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MRS TINA D. KRISTENSEN (Orcid ID : 0000-0001-9616-762X)

DR LOUISE BIRKEDAL GLENTHØJ (Orcid ID : 0000-0003-3621-8450)

MRS KRISTINE KRAKAUER (Orcid ID : 0000-0002-7821-6667)

DR BJØRN HYLSEBECK EBDRUP (Orcid ID : 0000-0002-2590-5055)

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Global fractional anisotropy predicts transition to psychosis after 12 months in individuals at ultra-high risk for psychosis.

White matter predicts transition to psychosis

Tina D. Kristensen[1,2], Louise B. Glenthøj[1,2], Karen Ambrosen[1], Warda Syeda[3], Jayachandra M. Ragahava[1,4], Kristine Krakauer[1,2], Christina Wenneberg[1,2], Birgitte Fagerlund[1,5], Christos Pantelis[1,3], Birte Y. Glenthøj[1,6], Merete Nordentoft[1,2,6], and Bjørn H. Ebdrup[1,5,6]

Author details

[1] Centre for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, and Center for Neuropsychiatric Schizophrenia Research, CNSR, Mental Health Centre Glostrup, University of Copenhagen, Glostrup, Denmark

[2] Copenhagen Research Centre for Mental Health (CORE), Copenhagen University Hospital, Denmark

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[3] Melbourne Neuropsychiatry Center, Department of Psychiatry, The University of Melbourne, Melbourne, Australia

[4] Functional Imaging Unit, Department of Clinical Physiology, Nuclear Medicine and PET, University of Copenhagen, Glostrup, Denmark

[5] Department of Psychology, Faculty of Social Sciences, University of Copenhagen, Copenhagen, Denmark

[6] Department of Clinical Medicine, Faculty of Health and Medical Sciences, University of Copenhagen, Copenhagen, Denmark

Corresponding author: Tina Dam Kristensen, PhD. Center for Clinical Intervention and Neuropsychiatric Schizophrenia Research, CINS, Mental Health Centre Glostrup, Nordstjernevej 41, DK-2600 Glostrup. tina.dam.kristensen@regionh.dk

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Abstract

Objective: Psychosis spectrum disorders are associated with cerebral changes, but the prognostic value and clinical utility of these findings is unclear. Here we applied a multivariate statistical model to examine the predictive accuracy of global white matter fractional anisotropy (FA) for transition to psychosis in individuals at ultra-high risk for psychosis (UHR).

Methods: 110 UHR-individuals underwent 3 Tesla diffusion weighted imaging and clinical assessments at baseline, and after 6 and 12 months. Using logistic regression, we examined the reliability of global FA at baseline as a predictor for psychosis transition after 12 months. We tested the predictive accuracy, sensitivity and specificity of global FA in a multivariate prediction-model accounting for potential confounders to FA (head motion in scanner, age, gender, antipsychotic medication, parental socioeconomic status, and activity level). In secondary analyses, we tested FA as a predictor of clinical symptoms and functional level using multivariate linear regression.

Results: Ten UHR-individuals had transitioned to psychosis after 12 months (9%). The model reliably predicted transition at 12 months (χ^2=17.595, *p*=0.040), accounted for 15-33% of the variance in transition outcome with a sensitivity of 0.70, a specificity of 0.88, and AUC of 0.87. Global FA predicted level of UHR-symptoms (R^2=0.055, F=6.084, *p*=0.016) and functional level (R^2= 0.040, F=4.57, *p*=0.036) at 6 months, but not at 12 months.

Conclusion: Global FA provided prognostic information on clinical outcome and symptom course of UHR-individuals. Our findings suggest that the application of prediction models including neuroimaging data can inform clinical management on risk for psychosis transition.

Keywords:

Ultra-high risk of psychosis; prediction; cerebral white matter; longitudinal; diffusion weighted imaging

Significant Outcomes:

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Global white matter fractional anisotropy significantly predicted transition to psychosis for UHR-individuals at 12 months.

Global white matter fractional anisotropy significantly predicted level of UHR-symptoms and functional level for UHR-individuals at 6 months.

Limitations:

- Moderate attrition rate (37%) at 12 months.
- Limited subsample of UHR-individuals with transition to psychosis (9%).
- Follow up period of 12 months.

Data Availability Statement:

The datasets generated and analyzed during the current study are not publicly available due to Danish legislation on data protection.

1. Introduction

Psychotic disorders are known to cause detrimental effects on both an individuals as well as at a societal level[1]. Thus, early identification of individuals at immediate risk for developing psychosis has been emphasized as a basis for the crucial preventive effort. For this purpose, the ultra-high risk state (UHR) represents a putative prodromal phase of psychosis, which provides the possibility to identify and clinically manage individuals at emerging risk of psychosis.

UHR is defined by criteria of attenuated psychotic symptoms, brief limited intermittent psychotic symptoms, and/or a genetic risk along with a functional decline[2]. Current clinical screening interviews are excellent at distinguish UHR-individuals from healthy controls but have been insufficient at discriminating UHR-individuals with transition to psychosis (UHR-T) from UHR-individuals with no transition to psychosis (UHR-NT). In order to provide more prognostic specificity, there is a need to

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improve prediction models for those already identified as UHR-individuals, potentially enabling a subgrouping in low- to high transition risk.

UHR-studies applying neuroimaging data provide a unique opportunity to examine the interplay between biological and clinical data involved in psychosis onset. A wealth of studies has implicated white matter (WM) in the pathophysiology of patients with manifest psychotic disorders[3,4]. However, knowledge of the changes in WM around the onset of psychosis is limited[5,6]. A few longitudinal studies have associated WM alterations prior to psychosis onset with a liability for psychotic development[7], but generally the studies involve small sample sizes and findings are inconsistent[8,9]. Thus, the overall relevance of applying WM as a potential baseline predictor for psychosis onset are not established[10], and it is unclear if WM alterations can increase the predictive accuracy of risk models of transition to psychosis in identified UHR-individuals and translate into clinically applicable models. In the current study in a large sample of UHR-individuals, we examined the predictive accuracy of baseline FA of transition to psychosis as the primary outcome, with symptom level and remission from UHR-status as secondary outcomes.

A wealth of studies has implicated white matter (WM) in the pathophysiology of patients with manifest psychotic disorders[3,4,11,12]. However, knowledge of the changes in WM around the onset of psychosis is limited[5,6]. A few longitudinal studies have associated WM alterations prior to psychosis onset with a liability for psychotic development[7,13–18], but generally the studies involve small sample sizes and findings are inconsistent[8,9]. Fractional anisotropy (FA) is the most commonly applied magnetic resonance imaging (MRI) measure to study WM organization[19]. A lower FA value is conventionally interpreted as impaired WM microstructure[20]. However, the underlying biological processes reflected in FA changes may be aided by applying additional WM indices, such as axial diffusivity (AD), radial diffusivity (RD), and mean diffusivity (MD). Combinations of these indices have been linked to loss of axonal coherence, demyelination, or neurodegeneration[21–24]. A recent small multimodal UHR study combining whole brain diffusion tensor imaging with proton magnetic resonance spectroscopy reported lower FA in major WM-tracts as predictive of transition to psychosis after two years[25]. Interestingly, a multicenter study in UHR-individuals reported a 36% increase of

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prognostic accuracy in prediction of transition outcome when adding MRI-data on grey matter to conventional clinically-based prediction models[26]. Such multimodal studies applying advanced statistical modelling are optimal for examining the interconnected influence of specific biomarkers and psychopathology in dynamic change-models. However, due to the clinically heterogeneity, along with the subtle and widespread WM alterations found in UHR-individuals, a global measure sensitive to WM changes may be appropriate when examining the predictive value of WM to transition to psychosis as the primary outcome. A further methodological issue in prediction studies are the impact of potential confounders. Studies in UHR-individuals are complicated by subtle symptomatology, frequent substance use and treatment with psychotropic medication. A meta-analysis on neuroimaging predictors of transition to psychosis revealed large differences in potential confounders across studies, such as gender, medication, and comorbidities[27]. Likewise, a critical review[28] emphasized the difficulties with several confounding factors hampering the quality of neuroimaging evidence, also including genetic and environmental risk factors in UHR-individuals. In addition, a recent systematic review[29] discussed the common prescription of low dose antipsychotic medication for UHR-individuals as potentially skewing transition rates of UHR-individuals[30] as well as the associated WM-changes[16]. Thus, predictor studies in UHR-individuals carefully designed to accommodate to potential confounders are warranted[31] as they may enhance the accuracy of prediction models of psychosis.

1.1. Aims of the Study

In the current study, we aimed to test the predictive accuracy of baseline white matter while evaluating the effect of potential confounders, such as antipsychotic medication. Specifically, we investigated if mean global fractional anisotropy at baseline could predict transition to psychosis after 12 months, and secondly could predict symptom levels at 6 and 12 months. We hypothesized that lower mean global fractional anisotropy would predict transition and persistent psychopathology after 12 months.

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2.0 Methods

Data was acquired as part of The FOCUS-trial[32]. UHR-individuals were recruited from psychiatric in- and outpatient facilities in Copenhagen, Denmark from April 2014 to December 2017. The trial protocol was approved by the Committee on Health Research Ethics of the Capital Region Denmark (study: H-6-2013-015). All participants provided written informed consent prior to inclusion in the study. The results from the main intervention trial have been described elsewhere[33]. In short, we found no effect of cognitive remediation on primary outcome of global neurocognition, and no effect on secondary outcomes including symptoms and level of functioning[34]; nor on WM organization[35].

2.1 UHR-individuals

We included 146 help-seeking UHR-individuals aged 18-40 meeting one or more UHR criteria according to the Comprehensive Assessment of At-Risk Mental States (CAARMS)[2] in the baseline sample. CAARMS criteria evaluates intensity and frequency of attenuated psychotic symptoms; and/or brief limited intermittent psychotic symptoms; and/or trait and vulnerability state along with a significant drop in functioning or sustained low functioning for the past year. Exclusion criteria were an incident of a psychotic episode of more than 1 week duration; clinical symptoms explained by a physical illness with psychotropic effect (e.g. delirium) or acute intoxication (e.g. cannabis use); a diagnosis of a serious developmental disorder (e.g., Asperger's syndrome or IQ below 70); or current treatment with methylphenidate.

For the current study, 110 MRI-scans were eligible, as 36 UHR-individuals were excluded due to scanner closure (N=16), refusal (N=15), technical problems (N=4), or poor MRI-quality (N=1). After baseline assessment, individuals were randomly allocated to treatment as usual (TAU: standard psychiatric care) or TAU plus the experimental intervention. TAU and the experimental intervention were organizational separated. (see Flow Chart in Supplementary Figure S2).

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2.2 Assessments

2.2.1 Image acquisition and processing

The acquisition and processing details have been described in detail in our previous cross-sectional study on associations between WM and cognition[36]. Briefly, the MRI scans were acquired on a 3 Tesla scanner (Philips Healthcare, Best, the Netherlands). We acquired two diffusion-weighted images (DWIs) using single shot spin-echo echoplanar imaging (EPI) sequence with 30 noncollinear diffusion-weighted (b=1,000 s/mm^2) directions and one non-diffusion weighted (b=0 s/mm^2) in opposite phase encoding directions, which enabled correction for susceptibility distortions[37]. We used tools from the FSL software library v5.0.10 and MRtrix3 (www.mrtrix.org) for image processing (see Supplementary Text S1 for details). Tract-based spatial statistics (TBSS)[38] was used to create FA skeleton maps using a threshold of 0.2. We computed the mean FA, AD, RD, and MD values in 48 white matter regions from skeletonized data and calculated mean global FA, AD, RD, and MD for each UHR-individual using the JHU DTI-based white matter atlas labels[39].

MRI quality metrics were assessed by visual inspection and further calculated from each subject using a quality assessment method described by Roalf et al.[40] Details on image acquisition and processing are provided in Supplementary Text S1.

2.2.2 Clinical assessments

Axis I and selected axis II diagnoses (schizotypal-, paranoid-, and borderline personality disorder) were assessed using the Structured Clinical Interview for DSM-IV (SCID)[41]. Level of UHR-symptoms was assessed with the CAARMS[42] composite score, using the positive symptoms subscale of CAARMS[43]. It assesses 4 domains: unusual thought content (UTC), non-bizarre ideas (NBI), perceptional abnormalities (PA), and disorganized speech (DS). Attenuated and/or brief, limited intermittent psychotic symptom was rated on a scale of 0-6 for the intensity (I) and frequency/duration (F) over the last 1 year. CAARMS composite score was calculated according to the formula: $(I_{UTC}*F_{UTC})+(I_{NBI}*F_{NBI})+(I_{PA}*F_{PA})+(I_{DS}*F_{DS})$[44]. Remission is established at follow-up, if the CAARMS-score (frequency- OR intensity scores of positive UHR-symptoms) is below cut-off for the UHR-criteria. Transition is identified by either a CAARMS-score (frequency- AND intensity scores of positive UHR-

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symptoms) above the threshold cut-off for psychosis; or a diagnose of a psychotic disorder within F20.x from the ICD-10, established by a psychiatrist in medical records from the psychiatric unit delivering the standard treatment.

Level of depressive symptoms was measured with the Montgomery-Åsberg Depression Rating Scale (MADRS)[45]; and functional level with Social and Occupational Function Assessment Scale (SOFAS)[46]. The clinical assessments were conducted by experienced psychologists and medical doctors with comprehensive training in using the assessment instruments. We assessed inter-rater reliability using intra-class correlations for the outcome measure of CAARMS, SANS and MADRS in 12 interviews (ICC ratings from 0.96 to 0.99).

The positive symptom subscale of CAARMS was used in LYRIKS. It assesses 4 APS domains: unusual thought content (UTC), Non-bizarre ideas (NBI), PA and disorganized speech (DS). Each symptom was rated on a scale of 0–6 for the maximum intensity (I) and frequency and duration (F) over the last 1 year.

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CAARMS composite score was calculated according to the formula:

(I

utc

* F

utc

) + (I

nbi

*F

nbi

) + (I

pa

* F

pa

) + (I

ds

* F

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ds
) (Lim et al., 2015; Mor-
rison et al., 2012
The positive symptom subscale of
CAARMS was used in LYRIKS. It assesses 4 APS
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thought content (UTC), Non-bizarre ideas (NBI),
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of 0–6 for the maxi-
mum intensity (I) and frequency and duration
(F) over the last 1 year.
CAARMS composite score was calculated
according to the formula:
(I

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utc

* F

utc

) + (I

nbi

*F

nbi

) + (I

pa

* F

pa

) + (I

ds

* F

ds

) (Lim et al., 2015; Mor-

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(I
utc
* F
utc

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) + (I

nbi

*F

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) + (I

pa

* F

pa

) + (I

ds

* F

ds

) (Lim et al., 2015; Mor-

rison et al., 2012

At 6 months follow up, 88 UHR-individuals completed clinical assessments of the trial. At 12 months follow up, 69 UHR-individuals completed clinical assessments at the trial. Eight out of the 10 UHR-T completed the planned assessments of clinical status at 6 months, and 4 out of 10 completed planned assessments of clinical status at 12 months follow up, or at any intermediate time if transition were suspected. For the UHR-individuals lost to trial follow-up, data on transition status and medication

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prescriptions were obtained from medical records from the standard care at psychiatric in- and outpatient centers.

2.3 Statistical analyses

All analyses were performed using SPSS version 25.0, Armonk, NY. Descriptive variables were reported as percent, means and standard deviations. Distributions of continuous data were tested for normality, and outliers were examined. Extreme outliers were identified using the interquartile range (IQR)-method[47]. In case of outliers, tests were performed with and without outliers to examine effects on the results. No outliers had any essential influence on the results, and all data were included. Group differences on ordinal data were tested using the Mann-Whitney U test or Fisher's exact test as appropriate. Nominal data were tested using Pearson's χ^2 test. Scaled data was tested using ANOVA. As the main analysis, the predictive value of mean global FA at baseline in determining subsequent illness outcome after 12 months (UHR-T versus UHR-NT) was examined using binary logistic regression with forced entry. We tested a multivariate model including mean global FA and potential confounders to FA. We performed a stepwise selection of covariates, following the recommendations from Addington et al. 2020[48], stating that selecting candidate confounders should be based on a combination of scientific literature and the data-driven variables from current study. Hence, we primarily selected covariates which either were supported by literature as common standard or highly recommended to enhance study quality (age and age squared[49–51], gender[52], motion in scanner[53,54], antipsychotic medication[30,55]). Secondly, we selected two data-driven covariates, which were significant or borderline significant in the group-comparison between UHR-T versus UHR-NT (activity-level[56], p=0.03; parental socioeconomic status[57,58], p=0.07), and further has been shown to affect FA. Due to the risk of overfitting, we decided to examine the effect of additional potential confounders (i.e. other psychotropic medication, substance use, allocation to treatment) in post-hoc tests. Sensitivity and specificity were calculated, and we estimated the receiver operator characteristic (ROC)-curves and area under the curve (AUC).

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Secondly, univariate linear regression analyses were performed, entering baseline FA as predictor for variables on clinical outcomes at 6 and 12 months of functional level (SOFAS), UHR-symptoms (CAARMS composite score), negative symptoms (SANS total score), and depressive symptoms (MADRS). Next, we entered the outcome variables, where FA was a significant predictor in a multivariate general linear model with mean global FA as predictor.

In exploratory analyses, we investigated the predictive value of global FA at baseline in determining remission from the UHR-state after 12 months (UHR-individuals with remission versus UHR-individuals with no remission). We applied binary logistic regression, testing a multivariate model identical to the examination of transition to psychosis.

Post hoc, we investigated the effect of various subgroupings regarding antipsychotic medication and allocation to the experimental treatment on the potential results. Furthermore, we examined associations between global FA and other psychotropic medication (antidepressants, mood-stabilizers, benzodiazepines), as well as recreational substance use (alcohol, tobacco, and cannabis).

Moreover, we explored baseline FA for all 48 regions of interest (ROIs) separately as predictors of transition to psychosis in a multivariate logistic regression model identical to the model applied on global FA. Finally, we explored if the WM indices of AD, RD, and MD contributed with additional information on the neurobiological underpinnings for the potential predictive value of global FA.

3 Results

Demographic and clinical characteristics of UHR-individuals at baseline are reported in Table 1. UHR-T had lower mean global FA at baseline (p=0.04, F=4.34, corrected) and a lower activity level (p=0.03, F=4.65) compared to UHR-NT. There were no other significant differences on sociodemographic or clinical characteristics at baseline, when comparing UHR-T to UHR-NT.

[Insert Table 1 here]

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Of the total baseline sample of 110 UHR-individuals, 88 (80%) attended the 6-months follow-up assessments, and 69 (63%) the 12-months follow-up assessments. UHR-individuals dropping-out at 6 months follow-up had lower global FA (p<0.01, F=9.63) compared to UHR-individuals completing assessments. At 12 months follow-up, dropouts had a younger age than completers (p=0.04, F=4.22). There were no other differences between dropouts and completers in baseline sociodemographic or clinical characteristics (See supplementary Table S3 for details). Remission from the UHR-state or continuous risk according to CAARMS-scores at 6 and 12 months could only be calculated for completers, as these data were not available in medical records.

Overall, UHR-individuals improved clinically during the 12 months period, displaying reduced UHR-symptoms over time (p=0.001, F=7.329) (Table 2). The prevalence of antipsychotic medicine prescriptions was increased over time (p=0.024, F=8.528). At 12 months follow-up, 10 UHR-individuals (9% of the baseline sample) had transitioned into psychosis, and 15 (14%) had remission from the UHR-state.

[Insert Table 2 here]

3.1 FA as predictor of transition to psychosis

The logistic regression analysis was performed with transition to psychosis or no transition to psychosis as the dichotomic outcome. Results are reported in Table 3.

The multivariate model including mean global FA at baseline and the potential confounders as predictor variables was significant reliable (χ^2=17.595, p=0.040). In the model, lower global FA significantly predicted transition to psychosis (p=0.025). The model accounted for between 15.4-33.0% of the variance in transition status, with 88.4% of the UHR-NT successfully predicted (specificity of 0.88), and 70.0% accurate predictions for the UHR-T (sensitivity of 0.70). Overall, 86.7% predictions were accurate, see Supplementary Table S4 for details in the classification table. AUC was 0.86 [95 % CI= 0.73-0.98] as displayed on the ROC-curve in Figure 1.

As an additional post-hoc test for controlling the stability of our results, we performed the bootstrapping procedure (1000 bootstrap samples) while rerunning the model tests. The results from

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the bootstrapping confirmed the significance of our results (Model test: B= -2.251, SE 0.356, *p*=0.001, 95% CI: -2.996—1.716).

[Insert Table 3 here]

[Insert Figure 1 here]

3.2 FA as predictor of clinical outcomes

In univariate linear regression, lower global FA at baseline significantly predicted a lower functional level (β=161.474, 95% CI=[11.203-311.744], Adj. R^2=0.040, t=2.137,F= 4.565, *p*=0.036) and more severe UHR-symptoms (β=-265.608, 95% CI=[-479.673—51.543], Adj. R^2=0.055, t=-2.467, F=6.084, *p*=0.016) at 6 months. Lower global FA at baseline could not predict level of UHR-symptoms and functional level at 12 months; neither negative- or depressive symptoms at 6 and 12 months, see Supplementary Table S5 for details.

In the multivariate test, global FA at baseline significantly predicted functional level (*p*=0.036, F=4.565) and UHR-symptoms (*p*=0.022, F=5.420) 6 months. For visual illustration of the linear relation between global FA at baseline and functional level and UHR-symptoms, see supplementary Figure S5.

In additional analyses we explored if global FA predicted change in functional level and UHR-symptoms from baseline to 6 months. Higher global FA at baseline predicted more reduction in UHR-symptoms (β = -280.474, 95% CI = [-524.259- -36.689], Adj. R^2 = 0.046, F= 5.231, *p*= 0.025, see Supplementary Figure S5 for illustration). In contrast, global FA did not predict the change in functional level (β = -48.554, [95% CI] = [-94.593-191.700], Adj. R^2 = -0.006, F= 0.455, *p*= 0.502).

3.3 Exploring FA as predictor of remission

At 12 months follow-up, 15 UHR-individuals (14% of the baseline sample, 22% of the sample of completers) were in remission from the UHR-state. The logistic regression analysis was performed with remission from the UHR-state or no remission as the dichotomic outcome. Results are reported in detail in Supplementary Table S7. The multivariate model including mean global FA at baseline and the potential confounders as predictor variables was not significant (χ^2=4.884, *p*=0.884). Global FA did

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not significantly predict remission from the UHR-state (p=0.387), with 46.7% of the UHR-individuals with remission successfully predicted, and 68.6% accurate predictions for the UHR-individuals with no remission. UHR-individuals with remission had significantly higher global FA at baseline, when compared to UHR-T, see Figure 2 for illustration, and had fewer negative symptoms at baseline compared to UHR-T (p=0.028), see Supplementary Table S8 for details. There were no other clinical differences at baseline comparing UHR-individuals with remission to UHR-T.

[Insert Figure 2 here]

3.4 *Post-hoc* analyses

The effect of psychotropic medicine and substance use was explored by comparing subgroups of UHR-individuals (current antipsychotic treatment, antipsychotic-naïve status), and results are presented in Supplementary Table S9. In brief, we found no differences between subgroups which influenced the main results. Current antipsychotic medication at baseline appeared with the largest effect size in the univariate logistic regression analyses (Supplementary Table S10) and was chosen as a covariate in the multivariate logistic regression model. Furthermore, we found no significant correlations between mean global FA at baseline and antidepressant medication, mood-stabilizers, benzodiazepines, recreational nicotine-, alcohol- or cannabis-use at either baseline or 6 months (Supplementary Table S11). Likewise, allocation to the experimental treatment (cognitive remediation) did not affect transition outcome (Supplementary Table S10).

The result of the *post-hoc* tests of baseline FA for each 48 regions of interest (ROIs) separately as predictors of transition to psychosis are reported in Supplementary Table S12. The eight ROIs which significantly predicted transition (uncorrected) and had a good model fit did not add any predictive accuracy of relevance (overall predictive accuracies of 84.8%-89.5%), compared to the result for global FA (see Supplementary Table S13 for details). Global FA correlated with global RD and MD, but not AD (Supplementary Table S13). There was no difference on global AD, RD, and MD when comparing UHR-T to UHR-NT (Supplementary Tables S14).

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4.0 Discussion

We aimed to test the predictive accuracy of baseline white matter FA while covarying with potential confounders. As expected, UHR-T presented with lower mean global FA at baseline, when compared to UHR-NT. Furthermore, a multivariate model including global FA and potential confounders to FA reliably predicted transition to psychosis, accounting for a good amount of the variance in transition status with fair sensitivity and good specificity.

At baseline, the UHR-T and UHR-NT groups were clinically indistinguishable, and this prognostic uncertainty is a hindrance for the tailoring of comprehensive preventive interventions for those UHR-individuals at most imminently risk for transition to psychosis. Our study supports the notion that predictive models may improve by integrating neuroimaging data on global WM at baseline with clinical data. In particular the increase in strength for detecting transition to psychosis is compelling, as the prognostic accuracy from current clinical screening interviews such as CAARMS has been reported with poor specificity on the identification of true positives of transition to psychosis[59,60].

Additionally, the prognostic accuracy appears further enhanced by adding potential covariates to FA in a multivariate model, including motion in scanner, age, gender, antipsychotic medication, parental socioeconomic status, and activity level. Thus, the result confirms the potential benefits of a multimodal approach, when aiming for improved risk prediction. Attempts towards a multimodal approach has been made by developing clinically based, transdiagnostic individualized risk calculators[61,62]. Therein, the staging model of psychosis onset is reconceptualized into a more dimensional model, allowing for a broader range of outcomes other than transition to psychosis[63,64], such as i.e remission[65,66]. This promising dimensional approach advocates for longitudinal prediction studies applying machine learning[67] from multimodal data on biomarkers in order to enhance our ability to predict the various clinical outcomes[68] and potential protective factors[69]. Interestingly, global FA was not able to predict remission from the UHR-state in our exploratory analyses Remarkable, global FA did not predict functional level and level of UHR-symptoms (i.e. remission status) at 12 months. The moderate attrition rate at 12 months may imply a Type 2 error on this result, due to the reduction of sample size. Moreover, we speculate if the effects of prescribed

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antipsychotic medication during the trial may have affected the associations between FA and psychopathology. Indeed, this would reflect a confounding effect proposed in a recent study, suggesting that the accuracy of prediction models are undermined due to antipsychotic medication, where prescription of antipsychotics could be regarded as a proxy for psychosis onset[30].

Global FA at baseline significantly predicted functional level and level of UHR-symptoms at 6 months, as well as the change in UHR-symptoms from baseline to 6 months. The directionality of the association between global FA and clinical measures was as expected, insofar as lower FA at baseline was associated with a lower functional level and more severe UHR-symptoms at 6 months, and higher FA at baseline was associated with more reduction in UHR-symptoms at 6 months. This is in accordance with our previous cross-sectional study on the current sample, where UHR-individuals presented with lower FA compared to healthy controls; and that lower FA globally was associated with worse cognitive functioning[36]. Studies generally suggest lower FA as associated with more severe illness characteristics of UHR-individuals, such as lower level of functioning[70] and more severe UHR-symptoms[8].Our post-hoc analyses of global AD, RD and MD indicated the global FA was linked to RD and MD, but not AD. Interestingly, this pattern have been associated with dysmyelination[21,22], but great caution in the interpretation is needed, as no causal interpretation can be inferred between MRI-derived measures and the biological underpinnings[71].

A priori, we decided to use global rather than regional FA as predictor in the current study. Indeed, global FA is an averaged measure which lacks specificity and may conceal important information, which otherwise potentially could have informed hypotheses on associations between specific symptoms and identified ROIs. However, associations to clinical measures on a specific regional level may be more susceptible for spurious variations on the directionality of FA[55,72], as well as individual variations due to the heterogeneity in UHR-individuals and the multidimensional nature of psychosis[73,74].

Our explorative post-hoc test of baseline FA in 48 ROIs demonstrated that some regions significantly predicted transition, yet none added further accuracy to the sensitivity or specificity of the predictor model, when compared to global FA. However, some of the significant ROIs (i.e. corpus callosum and cingulum) replicate findings from recent studies comparing WM indices between patients with

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psychosis to patients without psychosis and healthy controls[75]. Hence our results offer suggestions for future longitudinal studies investigating the interconnected influence of changes in regional WM to changes in psychopathology. Interestingly, a recent study on the functional connectome organization in UHR-individuals found that abnormal modular connectome organization at a global level at baseline significantly predicted conversion to psychosis after one year[76]. Thus, the global approach appears equally relevant as studies in specific regions, also considering the widespread findings in major WM tracts in UHR-individuals[77–80], along with the conceptualization of psychosis as a dysconnectivity disorder[81] accompanied by widespread brain-changes at a system-level, as proposed in i.e. dynamic network theory[82,83].

The clinical implications of including neuroimaging data in predictive models on transition to psychosis are not straightforward. The cost involved in establishing routine MRI-scanning, as well as translating research based data on group differences into individualized clinical practice remains unresolved challenges[67]. Nonetheless, a recent paper by Schmidt and Borgwardt[84] recommends the future implementation of MRI-scanning in routine clinical screening practice, in order to detect organic pathology, as well as improving the prediction of clinical outcomes, such as transition or treatment response. Our study support, that when UHR-status has been initially confirmed by clinical interviews, MRI-scanning for this select group of help-seeking UHR-individuals could further inform treatment decisions regarding i.e. prescription of antipsychotics and the adequacy of more comprehensive support and treatment to those patients with the most imminent risk of transition to psychosis.

The joint initiatives to coordinate multicenter studies and methodology, such as the enigma-DTI workgroup[85], the PRONIA study (https://www.pronia.eu) and PSYSCAN consortia[86] are an important development. Such multisite studies, examining multimodal datasets with large sample sizes, appear to increase accuracy of prediction models[87]. In particular, if these studies apply pattern recognition or machine-learning methods allowing for individual classifications[26], the neurobiological refinement of current clinical prediction models could be amplified, and ultimately facilitate tailored preventive interventions at the individual level. Future multimodal studies should investigate if enhanced prediction can be obtained using other potential biomarkers beyond FA, such as examined in recent

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studies on i.e. cellular and extracellular WM alterations[7], fixel-based analyses[88,89], functional activation[90] and connectivity[91,92], neural oscillations (EEG)[93], grey matter volume[94], cortical thickness[95], as well as GABA and glutamate levels (MR-spectroscopy)[25].

Methodological considerations

Strengths of this study comprise longitudinally multimodal assessments of white matter and clinical symptoms in a well-characterized, large sample of UHR-individuals. We applied a multivariate model, while covarying for multiple potential confounders. A general limitation to the study is the fact that the analyses were secondary to an RCT, and that the study was not powered or designed for the current research question. Nonetheless, we confirmed that the experimental intervention had no effect on the transition outcome and judge our study to be of relevance. An additional limitation to our study was the low transition rate of 9%. Although studies have generally shown a decline in transition rates compared with earlier findings[96,97], the low transition rate may be explained by several contributing factors. According to the study design, all included UHR-individuals received treatment as usual, which in Denmark consists of a comprehensive psycho-social-medical intervention. Treatment provided in specialist research clinics have been shown to clinically improve and delay transition[98]. Furthermore, our study included few UHR-individuals on the BLIPS-criteria (brief, limited psychotic episodes), while the vast majority were included on the APS-criteria (attenuated psychotic symptoms). Studies have shown the immediate risk for psychosis is higher among those with BLIPS-symptoms, compared with the APS-subgroup[99]. Lastly, the relatively short follow up period of 12 months impeded examination of transition status after 24 or 36 months, which would have been optimal according to common estimates of transition rates[100]. The moderate attrition rate at 12 months may also have had an impact on tests involving symptom measures. Attrition is an inherent limitation in clinical UHR-studies[101]. We believe that our attrition rate reflects a disadvantage of the extensive trial format, with the experimental intervention as an add on to TAU. The total treatment format may have been too extensive for participants, who may be more socially

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and vocationally active than patients with i.e. schizophrenia. This calls for carefully designed studies regarding feasibility.

Moreover, global FA is a crude measure providing limited information on underlying biological processes. Although we have included measures of AD, RD, and MD to enhance interpretability of FA alterations, future studies may complement the current findings by applying a multimodal, multivariate approach such as machine learning and include e.g. genetic, fMRI, MR-spectroscopy and grey matter measures, as well as longitudinal study designs for imaging data.

Finally, at inclusion, one-third of the UHR-individuals had been exposed to antipsychotic medication. However, we carefully examined the potential effects of antipsychotic medication, by testing several variables as covariates in the model.

In conclusion, mean global FA at baseline has prognostic information on the risk of transition to psychosis and symptom course for UHR-individuals. Application of prediction models including neuroimaging data can inform treatment decisions and management regarding the imminence of transition to psychosis in clinically identified UHR-individuals.

Conflict of interest

BHE is part of the Advisory Board of Eli Lilly Denmark A/S, Janssen-Cilag, Lundbeck Pharma A/S, and Takeda Pharmaceutical Company Ltd; and has received lecture fees from Bristol-Myers Squibb, Otsuka Pharma Scandinavia AB, Eli Lilly Company, Boehringer Ingelheim, and Lundbeck Pharma A/S. In the last 3 years, CP has received honoraria for talks at educational meetings and has served on an advisory board for Lundbeck, Australia Pty Ltd. BYG is the leader of a Lundbeck Foundation Centre of Excellence for Clinical Intervention and Neuropsychiatric Schizophrenia Research (CINS), which is partially financed by an independent grant from the Lundbeck Foundation based on international review and partially financed by the Mental Health Services in the Capital Region of Denmark, the University of Copenhagen, and other foundations. All grants are the property of the Mental Health

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Services in the Capital Region of Denmark and administrated by them. She has no other conflicts to disclose.

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Tables

In separate file (Tables_APS_2021)

Figure Legends

Figure 1. ROC curve of the prediction model

Graphical illustration of the predictive ability of the model tested in the logistic regression analyses. The dark blue colored line is the ROC (receiver operation characteristic) curve derived from the model, and the light blue area below the curves is the AUC (area under the curve). The grey diagonal line (ROC=0.5) marks the values where classification would be random; a roc-curve above the diagonal is better than random. Sensitivity = true positive rate; Specificity = True negative rate.

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Figure 2. Baseline mean global fractional anisotropy in UHR-individuals with transition to psychosis, sustained UHR-state, and remission from the UHR-state at 12 months.

Boxplots illustrating the group differences on mean global fractional anisotropy at baseline, when comparing UHR-individuals with transition to psychosis to UHR-individuals with no transition to psychosis or remission at 12 months. Note that the y-axis has been altered for visual clarity.

** Indicates a significant group difference*

Abbreviations: ns: not significant; UHR: ultra-high risk for psychosis

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Table 1.

Sociodemographic data at baseline for individuals at ultra-high risk for psychosis

VARIABLE MEAN (S.D.) / PERCENT	UHR-NT (N=100)	UHR-T (N=10)	SIGNIFICANCE GROUP EFFECT
Age mean (SD)	24 (4)	23 (4)	*p*=0.59
Gender			*p*=0.30
Male	46 %	60 %	
Female	54 %	40 %	
Estimated IQ	104 (12)	103 (17)	*p*=0.91
Parental SES			*p*=0.07
Low	11 %	10 %	
Medium	34 %	70 %	
High	55 %	20 %	
Ethnicity			*p*=0.24
High-income countries	92 %	80 %	
Low-income countries	8 %	20 %	
BMI mean (SD)	23 (5)	25 (7)	*p*=0.94
Activity level[b]	15 (17)	4 (7)	*p*=0.03*
Handedness			*p*=0.37
Right	88 %	80 %	
Left	12 %	20 %	
Alcohol consumption (last year)			*p*=0.93
Daily	3 %	0 %	
Weekly	32 %	30 %	
Monthly	36 %	30 %	
Once/twice	14 %	20 %	
Never	14 %	20 %	
Tobacco smoking (last year)			*p*=0.63
Daily	40 %	60 %	
Weekly	6 %	0 %	
Monthly	4 %	0 %	

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Once/twice	6 %	0 %	
Never	44 %	40 %	
Cannabis smoking (last year)			*p*=0.21
Daily	3 %	0 %	
Weekly	5 %	0 %	
Monthly	6 %	10 %	
Once/twice	13 %	40 %	
Never	73 %	50 %	
Diagnoses			
Affective disorder	58 %	50 %	*p*=0.44
Anxiety disorder	49 %	40 %	*p*=0.42
Personality disorder	32 %	50 %	*p*=0.21
Other diagnoses	17 %	40 %	*p*=0.10
Illness duration / months since first psychiatric contact	18 (30)	11 (21)	*p*=0.82
Mean global FA [[a]]	0.6007 (0.0149)	0.5899 (0.0206)	*p*=0.039, F=4.37 * [*p*=0.040, F=4.34]

Table 1

[a] *Group differences were tested with general linear modelling and corrected for age/gender/relative and absolute head motion in scanner.*

[b] *Activity level is measured as hours spend per week on education and/or work.*

** Indicates a significant effect of group.*

Abbreviations: BMI: body mass index; FA: fractional anisotropy; IQ: intelligence quotient; No.: number; NT: no transition to psychosis SD: standard deviation; SES: socio-economic status; T: transition to psychosis; UHR: ultra-high risk.

Table 2. Clinical data at baseline, 6- and 12 months follow-up

	Baseline		FU 6		FU 12		Time effect
Variable Mean (S.D.) / Percent (No)	**UHR-NT (N=100)**	**UHR-T (N=10)**	**UHR-NT (N=100)**	**UHR-T (N=10)**	**UHR-NT (N=100)**	**UHR-T (N=10)**	

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Medication								
Antipsychotic-naïve	55 % (55)	50 % (5)	33 % (33)	40 % (4)	29 % (29)	30 % (3)	*p*=0.006*
Between-group effect	*p*=0.509		*p*=0.449		*p*=0.601		*p*=0.506
Current[a] antipsychotics[b]	33 % (33)	40 % (4)	57 % (57)	60 % (6)	55 % (55)	60 % (6)	*p*=0.024*
Between-group effect	*p*=0.449		*p*=0.565		*p*=0.516		*p*=0.966
CPZ equivalent dose[c]	71 (175)	60 (106)	119 (200)	80 (93)	55 (1001)	125 (n/a)	*p*=0.192
Between-group effect	*p*=0.847		*p*=0.544		*p*=0.503		*p*=0.307
Current[a] antidepressants	25 % (25)	40 % (4)	22 % (22)	30 % (3)	24 % (24)	30 % (3)	*p*=0.660
Between-group effect	*p*=0.249		*p*=0.406		*p*=0.464		*p*=0.820
Current[a] mood-stabilizers	6 % (6)	0 % (0)	11 % (11)	0 % (0)	3 % (3)	0 % (0)	*p*=0.701
Between-group effect	*p*=0.557		*p*=0.332		*p*=0.749		*p*=0.701
Current[a] benzodiazepines	6 % (6)	20 % (2)	9 % (9)	40 % (4)	6 % (6)	30 % (3)	*p*=0.124
Between-group effect	*p*=0.155		*p*=0.017*		*p*=0.034*		*p*=0.365
Clinical data			**[N=80][d]**	**[N=8][d]**	**[N=65][d]**	**[N=4][d]**	
Number of treatment contacts[e]	-	-	27 (16)	39 (21)	48 (29)	65 (42)	*P*<0.001*
Between-group effect	-		*p*=0.041*		*p*=0.094		*p*=0.309
UHR-symptoms (CAARMS composite)	51 (15)	51 (7)	35 (16)	46 (15)	28 (16)	40 (10)	*P*=0.001*
Between-group effect	*p*=0.959		*p*=0.056		*p*=0.162		*p*=0.266
Negative symptoms (SANS)	1.49 (0.81)	1.93 (0.39)	1.32 (0.87)	2.00 (0.67)	1.19 (0.83)	2.00 (0.46)	*p*=0.919
Between-group effect	*p*=0.097		*p*=0.035*		*p*=0.059		*p*=0.351
Depressive symptoms (MADRS)	16 (7)	17 (5)	12 (7)	16 (5)	12 (7)	15 (5)	*p*=0.251
Between-group effect	*p*=0.556		*p*=0.144		*p*=0.394		*p*=0.747
Function (SOFAS)	55 (11)	51 (13)	61 (11)	59 (9)	61 (10)	57 (12)	*p*=0.209
Between-group effect	*p*=0.311		*p*=0.592		*p*=0.511		*p*=0.195

a Current = the last month. Data on prescribed medication for drop-outs were obtained from clinical journals.

b Atypical antipsychotics in low dose: aripiprazole, amilsulpride, olanzapine, paliperidone, quetiapine, risperidone.

c CPZ equivalent dose is the chlorpromazine equivalent dose calculated from the prescribed antipsychotic medication.

d The bracket [] indicates the sample size for the UHR-individuals completing clinical examinations. Information on medication for dropouts was obtained from clinical journals.

e Number of treatment contacts include the summed number of total sessions in the experimental intervention and in the psychiatric services, such as meeting with psychiatrist, case manager, counselling, and individual or group-based psychotherapeutic interventions.

** Indicates significant effects of time / group / time*group (uncorrected).*

Abbreviations: CAARMS: comprehensive assessment of at-risk mental state; MADRS: Montgomery-Åsberg Depression Rating Scale; N.: sample size; SANS: Scale for the Assessment of Negative Symptoms; SD: standard deviation; SOFAS: social and occupational function assessment scale; UHR: ultra-high risk.

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Table 3. Logistic regression analyses of mean global fractional anisotropy at baseline as predictor of transition to psychosis in individuals at ultra-high risk for psychosis

Predictor	*Omnibus test p* (χ^2)	*Cox and Snell* R^2	*Nagelknerke* R^2	*Hosmer & Lemeshow Test*	β	*SE* β	Walds χ^2	*df*	*p*	*Odds ratio (CI 95 %)*
Model	**0.040 (17.595)**	**0.154**	**0.330**	**0.399**				9		
Global FA					**-57.476**	**25.674**	**5.012**	**1**	**0.025**	**17.818 (4.010-79.173)**
Activity level[a]					-0.062	0.039	2.948	1	0.086	0.940 (0.871-1.014)
Absolute motion in MRI-scanner					-4.135	2.626	2.480	1	0.115	0.016 (0.00009-2.750)
Relative motion in MRI-scanner					4.292	4.329	0.983	1	0.321	73.8120 (0.015-353992.346)
Age					0.215	1.022	0.044	1	0.834	1.239 (0.167-9.192)
Age (squared)					-0.006	0.021	0.910	1	0.764	0.994 (0.955-1.035)
Gender					-0.355	0.822	0.187	1	0.665	1.427 (0.285-7.148)
Parental SES					0.816	0.649	2.643	1	0.104	2.873 (0.805-10.258)
Current[b] AP[c]					-0.803	0.873	0.873	1	0.350	2.261 (0.408-12.517)

Table 3.

Predictors that are significant at the P≤.05 level are given in bold.

[a] *Activity level is measured as weekly hours spend on work and education.*

[b] *Current = the last month.*

[c] *Atypical antipsychotics in low dose: aripiprazole, amilsulpride, olanzapine, paliperidone, quetiapine, risperidone.*

Abbreviations: AP: antipsychotic medication at baseline; FA: fractional anisotropy; MRI: magnetic resonance imaging; SES: socio-economic status.

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