidelines, number 1.2.3.1, which recommend that UHR patients be offered integrative interventions aimed at treating affective and anxiety symptoms and restoring better levels of global functioning, besides delaying and preventing the development of psychosis. In fact, the overall clinical and economic burden of the UHR state seems to be better pictured by persistent disability in non-transitioned patients (Fusar-Poli et al., 2015c; Yung et al., 2010)**.** The association between persistent or recurrent course of non-psychotic comorbid mental disorders and poor functional outcome suggests that treating these disorders early could have a broader impact on future trajectories than focusing only on prevention of schizophrenia in UHR patients (Fusar-Poli et al., 2014b). Unfortunately, to date, most treatments developed and tested in UHR samples have targeted psychosis transition as the unique outcome (Valmaggia et al., 2013). While the interventions tested in the available randomized controlled trials (RCTs), which include psychological therapies, medication or alternative therapies, may be useful in preventing psychosis onset (Stafford et al., 2013; Turner et al., 2014), their benefits on non-psychotic comorbid mental disorders and the associated functional outcomes remains unknown. It could be further speculated that those patients meeting UHR criteria together with affective psychopathology, could receive greater benefit from specific treatments aiming at reducing mood and anxiety symptoms (Fusar-Poli et al., 2014b). Second, at a conceptual level, the longitudinal impact of affective comorbid disorders on the functional status of UHR patients may be addressed by the clinical staging model. It posits that psychosis onset might arise from states of mixed, diagnostically non-specific, sub-threshold psychopathology, and develop into more defined and severe conditions with functional deterioration as they progress under the influence of diverse risk factors (Fusar-Poli et al., 2014b). However, this model has been challenged by recent large-scale longitudinal studies, showing that the UHR state does identify a specific risk for psychosis (OR = 13.8, 95% CI 4.2 – 45.0) (Webb et al., 2015). This study found that the UHR state is not associated with an increased risk of emergent bipolar disorders (OR = 0.94, 95% CI 0.16 – 5.70), non-bipolar mood disorders (OR = 0.83, 95% CI 0.34 – 2.02), and anxiety disorders (OR = 0.99, 95% CI 0.41 – 2.41). However, in this study, UHR patients were assessed with the SIPS (Structured Interview for Psychosis-Risk Syndromes) (McGlashan et al., 2010), which excludes symptoms “better

explained by another axis I disorder", differently from the CAARMS (McGlashan et al., 2010) , thus potentially affecting the observed frequency of comorbid disorders.

There are some limitations to this study. We could not obtain follow-up assessments from a substantial proportion of the sample that dropped out from the initial assessment. However, the dropouts were not significantly different in clinical presentation, proportion of ARMS subgroups at intake and sociodemographic features from those who were followed up, except for gender. The two groups were also overlapping in terms of global functioning. However, we could not completely control for potential differences between followed up and dropouts, because these differences could be due to patient choice or other non-random factors. Nonetheless, previous evidence in our UHR sample showed that approximately half (53.2 %) of the group disengaging from our high risk service (OASIS (Fusar-Poli et al., 2013b)) subsequently received a diagnosis of some mental disorder (Green et al., 2011). Disengagement can thus be secondary to constraints around service accessibility and poorer network of support, rather than to differences in UHR psychopathology domains (Green et al., 2011). Another limitation is the small statistical of the study due to the small sample size of some groups in the analyses. A further limitation is that the GAF scale we used to assess functional outcome encompasses both symptom severity and disability, whereas a measure of occupational and social functioning not directly affected by psychopathology, such as the SOFAS might have been more informative. However, it has been recently reported that GAF and SOFAS total scores are in almost perfect linear linking, so that they can be considered exchangeable (Samara et al., 2014).

In conclusion, the current study found a high prevalence of Axis-I and Axis-II non-psychotic comorbid mental disorders in UHR patients, which tended to persist/recur, worsening the 6-year functional outcome. Our findings highlight the importance of investigating outcomes other than transition to psychosis in UHR samples, since a large proportion still presented with APS, non-psychotic comorbid mental disorders and functional impairment at follow-up. Our study may be clinically informative in that it suggests that UHR patients presenting with non-psychotic comorbid mental disorders of persistent or recurrent course may be more prone to long-term functional impairment. Future large scale studies are required to confirm our results.

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Table 1. Comparisons of socio-demographics, clinical characteristics and global functioning between dropouts (N=80) and non-dropouts (N=74) UHR patients.

Categorical variables	UHR dropouts n (%)	UHR Non-dropouts n (%)	P
Gender			0.014
Male	56 (70%)	37 (50%)	
Female	24 (30%)	37 (50%)	
total	80	74	
Ethnicity			0.231
White British	27 (34%)	35 (47.3%)	
White other	13 (16%)	10 (13.5%)	
Black	29 (36%)	17 (23.0%)	
Other	11 (14%)	12 (16.2%)	
total	80	74	
Marital status			0.361
Single	65 (81%)	64 (86.5%)	
Married/living together	11 (14%)	5 (6.8%)	
Divorced/separated	4 (5%)	5 (6.8%)	
total	80	74	
Employment			0.318
Student	20 (25%)	26 (35.1%)	
Employed	24 (30%)	22 (29.7%)	
Unemployed	36 (45%)	26 (35.1%)	
total	80	74	
Family history of psychosis			0.499
Yes	13 (16%)	9 (12.2%)	
No	67 (84%)	65 (87.8%)	
total	80	74	
Intake group**			0.827
GRD	0	0	
APS	68 (85%)	61 (82.4%)	
BLIP	12 (15%)	13 (17.6%)	
total	80	74	
Comorbidities			0.878
None	26 (33%)	47 (63.5%)	
Anxiety and/or depression	30 (38%)	27 (36.8%)	
Other	23 (29%)	0	
total	79	74	
GAF score at baseline			0.481
<60	44 (61%)	47 (63.5%)	
>60	28 (39%)	22 (29.7%)	
total	72	69	
Continue variables (mean)	Mean (SD)	Mean (SD)	P
Age	23.63 (SD 4.35)	23.20 (SD 4.90)	0.572
GAF score at baseline	57.72 (SD 11.01)	57.93 (SD 10.81)	0.911
CAARMS composite score	28.50 (18.00 – 36.00)*	27.50 (20.50 – 38.75)*	0.307
PANSS			
Positive scale	13.33(SD 3.62)	13.33 (SD 4.41)	1.000
Negative scale	14.00(SD 15.62)	13.60 (SD 5.38)	0.740
General Psychopathology	35.92 (SD 9.36)	31.16 (SD 8.24)	0.143
Total score	63.16 (SD 12.95)	59.56 (SD 15.42)	0.267
HAM-D	16.88 (SD 8.30)	15.82 (SD 7.88)	0.565
HAM-A	16.05 (SD 9.41)	12.93 (SD 7.75)	0.103

APS, attenuated psychotic symptoms; BLIPS, Brief Limited Intermittent Psychotic Symptoms; CAARMS, comprehensive assessment of at risk mental states; GAF, global assessment of functioning; GRD, genetic risk syndrome; Ham-A, Hamilton anxiety scale; Ham-D, Hamilton depression scale; PANSS, Positive and negative symptom scale.

* Median and quartiles

** The overlapping subgroups have been combined as follows: GRD < APS < BLIPS (Fusar-Poli et al., 2015a)

Table 2. Prevalence of Axis-I and Axis-II non-psychotic comorbid mental disorders at 6-year follow-up in UHR patients.

	UHR patients assessed at follow-up (N=74)	
Disorder	N	%
Any Disorder	42	56.8
Any Axis-I Disorder	38	51.4
Mood disorder	25	33.8
Major depressive disorder	18	24.3
Dysthymic disorder	6	8.1
Bipolar Disorder I	1	1.4
Bipolar Disorder II	2	2.7
Other[a]	3	4.1
Anxiety disorder	16	21.6
Panic disorder	7	9.5
Agoraphobia without panic	1	1.4
Social phobia	5	6.8
Specific phobia	1	1.4
Generalized anxiety disorder	6	8.1
Other[b]	3	4.1
Obsessive-Compulsive and related disorders	6	8.1
Obsessive-Compulsive disorder	4	5.4
Body Dysmorphic disorder	2	2.7
Post-Traumatic Stress Disorder	1	1.4
Somatoform disorder[c]	1	1.4
Eating disorder[d]	2	2.7
Mood and Anxiety disorders	5	6.8
Any Axis-II Disorder	16	21.6
Paranoid Personality Disorder	11	14.9
Borderline Personality Disorder	5	6.8

[a] Mood disorder not otherwise specified and substance-induced mood disorder

[b] Anxiety disorder not otherwise specified

[c] Somatisation disorder, Pain disorder, Undifferentiated Somatoform disorder and Hypochondriasis

[d] Anorexia nervosa, bulimia nervosa, binge-eating disorder or eating disorder not otherwise specified

Table 3. Course of non-psychotic comorbid mental disorders in UHR patients

	UHR patients (N=74)	
Status of Nonpsychotic Disorder	N	%
Present at baseline		
Any disorder	52	70.3
Any mood disorder	27	36.5
Any anxiety disorder	8	10.8
Mood and anxiety disorders	4	5.4
Personality disorders	5	6.8
Remitted		
Any disorder	20	27.0
Any mood disorder	16	21.6
Any anxiety disorder	4	5.4
Mood and anxiety disorders	4	5.4
Personality disorders	3	4.1
Incident		
Any disorder	10	13.5
Any mood disorder	14	18.9
Any anxiety disorder	12	16.2
Mood and anxiety disorders	5	6.8
Personality disorders	14	18.9
Persistent or recurrent		
Any disorder	32	43.2
Any mood disorder	11	14.9
Any anxiety disorder	4	5.4
Mood and anxiety disorders	0	0
Personality disorders	2	2.7
Never present		
Any disorder	12	16.2
Any mood disorder	33	44.6
Any anxiety disorder	52	70.3
Mood and anxiety disorders	65	87.8
Personality disorders	51	68.9

Figure captions

Figure 1. Composition of our Sample of UHR patients over 6-year Follow-up

Figure 2. Clinical Status of UHR patients at 6-year Follow-up

UHR, ultra-high risk for psychosis; APS, attenuated psychotic symptoms

Figure 3. Course of Co-morbid Non-Psychotic Disorders in UHR patients