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Impact of Comorbid Affective Disorders on Longitudinal Clinical Outcomes in Individuals at Ultra-high Risk for Psychosis

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Introduction: **Diagnoses of anxiety and/or depression are common in subjects at Ultra-High Risk for Psychosis (UHR) and associated with extensive functional impairment. Less is known about the impact of affective comorbidities on the prospective course of attenuated psychotic symptoms (APS).** ***Method:*** **Latent class mixed**

modelling identified APS trajectories in 331 UHR subjects assessed at baseline, 6, 12, and 24 months follow-up. The prognostic value of past, baseline, and one-year DSM-IV depressive or anxiety disorders on trajectories was investigated using logistic regression, controlling for confounders. Cox proportional hazard analyses investigated associations with transition risk. *Results:* 46.8% of participants fulfilled the criteria for a past depressive disorder, 33.2% at baseline, and 15.1% at one-year follow-up. Any past, baseline, or one-year anxiety disorder was diagnosed in 42.9%, 37.2%, and 27.0%, respectively. Participants were classified into one of three latent APS trajectory groups: (1) persistently low, (2) increasing, and (3) decreasing. Past depression was associated with a higher risk of belonging to the increasing trajectory group, compared to the persistently low (OR = 3.149, [95%CI: 1.298–7.642]) or decreasing group (OR = 3.137, [1.165–8.450]). In contrast, past (OR = .443, [.179–1.094]) or current (OR = .414, [.156–1.094]) anxiety disorders showed a trend-level association with a lower risk of belonging to the increasing group compared to the persistently low group. Past depression was significantly associated with a higher risk of transitioning to psychosis (HR = 2.123, [1.178–3.828]). *Conclusion:* A past depressive episode might be a particularly relevant risk factor for an unfavorable course of APS in UHR individuals. Early affective disturbances may be used to advance detection, prognostic, and clinical strategies.

Key words: ultra-high risk/comorbid/anxiety/depression /psychosis/schizophrenia/prediction

Introduction

Of all individuals meeting the criteria for the ultra-high risk state for psychosis (UHR), meta-analysis estimate that 23% (95%CI: 18%–29%) will develop a psychotic disorder within two-years after presentation to clinical services.[1,2] The risk of psychosis is the highest in the subgroup with brief intermittent psychotic symptoms (BLIPS), lowest in the group with genetic risk in combination with a significant decline in functioning (Genetic Risk and Deterioration syndrome, GRD), and intermediate in the subgroup with subthreshold attenuated psychotic symptoms (APS).[3] UHR individuals often display considerable impairment in functioning and a reduction in quality of life.[4] However, they represent a highly heterogeneous group in terms of clinical and functional outcome. With regard to comorbid (supplementary eIntroduction 1.1 elaborates on the term "comorbid") psychiatric diagnosis, apart from substance misuse[5] and personality disorders,[6] mood (41%), and/or anxiety disorders (15%) are reported as the most frequent co-occurring conditions.[7–10] These comorbid affective diagnoses tend to persist and are associated with increased experienced distress and a lower level of global and psychosocial functioning over time.[7,11–13] Affective symptoms have furthermore been reported as the primary subjective reasons for UHR individuals to seek help at specialized early intervention services.[13]

Over the last two decades, the main focus of UHR-research has been the identification of predictors for transition to psychosis.[14] Regarding the prognostic validity of comorbid affective disorders, meta-analyses found no effect on the risk of transition.[7,8] There has been limited research investigating the association between affective comorbidity and long-term course of psychotic symptoms other than transition risk[15] (supplementary eIntroduction 1.2 summarizes associations with other outcome variables).

One previous study found no association between the presence of a current comorbid depressive disorder and the likelihood of remission from UHR state.[5] However, the authors reported a significant association between the presence of a current anxiety disorder and persistence of symptoms. In contrast, another previous study reported that both depressive and anxiety disorder predicted persistence of paranoid symptoms.[16] Only one study reported a combination of current and/or lifetime comorbid depression and found that this was associated with a decreased likelihood of remission from the UHR state.[17] Another study assessed comorbidity repeatedly and found no association between persistence or recurrence of affective disorders and persistence of APS over a six-year period.[12] Overall, it seems that the evidence is inconsistent and mainly limited to associations between co-occurring affective disorders assessed at baseline and remission status at a specific time point. However, depressive symptoms often seem to appear prior to APS onset and may affect the clinical course.[18,19] In accordance, a general population study found a decrease in positive and an increase in negative affect to be associated with persistence of psychotic experiences over time as compared to transient psychotic experiences.[20] To the best of our knowledge, no study has investigated the relative impact of past, baseline, or prospectively assessed comorbid depressive and anxiety disorder on UHR trajectories. Hence, the added value of repeatedly assessed comorbid affective disorders on clinical trajectories of APS in UHR individuals remains unclear.

The current study aimed to address this question by examining trajectories of APS severity over a two-year period in UHR individuals with latent class mixed modelling (LCMM). We subsequently investigated the prognostic value of past, baseline, or one-year comorbidity of anxiety or depression on these trajectories. As a secondary aim, we sought to investigate whether past, baseline, or one-year affective comorbidity was associated with higher transition risk to psychosis.

Method

Study Design and Participants

The data analyzed in this study were collected within the multicenter European Gene-Environment Interactions (EU-GEI) study, from May, 2010 to April, 2015. The aim of the EU-GEI study is to identify the interactive genetic, clinical, and environmental determinants, involved in the development, severity, and outcome of psychotic disorders.[21] The design and inclusion criteria of the prodrome/high-risk study of EU-GEI have previously been described in detail.[22] In short, the overall design of the study was naturalistic and prospective, consisting of a baseline and two or three follow-up time points depending on the outcome measure. Subjects were recruited from 11 mental healthcare institutions in: London, Amsterdam, The Hague, Vienna, Basel, Cologne, Melbourne, Kortenberg, Paris, Barcelona, and Sao Paulo. The study protocol was approved by the Medical Ethics Committees of all participating sites. EU-GEI was conducted in accordance with the Declaration of Helsinki.

Subjects presenting at participating healthcare institutions aged 15–35 were eligible for the study if they met criteria of the Comprehensive Assessment of At-Risk Mental States (CAARMS)[23] for the UHR state classified into one or more of the following three groups: (1) GRD: schizotypal personality disorder or having a first degree relative with a psychotic disorder and experiencing a significant decline in or chronic low psychosocial functioning, (2) APS: having positive psychotic symptoms that do not reach the threshold levels for psychosis, (3) BLIPS: an experience of a recent brief psychotic episode which remitted within a week without the use of antipsychotic medications. Psychometric features of the UHR state have been described elsewhere.[24] Exclusion criteria were the prior experience of a psychotic episode of more than one week or symptoms relevant for inclusion explained by a medical disorder or drug or alcohol dependence as assessed by the CAARMS, or an intelligence quotient (IQ) below 60.

Assessment

Participants were invited for face-to-face follow-up meetings at 6 months (some sites only), 12 months, and 24 months after baseline. In case face-to-face meetings were not possible, information regarding the transition to psychosis was followed up for 2 years using available clinical records, and this follow-up was extended when additional clinical data was available.

The presence of a comorbid depressive or anxiety disorder was assessed with the SCID-I.[25] This included the diagnosis of a past or current depressive episode, as well as a past and current diagnosis of any anxiety disorder including social phobia, specific phobia, panic disorder, obsessive-compulsive disorder (OCD), agoraphobia, general anxiety disorder (GAD), or anxiety disorder not otherwise specified (NOS).

Prodromal psychopathology was assessed with the CAARMS,[23] a semi-structured interview with a total of 27 items, clustered in seven subscales. In the current study, APS trajectories were identified based on the CAARMS positive symptom subscale (unusual thought content, non-bizarre ideas, perceptual abnormalities, disorganized speech). Symptom severity was operationalized by summing intensity*frequency scores of the corresponding items, as has previously been described.[11,26] Transition to psychosis was defined as the development of psychotic disorder according to the CAARMS.[23]

Covariates

The following risk factors for the onset of psychosis were identified in recent meta-analyses and were included as a priori defined covariates in all analyses.[27,28]

Gender, ethnicity, current employment, baseline global functioning assessed using the disability score of the General Assessment of Functioning (GAF) scale,[29] negative, cognitive, motor, and general symptoms assessed with the CAARMS (supplementary eMethod 2.1 elaborates on the adapted general subscale) and childhood trauma measured with the Childhood Trauma Questionnaire (CTQ).[30]

Statistical Analysis

For the design of the study, we followed state-of-the-art guidelines (GRoLTS checklist) for reporting latent trajectory studies.[31] Latent class mixed model analysis (LCMM) was used to identify and visualize clusters of participants with similar distinct APS outcome trajectories over time within one sample (supplementary eMethod 2.2 elaborates on possible distinct trajectories). Missing values on main outcome and covariates at baseline were replaced applying multiple imputation procedures to be able to include participants with at least one assessment. With maximum likelihood (ML) estimation LCMM then makes use of all available data, regardless of intermittent missing data and/or later dropout. Subject and time were used to infer latent class trajectories of APS. The actual individual time of measurement (days since baseline) was used to account for possible deviation around the planned assessment date. The maximum observational period was set to <1000 days to avoid including large outlying values (>2SD). We chose to use unconditional LCMM to first describe the "raw" latent trajectories in the UHR population without imposing any conditions/predictors on the model. In a subsequent step, we explored the prognostic validity of past, baseline, and one-year comorbidity of anxiety and depression on these unconditional trajectories (accounting for the a priori defined confounders).

Starting with a one-class model, we fitted models with increasing numbers of classes until we reached the inflection point of the Akaike information criterion (AIC). The AIC can be used to identify the point at which the benefits of improved model fit are outweighed by the cost of the model in terms of its complexity and thus helps to prevent overfitting of the data. In addition, we examined the somewhat stricter Bayesian information criterion (BIC), and the log-likelihood (LL). The latter is a measure of goodness of model fit regardless of model complexity. Finally, posterior probabilities of class membership for each patient were computed using the Bayes theorem.[32] According to the GRoLTS checklist the final model was selected based on both statistical (log-likelihood, AIC, BIC) and clinical (class size, distinctness of class-specific trajectories, likelihood of class membership based on posterior probabilities) considerations. For more detailed information on LCMM see supplementary eMethod 2.3.

According to the standard Three-Step Method,[31] unconditional trajectories were identified as described above (step 1) and class membership was saved and merged with the original data (step 2). Multinomial logistic regression analyses were subsequently used to examine predictors of APS trajectory class membership as the response variables and past, baseline, or one-year comorbid diagnosis of anxiety/depression as candidate explanatory variables (step 3). A priori selected covariates were entered in a first block to the model, followed by comorbidity in a second block.

To assess the effect of past, baseline, and one-year affective comorbidity on the development of psychotic disorders within the two-year follow-up interval Cox proportional hazard regression analyses were conducted after assessing the proportional hazards assumption.

The overall cumulative risk of psychosis onset for individuals with presence versus absence of a comorbid affective disorder was plotted with the Kaplan–Meier cumulative event function and 95% confidence intervals (CI). We reported the numbers of those at-risk and truncate the event function when less than 30 subjects were still at risk.[33]

LCMM was conducted using the lcmm R package.[34] Cox proportional hazard regression analyses were analyzed using survival R package[35] and survminer R package[33] to plot Kaplan–Meier functions with R version 3.6.2. All other analyses were performed using SPSS version 26.

Results

Sample Characteristics

In total, 345 UHR subjects participated in the EU-GEI study. The sample of the current study consisted of 331 individuals, as 14 participants had no valid SCID data and had to be excluded (see flow-chart figure 1 for more information including follow-up data). Median follow-up

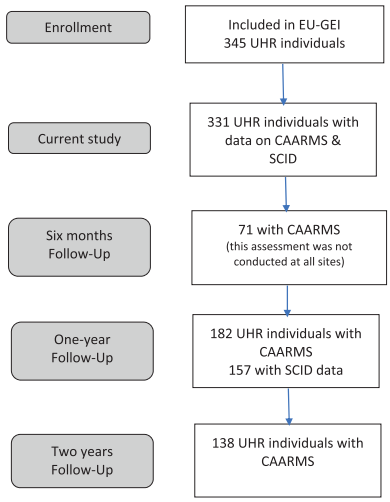

Fig. 1. Flowchart of included participants. *Abbreviation:* CAARMS: the Comprehensive Assessment of At-Risk Mental States; SCID: Structured Clinical Interview for DSM-IV-TR Axis I Disorders, UHR: ultra-high risk.

periods were 202 days (min = 41, max = 283) for 6 months assessment, 397 days (min = 277, max = 554) for one-year, and 760 days (min = 533 and max = 992) for two-years assessment.

At baseline, 110 (33.2%) participants had current comorbid depression and 123 (37.2%) current anxiety disorder. Retrospectively, 155 (46.8%) individuals reported a past major depressive episode, whereas 142 (42.9%) reported at least one past anxiety disorder. Regarding persistence across these two assessments, n = 50 (15.1%) individuals reported persistence in depression, whereas n = 104 (31.4%) fulfilled the criteria for an anxiety disorder both at baseline and in the past. At one-year follow-up 24 (15.3%) and 43 (27.4%) participants fulfilled the criteria for depressive or anxiety disorder, respectively. Data regarding missingness at baseline, and comparisons between dropouts and completers at one-year are presented as supplementary eResults 3.1 & 3.2. Comparing completers and dropouts at one-year follow-up showed no significant differences on any of the sociodemographic or clinical variables at baseline, except for slightly lower years of education and a higher percentage of baseline depressive disorders in dropouts.

Sociodemographic characteristics and baseline clinical variables by trajectory are presented in table 1.

Trajectories of Attenuated Psychotic Symptom Severity

A 3-class model was selected for APS trajectories as the associated AIC was the lowest among the tested models. The BIC was similar to the 2-class solution and considerably lower than the 4-class solution (table 2). For the 3-class model, mean class probabilities were moderate to high (0.70–0.88), suggesting individuals had a 70%–88% probability to be correctly assigned to one of the three

Table 1. Baseline Information on Sociodemographic and Clinical Variables by Trajectory Class

	Class 1 (Persistently Low) *N* = 238	Class 2 (Decreasing) *N* = 65	Class 3 (Increasing) *N* = 28	Group Comparisons
Age	22.39 (4.95)	22.53 (4.70)	23.38 (6.57)	F = .471, *P* = .625
Gender (% male)	52.52	56.92	60.71	X = .941, *P* = .625
Ethnicity (% caucasian)	72.26	63.08	78.57	X = 2.95, *P* = .229
Years of education	14.28 (2.98)	14.44 (3.37)	13.76 (3.36)	F = .354, *P* = .702
Cannabis use (% yes)[a]	27.31	26.15	28.57	X = .064, *P* = .969
Cannabis abuse (% yes)	11.22	16.31	22.21	X = 2.360, *P* = .307
Currently employed (yes %)	75.98	83.87	74.07	X = 1.915, *P* = .284
UHR intake group (%)				X = 36.595, *P* < .001
APS	78.2	60.7	74.1	
GRD	10.7	0	7.4	
BLIPS	1.8	13.1	0	
Combination	9.3	26.2	18.5	
Medication use (%)[b]				
Antidepressants/mood stabilizers	29.9	32.7	22.7	X = .717, *P* = .699
Anxiolytics	10.0	10.2	0	X = 2.426, *P* = .297
Antipsychotics	8.5	12.2	13.6	X = 1.114, *P* = .573
CAARMS				
Positive	29.84 (13.35)	63.84 (14.44)	34.71 (12.88)	F = 161.67, *P* < .001
Negative	29.45 (18.41)	28.78 (18.29)	29.18 (16.30)	F = 0.04, *P* = .965
Cognitive	9.50 (5.92)	10.96 (6.07)	10.55 (6.72)	F = 1.68, *P* = .186
Emotional	12.31 (11.04)	13.33 (11.36)	12.39 (11.68)	F = .210, *P* = .810
Social	31.08 (19.72)	33.08 (18.31)	32.99 (21.87)	F = .336, *P* = .715
Motor	6.15 (7.90)	10.08 (12.72)	8.69 (11.32)	F = 4.95, *P* = .008
General	20.87 (15.52)	28.70 (18.81)	26.28 (17.66)	F = 6.482, *P* = .002

Abbreviations: CAARMS: the Comprehensive Assessment of At-Risk Mental States, APS: attenuated psychotic symptoms, BLIPS: brief intermittent psychotic symptoms, GRD: Genetic Risk and Deterioration syndrome.
[a]Assessed with the Cannabis Experiences Questionnaire (CEQ).
[b]Information available in a subsample of *n* = 272.

Table 2. Model Fit Parameters for LCMM of Attenuated Psychotic Symptoms With One to Five Classes

Number of Classes	Number of Parameters	AIC	BIC	Max Log-likelihood	Posterior Probability	Sample Size Per Class
1	6	6261.687	6284.500	−3124.844		
2	9	6216.362	6250.581	−3099.18	.86–.92	303/28
3	**12**	**6205.759**	**6251.384**	**−3090.879**	**.70–.88**	**28/238/65**
4	15	6209.673	6266.705	−3090.000	.51–.82	18/34/249/30
5	18	6215.673	6284.111	−3089.836	.53–.87	27/239/30/35/0

Note: 3-class model fit parameters are highlighted in bold.
Abbreviations: AIC: Akaike information criterion, BIC: Bayesian information criterion, LCMM: Latent class mixed modelling.

latent classes. After visual inspection of the identified trajectories, the classes could be defined as: (1) persistently low symptom severity (*n* = 238), (2) increasing symptom severity (*n* = 28), and (3) decreasing symptom severity *n* = 65), see figure 2. For observed individual courses of CAARMS positive scores by most likely trajectory membership see supplementary eFigures 2a-c.

Predictors of Latent Trajectory Class Membership

Multinomial logistic models were conducted to investigate whether past, baseline, or one-year comorbid diagnosis of depression or anxiety disorder were associated with a higher likelihood for the unfavorable, increasing trajectory of APS, accounting for a priori selected covariates.

Adding past comorbidity to a priori defined covariates improved the model's fit (-2LL: 470.631–461.381) and increased Nagelkerke R^2 from .128 to .160. Past anxiety disorder showed a trend-level association with a lower likelihood (odds ratio (OR) = .443, *P* = .077) of belonging to the increasing trajectory group compared to the persistently low trajectory group. In contrast, a past diagnosis of depression was significantly associated with a higher

likelihood to belong to the increasing group compared to the persistently low group (OR = 3.149, P = .011) or the decreasing group (OR = 3.137, P = .024) (table 3).

Adding baseline comorbidity to the model after accounting for covariates, slightly improved model fit (-2LL: 470.631–466.858) and increased Nagelkerke R^2 from .128 to .142 approximated explained variance. Baseline anxiety disorder was associated with a lower likelihood to show an increase in APS severity over time again on a trend-level (OR = .414, P = .075) compared to the persistently low course. No significant associations were found for baseline depression (table 3).

Neither the presence of an anxiety nor of a depressive diagnosis at one-year follow-up predicted any of the three trajectories in the smaller subsample of n = 157 (persistently low n = 115, increasing n = 18, decreasing n = 24) (see table 3). Although the model fit slightly improved (-2LL: 220.573–218.010) and Nagelkerke R^2 increased from .154 to .172.

When including both baseline and lifetime comorbidities in one model (Nagelkerke R^2 = .167), only past depression remained a significant predictor of the increasing trajectory group compared to the persistently low group (P = .011, OR = 3.201 [95%CI = 1.308–7.831]) and the decreasing group (P = .022, OR = 3.226 [95%CI = 1.187–8.772]), respectively.

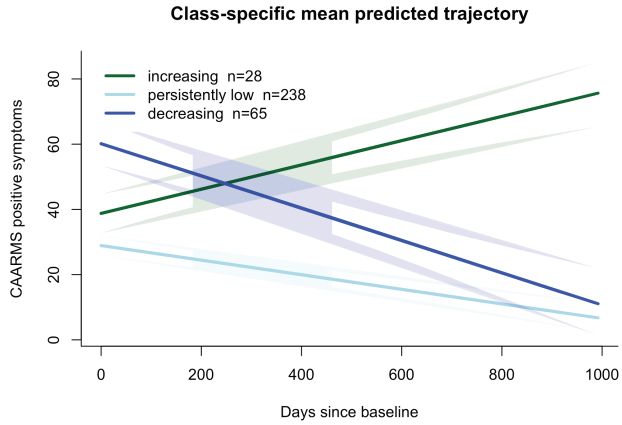

Fig. 2. Model estimated class-specific mean predicted trajectories of attenuated psychotic symptoms with 95% confidence intervals. Trajectories were classified as "persistently low" (n = 238; 71.9%), "increasing" (n = 28; 8.5%), and "decreasing" (n = 65; 19.6%) symptom severity.

Comorbid Affective Disorders and Risk for Transition

Transition to psychosis data were available on 99% (n = 328) of the current sample. Within the two-year period, 55 (16.7%) UHR individuals transitioned to

Table 3. Results of Multinomial Regression Analysis of *Past, Baseline (n = 331), and One-year (n = 157)* Comorbid Anxiety and Depression in Predicting Attenuated Psychotic Symptom Trajectories

	Past Comorbidity			Baseline Comorbidity			One-year Comorbidity		
	Exp(B)	95% CI	*P*	Exp(B)	95% CI	*P*	Exp(B)	95% CI	*P*
Increasing vs. persistently low trajectory									
Ethnicity	.694	.251–1.921	.482	.679	.245–1.881	.457	1.032	.286–3.734	.961
Gender	.551	.230–1.322	.182	.644	.276–1.505	.310	.701	.229–2.145	.533
Currently employed	1.201	.485–2.976	.629	1.206	.485–2.996	.687	1.672	.517–5.403	.390
GAF	1.001	.961–1.042	.972	1.000	.960–1.042	.998	.998	.944-1.054	.933
Trauma	1.028	1.000–1.057	**.047**	1.024	.997–1.053	.087	1.017	.982–1.053	.345
Negative symptoms	.988	.961–1.015	.375	.990	.962–1.018	.466	.971	.953–1.009	.128
Cognitive symptoms	1.029	.956–1.107	.453	1.024	.951–1.102	.527	1.004	.910–1.108	.932
Motor symptoms	1.034	.990–1.080	.134	1.029	.986–1.073	.189	1.023	.966–1.084	.433
General symptoms	1.012	.985–1.041	.390	1.015	.988–1.043	.281	1.037	1.000–1.076	**.047**
Anxiety	.443	.179–1.094	**.077**	.414	.156–1.094	**.075**	1.187	.361–3.898	.778
Depression	3.149	1.298–7.642	**.011**	1.093	.429–2.783	.852	.508	.097–2.665	.423
Increasing vs. decreasing trajectory									
Ethnicity	.387	.128–1.176	.094	.383	.126–1.166	.091	.671	.145–3.113	.611
Gender	.793	.297–2.121	.645	.944	.362–2.459	.906	1.926	.455–8.149	.373
Currently employed	.849	.308–2.343	.752	.855	.309–2.366	.762	.751	.180–3.143	.695
GAF	.983	.939–1.028	.450	.983	.939–1.028	.454	.969	.908–1.034	.347
Trauma	1.019	.989–1.051	.218	1.015	.984–1.046	.353	1.018	.974–1.064	.432
Negative symptoms	1.009	.977–1.041	.596	1.010	.978–1.043	.546	.975	.931–1.020	.271
Cognitive symptoms	1.002	.923–1.087	.967	.996	.918–1.081	.928	1.032	.916–1.164	.602
Motor symptoms	.994	.949–1.040	.786	.989	.946–1.034	.629	1.009	.966–1.053	.383
General symptoms	.980	.950–1.010	.188	.982	.953–1.013	.250	.980	.950–1.010	.688
Anxiety	.511	.187–1.394	.190	.440	.151–1.282	.133	2.662	.500–14.169	.251
Depression	3.137	1.165–8.450	**.024**	1.266	.441–3.3640	.661	.489	.069–3457	.473

Note: Significant and trend-level associations are highlighted in bold.

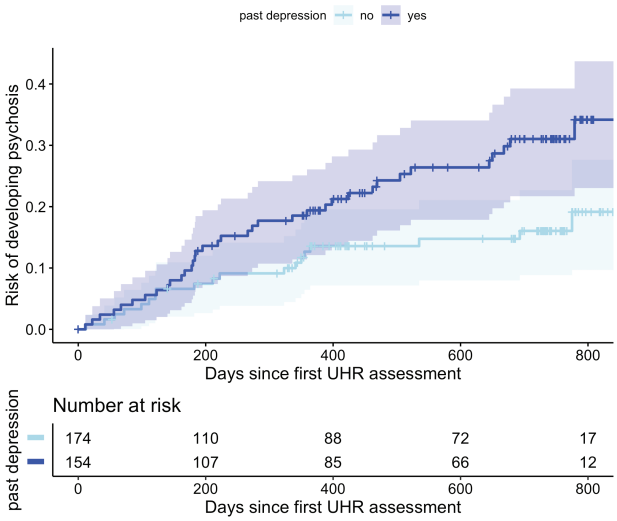

Fig. 3. Cumulative event Kaplan–Meier function for risk of development of psychotic disorders with 95% Confidence Intervals in 328 ultra-high risk (UHR) individuals stratified for past depression.

psychosis, this included 19 individuals from the increasing group, 22 from the persistently low, and 14 from the decreasing group. The average follow-up time was 423.78 days (SD = 325.05). The last transition was observed at 779 days when 29 individuals were still at-risk. The median time to transition was 219.0 days (25th–75th percentiles 121–398).

Cox proportional hazard regression analyses showed a 2-fold (HR = 2.132; 95%CI: 1.178–3.828, P = .012) higher cumulative risk to develop a psychotic disorder in the group with a past depressive episode (n = 36 [23.4%]) compared to the group without past depression (n = 19 [10.9%]), while controlling for the same a priori defined covariates. The corresponding Kaplan–Meier cumulative risk of psychosis curve is depicted in figure 3. No significant differences for transition risk were found with regard to baseline or one-year depression or past, baseline, or one-year anxiety disorder (see table 4). For remaining Kapan–Meier curves see supplementary eFigures 3a-e.

Discussion

To our knowledge, this is the first study investigating repeatedly assessed diagnoses of comorbid anxiety or depression as potential predictors of distinct trajectories of APS severity. We found that the severity of APS can be clustered across three trajectories: persistently low, increasing, and decreasing. Controlling for several known predictors (supplementary eDiscussion 4.1 elaborates on baseline CAARMS differences between trajectory groups) of risk to transition, we demonstrated that past depression had a negative impact on the course of APS in UHR. In contrast, past and baseline anxiety disorder showed a trend association for a persistently low course.

Table 4. Hazard Ratio (HR) for Past, Baseline, and One-year Affective Comorbidities and Transition Risk Adjusted for Covariates

	HR	95% CI	P
Depression			
Past	2.132	1.178–3.828	**.012**
Baseline	1.020	.533–1.952	.953
One-year	1.568	.519–4.736	.425
Anxiety			
Past	1.203	.683–2.120	.522
Baseline	.872	.485–1.569	.649
One-year	.840	.296–2.384	.743

Note: Significant and trend-level associations are highlighted in bold.

No effects were found for affective disorders assessed at one-year follow-up.

Almost half (46.8%) of the UHR participants in the current study reported a past depression, and 33.2% fulfilled the criteria for a current depressive episode at baseline. Similarly, 42.9% reported any past, and 37.2% any baseline anxiety disorder. The prevalence of baseline comorbid depression is slightly lower than meta-analytical estimations of 41%, whereas the prevalence of baseline comorbid anxiety exceeds previously reported mean estimates of 15%.[36] Contrasting findings might be explained by a more narrow focus on depressive episodes on the one hand and inclusion of a broader range of anxiety disorders (eg, including specific phobia, general anxiety disorder, and OCD) on the other hand. Indeed, studies addressing similar wider diagnostic spectra for anxiety disorders have confirmed comparably high (38.5%)[37] or even higher (51%)[38] prevalence rates in UHR individuals. Remission of comorbid depressive disorders over the course of the study in more than half of subjects and persistence in anxiety disorders in the majority of participants is in line with previous observations.[39]

According to our first aim to examine trajectories of APS, we identified a 3-class model with the vast majority (91.5%) of UHR individuals belonging to the persistently low or decreasing trajectory group, whereas a small group (8.5%) showed an increase of APS severity over a 2-year period. Regarding the prognostic validity of repeatedly assessed affective comorbidities, a past diagnosis of depression was associated with 3-fold higher odds of increased APS severity over time compared to the persistently low (OR = 3.149) and the decreasing group (OR = 3.137), respectively. In contrast, a past (OR = .443) and baseline (OR = .414) comorbid diagnosis of anxiety, showed trend-level associations with a lower likelihood to belong to the increasing symptom severity trajectory group. However, the presence of considerably large confidence intervals needs to be acknowledged. Non-significant associations between comorbidity at one-year and APS trajectories were limited by a smaller

sample size. Few previous studies have investigated trajectories of APS or psychotic-like experiences with similar methodological approaches.[40–42] Only one study reported on positive associations between an unfavorable course of self-reported psychotic-like experiences and elevated scores in depression and anxiety in a sample of adolescents.[42] No study investigated the prognostic value of comorbid DSM-IV affective disorders on identified trajectories. Studies investigating remission from the UHR state also found no associations with the presence of a baseline comorbid diagnosis of depression.[5]

However, a lower likelihood for remission was found in UHR individuals with a lifetime (past or present) diagnosis compared to those with no history of depression.[17] Regarding associations with baseline comorbid anxiety disorders, two previous studies found associations with a lower number of APS remission at follow-up.[5,38] The authors argued that the co-occurrence of anxiety disorders and subclinical positive symptoms might constitute a specific subgroup of UHR individuals, where anxiety was specifically associated with more suspiciousness, but not with any other APS.[38] These psychotic experiences might be closely linked to anxiety content, persist over time, but not ultimately progress to diagnosable psychosis.[43,44] In support of this hypothesis, one study reported a lower likelihood for transition to psychosis in UHR individuals with current anxiety disorders in the European Prediction of Psychosis (EPOS) Study.[43]

With regard to our secondary aim, Cox regression analyses showed a more than 2-fold higher risk to develop a psychotic disorder for individuals reporting a past depressive disorder (HR = 2.132). However, no effect of baseline or one-year depression or past, baseline, or one-year anxiety disorders was found. This is in line with previous meta-analytical findings reporting no association between current comorbid affective disorders and transition risk.[36] To the best of our knowledge, no previous study investigated associations with past diagnoses.

Current findings suggest that particularly the experience of a past depressive episode might negatively influence the course of APS in UHR individuals. Affective dysregulation and mood disorders possibly proceeding APS onset during adolescents and time of major neurobiological development have been suggested to lead to and reinforce psychotic experiences.[45] In this line, an affective pathway to psychosis has been suggested with affective dysregulation as the main connective component between early traumatic or stressful experiences and psychosis onset.[9,46,47] Furthermore, indirect effects of affective symptoms via decline in psychosocial and global functioning on longitudinal outcome in UHR populations have been suggested.[14,48] One study showed that especially functional deterioration starting well before the 12 months prior to baseline assessment was associated with an increased risk of psychosis.[49] In contrast, psychotic symptoms co-occurring with anxiety disorders have not been associated with increased severity over time or the risk to convert to full-blown psychosis[44] (supplementary eDiscussion 4.2 elaborates on the co-occurrence of (subclinical) psychotic and affective symptoms).

Clinical and Research Implications

The current findings may have clinical implications for the detection, prognostic assessment, and intervention in UHR individuals. From detection and prognostic perspectives, the assessment of early depressive episode, might be valuable in the prediction of an unfavorable course in a small subgroup of UHR individuals. Broadening the UHR state to enhance a transdiagnostic perspective[50–53] may have potential benefits in this regard. A suggestion has been to expand it to other subsyndromal dimensions such as subthreshold bipolar states, mild-moderate depression, and borderline personality features.[51] However, the prognostic validity of this approach awaits empirical validation. Another promising approach would be to incorporate prediction models based on individual patients data to enhance stratification or personalization of predictions within UHR samples.[1,54]

From an interventional perspective, currently, there is no meta-analytical evidence that preventive psychological treatments targeting APS are superior to needs based interventions.[55,56] However, wide confidence intervals of effects suggest that interventions may be effective for some UHR subgroups.

In this line, identified trajectories and potential differential effects of comorbid depressive and anxiety disorders suggest different needs for clinical interventions. It is important to acknowledge that the percentage of subjects with an increasing course or transition to psychosis is relatively small. However, accurate detection of this small subgroup of patients and their prioritization into preventive healthcare pathways that focus on affective dysregulation may optimize the efficiency of preventive approaches, saving on the vast majority which may not need such type of intervention. Another subgroup of UHR individuals might profit from a specific focus on reported anxiety disorders, which might help to reduce content-related subclinical psychotic symptoms.

Limitations

Results should be interpreted in light of several limitations. First, predictors included in the current analyses left considerable variance unexplained. These results suggest that critical factors that might more directly affect the course of APS over time were not included as potential determinants. For example, it was not possible to take the effect of pharmacological interventions into account as this information was only available in a subgroup of participants. Noteworthy, within this subgroup, no significant differences in antipsychotics or antidepressants

use were found between the trajectories. Although a priori selected confounders were identified as risk factors for transition, other factors could also have been relevant in predicting APS trajectories. Third, the relatively small group of participants in the increasing and decreasing trajectory group, in combination with considerable dropout during the course of the study, limits the reliability of assessed associations between identified trajectories and comorbid diagnosis at one-year follow-up. The question of whether a repeated assessment of affective comorbidities may provide valuable information in the prediction of clinical outcome in UHR individuals thus needs further investigation. Fourth, due to too small sample sizes, we were unable to differentiate the group of UHR individuals who were diagnosed with both anxiety and depression from those diagnosed with only one of the two. Hence, more research is needed to investigate the effect of a combination of comorbid diagnoses. This is a relevant limitation, as previous studies have shown higher functional impairment and CAARMS symptom severity in the group with combined anxiety and depression compared to either alone.[36] Fifth, the percentage of baseline comorbid diagnosis of depression was larger in participants lost to follow-up. This might have led to an underestimation of the association between baseline depressive disorders and the prospective course of APS. Sixth, past affective comorbidities were assessed retrospectively, which might limit the reliability of these data. If possible, future studies should integrate information from clinical case records and/or family members. In addition, future prospective investigations in earlier stages of the at-risk mental stage (eg, prior to help-seeking) would shed more light on the impact and possible mechanisms of early affective disturbances on clinical outcome.

Conclusion

A large group of UHR individuals fulfill the criteria for co-occurring depressive or anxiety disorders. Results of the current study suggest that particularly the experience of a past depressive episode might be a relevant risk factor for an unfavorable course of APS in UHR individuals and increase the risk of transition to psychosis.

Supplementary Material

Supplementary data are available at *Schizophrenia Bulletin* online.

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