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# Characterizing the Clinical Trajectory and Predicting Persistence and Deterioration of Attenuated Psychotic Symptoms in Ultra-High-Risk Individuals

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***Background*: Almost 40% of individuals at ultra-high risk (UHR) for psychosis experience persistent attenuated psychotic symptoms (APS) yet it is unclear (1) whether they share overlapping clinical and functional outcomes compared to individuals who transition to psychosis, (2) when symptom and functioning trajectories begin to diverge between UHR individuals with different clinical outcomes, and (3) whether non-remission (persistent APS or transition) can be predicted using baseline and/or longitudinal data.**

***Study Design*: Participants were drawn from 2 randomized clinical trials: Neurapro (*n* = 220; discovery sample) and STEP (*n* = 180; external validation sample). First, 12–24 month symptoms and functioning were compared between UHR individuals with persistent APS, sustained remission, or transition to psychosis. Next, short-term changes in symptoms and functioning were compared between groups to determine timepoints at which trajectories began to diverge. Finally, we used support vector machines to predict non-remission (persistent APS or transition) vs sustained remission using data from baseline, 6-month follow-up, and combined baseline and 6-month follow-up.**

***Results*: Individuals with persistent APS had substantially poorer outcomes compared to those who remitted, and more closely resembled individuals who later transitioned to psychosis. Despite few baseline differences between groups, clinical and functional trajectories of the persistent APS and transition groups rapidly diverged from those who remitted. Prediction of non-remission was poor using baseline data but improved substantially when using 6-month follow-up or combined baseline-6-month data.**

***Conclusions*: Ultra-high-risk individuals with persistent APS display similar clinical and functional trajectories to transitioned cases, suggesting that more intensive**

**and sustained intervention is required for this subgroup. However, prospective identification of individuals with poor clinical outcomes (ie, persistence or deterioration of attenuated psychotic symptoms) may require longitudinal monitoring of symptom and functioning trajectories for several months.**

**Key Words:** psychosis/ultra high risk/attenuated positive symptoms/prediction/longitudinal

## Introduction

The ultra-high-risk (UHR) for psychosis approach has been used for several decades to identify individuals at heightened risk of developing psychotic disorders.[1] Approximately 25% of UHR individuals transition to psychosis compared to just 3.9% of other help-seeking populations and 0.5% of the general population.[2–4] However, around 75% of UHR individuals do not transition to psychosis, and approximately half of this non-transitioning population continues to experience persistent attenuated psychotic symptoms (APS) after 3 years.[5]

Despite persistent APS being observed in a large proportion of UHR individuals, there are few studies characterizing this cohort and findings are inconsistent. Two previous studies found that 41% and almost 60% of UHR individuals were still experiencing at least 1 APS at 24-month follow-up.[6,7] In both studies, there were no differences in baseline functioning between those with persistent APS and those remitted. However, while 1 study found no differences in social or role functioning between those with persistent APS and those who remitted at 12-month follow-up,[6] a more recent study found that those with stable or worsening APS experienced higher negative, general, and disorganized symptoms and poorer social functioning at 2-year follow-up compared to those who remitted.[7] Persistent APS at 2–14 year follow-up has also been associated with an increased prevalence of non-psychotic mental disorders at follow-up points compared to those who remit.[8] Together, these findings provide initial evidence that UHR cases with persistent APS may have a range of poor clinical and functional outcomes. However, studies are yet to examine how outcomes in those with persistent APS compare to those who transition to psychosis. Furthermore, previous studies have defined remission based on a single follow-up timepoint. However, around 25% of UHR individuals will experience recurrence or relapse of APS following remission,[9] and it is therefore important to also consider sustained remission.

Poor outcomes in individuals with persistent APS indicate that more intensive and prolonged clinical care may be required in this group, and highlights the need for early identification of individuals most likely to follow this trajectory.[5] However, the absence of clear baseline differences between UHR individuals who remit and those who experience persistent APS in previous studies[6,7] suggests that prospective identification of these subgroups upon entry to clinical services may be difficult. As such, a critical first step in the early intervention process is to pinpoint the timeframes over which divergence in symptoms and functioning begins to emerge between different UHR subgroups and identify which measures are most sensitive to this divergence.

The disconnect between baseline presentation and follow-up outcomes in UHR subgroups highlights the dynamic nature of early psychopathology, with symptoms and functioning fluctuating significantly over time and between individuals.[10,11] Recent calls emphasize the need to incorporate longitudinal data into prediction models to enhance their accuracy, generalizability, and clinical relevance.[11] One such approach is joint modeling, which integrates longitudinal mixed-effects data into time-to-event predictions and has been shown to predict the transition to psychosis in UHR individuals with greater accuracy than static baseline models.[12–15] However, another approach is to incorporate data from a follow-up timepoint into a more traditional machine learning framework, such as a support vector machine. Given that clinical services for UHR individuals typically span 12–24 months,[16] this approach would enable clinicians to refine outcome predictions at clinically significant timepoints, such as after a specific number of therapy sessions, allowing for better-tailored patient management early on in treatment.

The aims of the current study were to: (1) compare clinical and functional measures at baseline and 12–24 month follow-up between UHR individuals who achieve sustained UHR remission, those with persistent APS, and those who transition to psychosis by 24-month follow-up, and (2) compare clinical and functional trajectories between persistent APS, remitted, and transitioned groups over 6 months to determine if trajectories begin to diverge within a clinically relevant timeframe. A third exploratory aim was to determine whether baseline, 6-month, or combined baseline and 6-month data could be used to predict clinical outcomes. For the third aim, data from the persistent APS and transition groups were combined into a "non-remission" group due to: the fact that predicting the general category of "non-remission" may be useful for clinical trial stratification and organization of clinical services; previous studies indicating poor clinical outcomes in the persistent APS subgroup (see above); and the statistical limitations of a small sample size of transitioned cases. The analyses addressing these aims were conducted across 2 independent UHR samples, allowing for external validation of findings.

## Methods

### *Participants*

Longitudinal clinical outcomes over 12–24 months were obtained for UHR individuals from 2 double-blind,

randomized placebo-controlled trial studies: Neurapro[17] and STEP.[18] Notably, risk models can be constructed from clinical trial data[19] and neither clinical trial demonstrated treatment effects.[20–22] Further details, including inclusion and exclusion criteria, are provided in Supplementary Materials. To be included in the current study, participants were required to have at least one year of follow-up data or have transitioned to psychosis at any point in the study. Table S7 summarizes baseline clinical and functional measures across the 2 studies.

*Neurapro* Neurapro study participants were aged between 13 and 40 years. Following baseline assessment, regular follow-up assessments were conducted monthly from months 1 to 6, and then at 9-, 12-, and 24-months, resulting in a total of 10 timepoints. From an original baseline sample of $n = 304$, the current study included a total of 220 participants who had at least 1 year of follow-up assessment data or who transitioned to psychosis.

*STEP* Individuals included in the STEP study were UHR individuals aged between 12 and 25 years old. Following baseline assessment, regular follow-up assessments were conducted at weeks 4 and 6 and months 3, 6, 9, 12, 18, and 24, resulting in a total of 9 timepoints. From an original baseline sample of $n = 342$, the current study included a total of 180 participants who had at least 1 year of follow-up assessment data or who transitioned to psychosis.

For both studies, comparisons of included vs excluded participants and details of the number of included participants who completed assessments at each timepoint are provided in Supplementary Materials.

### *Outcome Definitions*

Across both studies, the Comprehensive Assessment of At-Risk Mental States (CAARMS)[23] was used to stratify participants into 3 outcome groups up to 24-month follow-up:

(1) Sustained remission: Working backwards from their last follow-up assessment, participants must fall below UHR criteria based on the CAARMS[23] for a period of at least 6 months with no return to UHR status.[9]
(2) Transition: Defined using previously established CAARMS criteria[23] or state medical records.
(3) Persistent APS: Participants who do not meet either sustained remission or transition criteria at (ie, persistence of attenuated positive symptoms at a level that meets UHR criteria based on the CAARMS at 12–24 month follow-up, with any period of remission lasting less than 6 months).

For aim 3, groups 2 and 3 were combined into a "non-remission" group and compared to group 1, the "remitted" group.

### *Measures*

*Clinical Measures.* Symptoms were measured using the Brief Psychiatric Rating Scale (BPRS),[24] Scale for Assessment of Negative Symptoms (SANS),[25] CAARMS,[23] and the Montgomery-Asberg Depression Rating Scale (MADRS).[26] Psychiatric diagnoses were assessed using the Structured Clinical Interview for DSM-IV Axis I Disorders—Patient Edition[27] in the Neurapro sample, and the Structured Clinical Interview for DSM-5 (SCID-5) Research Version[28] in the STEP sample.

*Functioning Measures.* Functioning was measured using the Social and Occupational Functioning Assessment Scale (SOFAS)[29] and the Global Functioning: Social and Role Scales.[30,31] Quality of life was measured using the Assessment of Quality of Life (AQoL-8D).[32]

*Cognition.* In the Neurapro sample, cognitive functioning was assessed using the Brief Assessment of Cognition in Schizophrenia (BACS).[33] Domains examined in the current study include executive function, verbal memory, working memory, attention and processing speed, motor speed, and verbal fluency.

### *Data Analysis*

Primary analyses were conducted in R version 4.1.2. Analyses are based on available data at each visit. Missing data, for example, missing single follow-up visits, drop-outs, or missing data from one or more measures at a single timepoint, were not imputed. Machine learning analyses were performed using Neurominer v1.2 within Matlab 2023b (MathWorks Inc.), and data were imputed using methods described below.

*Between-Group Comparisons of Symptoms and Functioning at Baseline and Follow-up*. Clinical and functioning measures were compared between groups at baseline and 12- and 24-month follow-up separately in each sample. Overall differences between the 3 clinical outcome groups (persistent APS, remission, and transition) were compared using analysis of variance (ANOVA) and results were corrected for multiple comparisons using the false discovery rate (FDR).[34] For measures surviving FDR correction, post hoc pairwise comparisons were conducted using Tukey *t*-tests. DSM diagnoses were compared using chi square tests.

*Comparison of Post-transition Outcomes*. Functioning was measured at a post-transition assessment in 32 individuals in the Neurapro study and 14 individuals in the STEP study. ANOVAs were used to compare between-group differences in functioning at the post-transition assessment in those who transitioned to psychosis with 12- and 24-month outcomes in the remission and persistent APS groups. Results were FDR-corrected and pairwise comparisons were conducted using Tukey t-tests.

*Clinical and Functional Trajectories*. A series of linear mixed-effect models (LMMs) were performed using the lme4 package[35] to examine group by time interactions across clinical and functioning measures over the first 6 months of Neurapro and STEP. Group, time, and the group by time interaction were included as fixed effects. Participant ID was added as a random effect. FDR-correction was used to control for multiple comparisons separately across main effects and interactions. For significant interactions, we used the emmeans package[36] to compare estimated marginal means at each timepoint to determine the timepoint at which trajectories began to diverge between each pair of groups. The divergence point was defined as the timepoint at which 2 groups began to consistently differ (ie, $P$-value < .05) on a measure with no subsequent return to non-significant group differences. Group differences that emerged at 6 months are also shown for indicative purposes.

*Prediction of Clinical Outcomes*. The machine learning software NeuroMiner version 1.2. (https://github.com/neurominer-git/NeuroMiner_1.2) was used to construct support vector machine (SVM) classifiers to predict outcomes (non-remission vs remission). SVM is a supervised learning technique that has been widely used in psychiatry,[37,38] including successful applications in UHR populations.[39–42] Importantly, SVMs reduce overfitting by maximizing the margin between classes, focusing on support vectors to improve generalization.[43] Additionally, tuning the C-hyperparameter allows for regularization, balancing model complexity with accuracy. Cross-validation further ensures robustness by optimizing hyperparameters and preventing overfitting to specific subsets of the data. Models were developed using measures that are commonly included in prediction models and would be feasible to obtain in clinical settings (see Table S4 for a full list of variables). Participants with more than 25% missing data were excluded from analyses. Neurapro data were used as the discovery dataset. In a first step, we utilized baseline data from the full Neurapro sample ($n$ = 215: non-remission = 107; remission = 108) to predict outcomes. Next, in a sample of individuals with both baseline and 6-month data ($n$ = 179: non-remission = 76; remission = 103), we used SVMs to predict outcomes using 3 datasets: (1) baseline data only, (2) 6-month follow-up data only, and (3) combined baseline and 6-month follow-up data. Participants who transitioned to psychosis prior to 6-month follow-up were excluded from initial analyses so that post-transition data were not included in prediction models, however, 2 supplementary analyses were performed: (1) participants who transitioned to psychosis prior to 6-month follow-up included in model ($n$ = 186: non-remission = 83; remission = 103), and (2) only participants who transitioned to psychosis *and* commenced antipsychotic treatment prior to 6-month follow-up were excluded ($n$ = 180: non-remission = 77; remission = 103).

All models were developed using nested 10-fold cross-validation with 10 permutations at both the inner (CV1) and outer (CV2) cycles, and classification performance was assessed based on balanced accuracy (BAC). The reliability and significance of predictors were determined using sign-based consistency and the cross-validation ratio (details in Supplementary Materials). The resulting models were applied to the STEP data for external validation ($n$ = 176 for baseline-only analysis [non-remission = 104; remission = 72], and $n$ = 149 for combined baseline and 6-month analysis [non-remission = 84; remission = 65]). In line with previous studies, we employed a study-specific calibration procedure to account for differences in sample characteristics across the discovery and validation samples.[39] This involved mean centering each STEP predictor to the respective Neurapro variable by subtracting the difference in study means from the relevant STEP predictor. Full details of the prediction models are provided in Supplementary Materials.

*Supplementary Analyses*. In the Neurapro sample only, group differences in cognitive abilities were compared at baseline and 12 months using ANOVAs and post hoc tests as described above.

## Results

Primary results for the Neurapro sample are presented below. External validation using the STEP sample is provided in Supplementary Materials.

Among the Neurapro sample, 111 participants (51.5%) were in sustained remission, 69 participants (30.1%) had persistent APS, and 40 participants (18%) transitioned to psychosis.

### *Baseline Demographic and Clinical Comparisons*

Demographic data and key baseline characteristics are displayed in **Table 1**. A full list of baseline measures is provided in Table S9. In the Neurapro sample, individuals with persistent APS were significantly younger than those who achieved sustained remission and those who transitioned. However, there were no significant differences in gender, baseline rates of alcohol use disorders, cannabis use disorders, depressive disorders, or anxiety disorders, or in study treatment (ie, fish oil vs placebo) between groups (see Supplementary Materials). There were no significant differences between groups in terms of their inclusion criteria (vulnerability/attenuated positive psychotic symptoms/brief limited intermittent psychotic symptoms). As seen in **Table 1** and Table S2, individuals with persistent APS had lower role functioning and AQoL mental health scores and higher general psychopathology compared to those who remitted. No differences were observed between those with persistent APS and those who transitioned on any measure.

**Table 1.** Demographics and Baseline Clinical Characteristics

| | Neurapro | | | | | | | | | STEP | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Remission | | APS | | Transition | | | | | Remission | | APS | | Transition | | | | |
| | N | % | N | % | N | % | $\chi^2$ | $Eta^2$ | PairwiSE | N | % | N | % | N | % | $\chi^2$ | | Pairwise |
| Sex (female) | 52 | 47% | 45 | 65% | 21 | 53% | 5.8 | – | – | 43 | 57% | 41 | 61% | 18 | 49% | 1.54 | – | – |
| Any DSM diagnosis | 92 | 83% | 61 | 90% | 37 | 95% | 4.3 | – | – | 63 | 84% | 63 | 96% | 35 | 97% | 7.52 | – | – |
| UHR criteria at inclusion[a] | | | | | | | | | | | | | | | | | | |
| Vulnerability | 26 | 23% | 11 | 16% | 12 | 13% | 2.92 | – | – | 7 | 9% | 10 | 15% | 3 | 8% | 1.47 | – | – |
| APS | 98 | 88% | 65 | 94% | 36 | 90% | 1.74 | – | – | 74 | 99% | 67 | 99% | 36 | 97% | 0.31 | – | – |
| BLIPS | 6 | 5% | 3 | 4% | 3 | 7.5% | 0.49 | – | – | 2 | 3% | 1 | 1% | 1 | 3% | 0.28 | – | – |
| | Mean | SD | Mean | SD | Mean | SD | *F*–value | $Eta^2$ | Pairwise | Mean | SD | Mean | SD | Mean | SD | *F*–value | $Eta^2$ | Pairwise |
| Age | 19.4 | 4.9 | 17.7 | 3.3 | 19.9 | 5.3 | 4.1 | 0.04 | APS < remission; APS < transition | 17.5 | 3.2 | 17.7 | 3.0 | 17.7 | 2.7 | 0.1 | – | – |
| Positive symptoms | 35.8 | 19.4 | 39.4 | 16.2 | 39.8 | 17.2 | 1.2 | – | – | 32.5 | 16.3 | 39.8 | 16.9 | 44.3 | 22.4 | 6.2* | 0.07 | APS > remission; Transition > remission |
| Negative Symptoms | 22.8 | 18.4 | 26.5 | 15.4 | 33.4 | 17.2 | 5.3* | 0.05 | Transition > remission | 22.3 | 14.1 | 26.5 | 14.5 | 33.6 | 16.9 | 6.8* | 0.07 | Transition > remission |
| BPRS Total | 40.4 | 9.5 | 44.5 | 10.4 | 50.6 | 13.3 | 13.5* | 0.11 | Transition > remission | 43.8 | 8.0 | 47.9 | 8.5 | 51.2 | 11.4 | 8.9* | 0.09 | APS > remission; Transition > remission |
| Depression | 17.9 | 9.6 | 21.7 | 8.2 | 21.3 | 8.6 | 4.7* | 0.04 | APS > remission | 19.9 | 9.8 | 24.6 | 8.4 | 26.4 | 10.6 | 7.4* | 0.08 | APS > remission; Transition > remission |
| SOFAS | 55.2 | 12.5 | 53.0 | 11.3 | 50.1 | 9.4 | 3.0 | – | – | 58.9 | 10.0 | 56.8 | 12.3 | 55.2 | 10.4 | 1.6 | – | – |
| Global functioning—social | 6.7 | 1.1 | 6.4 | 1.3 | 6.0 | 1.4 | 5.4* | 0.05 | Transition > remission | 6.5 | 1.2 | 6.7 | 1.2 | 6.4 | 1.2 | 0.7 | – | – |
| Global functioning—role | 6.3 | 1.3 | 5.7 | 1.6 | 5.8 | 1.3 | 5.3* | 0.05 | APS > remission | 6.6 | 1.6 | 6.4 | 1.5 | 6.4 | 1.6 | 0.7 | – | – |
| AQOL mental health | 52.9 | 17.9 | 43.0 | 17.3 | 49.1 | 21.7 | 5.6* | 0.06 | APS > remission | 35.5 | 14.9 | 46.5 | 11.8 | 40.2 | 17.5 | 9.6* | 0.11 | APS > remission; Transition > remission |
| AQOL physical health | 77.8 | 12.1 | 73.2 | 11.5 | 71.8 | 15.7 | 4.03* | 0.04 | – | 78.4 | 10.3 | 72.2 | 10.7 | 67.6 | 11.1 | 12.44* | 0.14 | APS > remission; Transition > remission |

[a]Participants may meet more than one inclusion criterion.
* FDR–corrected $P < .05$.

*Comparison of 12–24-Month Outcomes Across Groups*

*12 Months:* Effect sizes for key clinical and functioning measures in the Neurapro sample are shown in **Figure 1**, with full details provided in Table S11. Individuals with persistent APS had poorer functioning on the SOFAS, global social and role scales, and multiple AQoL subdomains compared to those who achieved sustained remission, as well as higher positive and negative symptoms, depressive symptoms, and general psychopathology scores. Very similar differences were observed in those who transitioned compared to those who achieved sustained remission. Individuals who transitioned had higher positive and negative symptoms and poorer role functioning compared to those with persistent APS.

*24 Months:* Effect sizes for key clinical and functioning measures in the Neurapro sample are shown in **Figure 1**, with full details provided in Table S13. Individuals with persistent APS had poorer functioning on the SOFAS, multiple AQoL subdomains, and global role and functioning scales compared to those who achieve sustained remission, as well as higher positive symptom, depression, and CAARMS subdomain scores. These same differences were also observed in those who transitioned compared to those who achieve sustained remission. Individuals who transitioned had higher positive symptoms, CAARMS cognitive change, and general psychopathology compared to those with persistent APS.

*Comparison of Post-transition Outcomes*

Post-transition functioning was lower in the transition group than that observed in the remission and persistent APS groups at both 12- and 24-month follow-up (Figure S1 and Table S15).

*Clinical and Functional Trajectories*

Full LMM details are provided in Table S17. Following FDR correction, group-by-time interactions were observed for 10 measures in the Neurapro sample. These included measures of positive symptoms (CAARMS and BPRS total positive symptoms, unusual thought content, perceptual abnormalities), depressive symptoms, functioning (SOFAS, global functioning social and role scales), and quality of life (happiness). As seen in **Figure 2**, divergence points between both persistent APS individuals and those who transitioned to psychosis compared to those who remitted were evident early (within the first 3 months) across most of the measures in the Neurapro sample. Conversely, divergence between those with persistent APS and those who transitioned tended to occur later or not at all.

*Prediction of Clinical Outcomes*

Balanced accuracy (BAC) for prediction of outcome (non-remission vs remission) in the full baseline-only model was 59.5% in the discovery sample, and 59.9% in the external validation sample (area under the receiver operating characteristic curve (AUC) [CI]: 0.65 [0.58-0.7s]; sensitivity: 59.8%; specificity: 59.3%). Full details are provided in Table S19. Results for the baseline-6-month analyses are displayed in **Table 2**. In the external validation sample, balanced accuracy for prediction of outcome (non-remission vs remission) was lowest using baseline-only data (BAC 63.9%) and highest using 6-month only data (BAC 72.1%) and combined baseline and 6-month data (BAC 73.2%). Results were very consistent when (1) Neurapro participants who had already transitioned to psychosis by 6-months were included in the discovery model, and (2) only Neurapro transitioned participants who had started antipsychotic medication by 6-months were excluded from the discovery model (see Tables S20 and S21 for details). In the combined model, predictors most reliably associated with non-remission included perceptual abnormalities, non-bizarre ideas, and CAARMS total positive and negative symptoms at the 6-month follow-up, as well as unusual thought content at baseline (**Figure 3**). Predictors most reliably associated with remission included older age, male sex at birth, role functioning at baseline, and social and role functioning at follow-up. Top predictors for the baseline-only and 6-month follow-up-only models are displayed in Figures S5 and S6.

**External Validation Results: STEP**

Among the STEP sample, 75 participants (41.6%) were in sustained remission, 68 participants (37.8%) had persistent APS, and 37 participants (20.6%) transitioned to psychosis.

*Baseline Demographic and Clinical Comparisons*

In the STEP sample, no significant age or sex differences were observed between clinical outcome groups. As seen in **Table 1** and Table S2, between-group differences were observed across several symptom, functioning, and quality of life measures at baseline. There were no differences between groups in terms of their inclusion criteria (vulnerability/attenuated positive psychotic symptoms/brief limited intermittent psychotic symptoms).

*Comparison of 12–24-Month Outcomes Across Groups*

*12 Months:* Similar group differences were observed in the STEP study compared to the Neurapro study, with substantial overlap (86%) in the variables that were significant across both studies (67% overlap APS vs remission; 58% overlap APS vs transition; 83% overlap remission vs transition). See Figure S2 and Table S12 for full details.

*24 Months:* Similar group differences were observed in the STEP study compared to the Neurapro study, with substantial overlap (86%) in the variables that were significant across both studies (86% overlap APS vs remission;

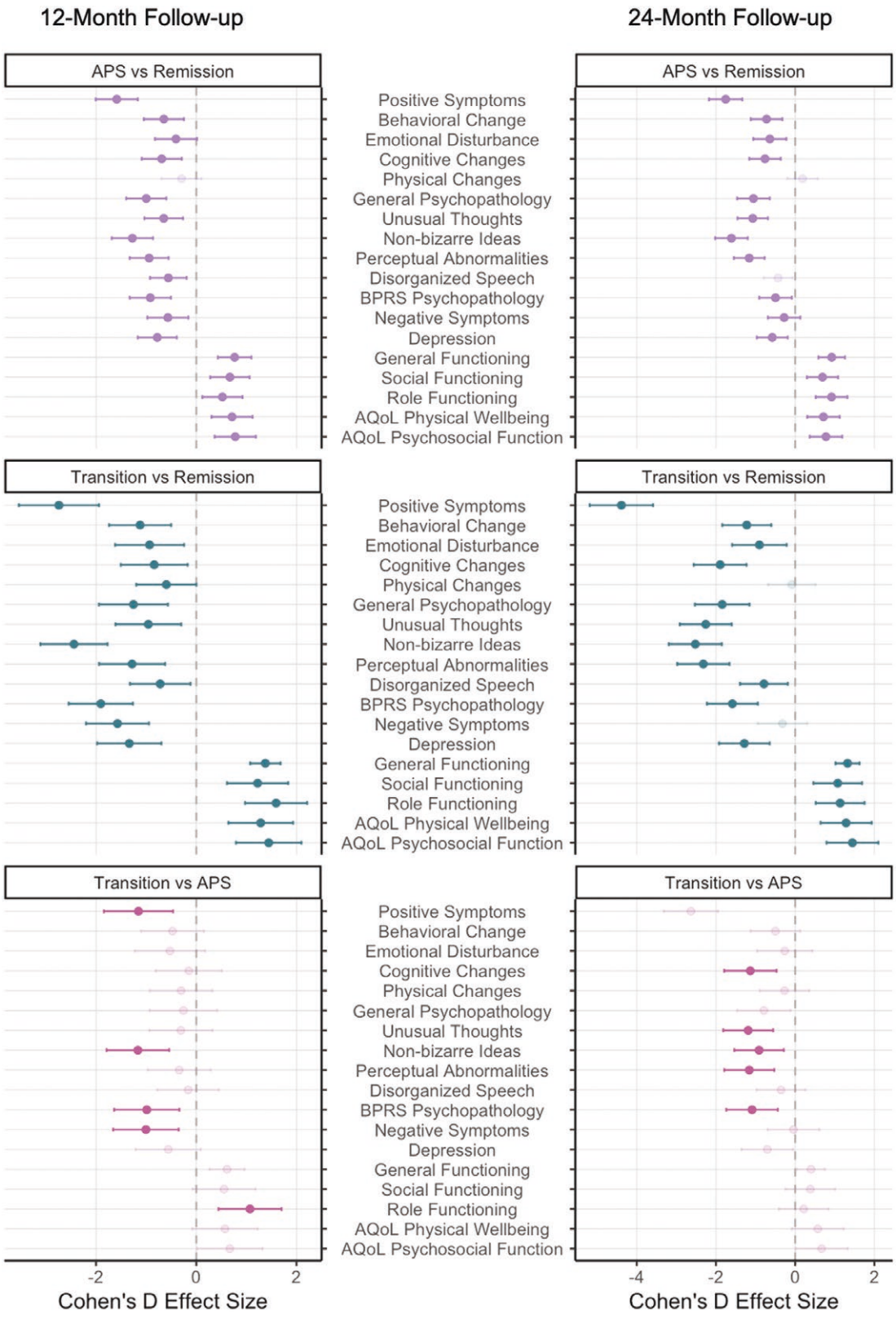


**Figure 1.** Cohen's *D* Effect Sizes and Confidence Intervals for Between-Group Comparisons of Clinical and Functioning Measures at 12- and 24-Month Follow-up in the Neurapro Sample. Transparent Points Indicate No Significant Pairwise Difference.

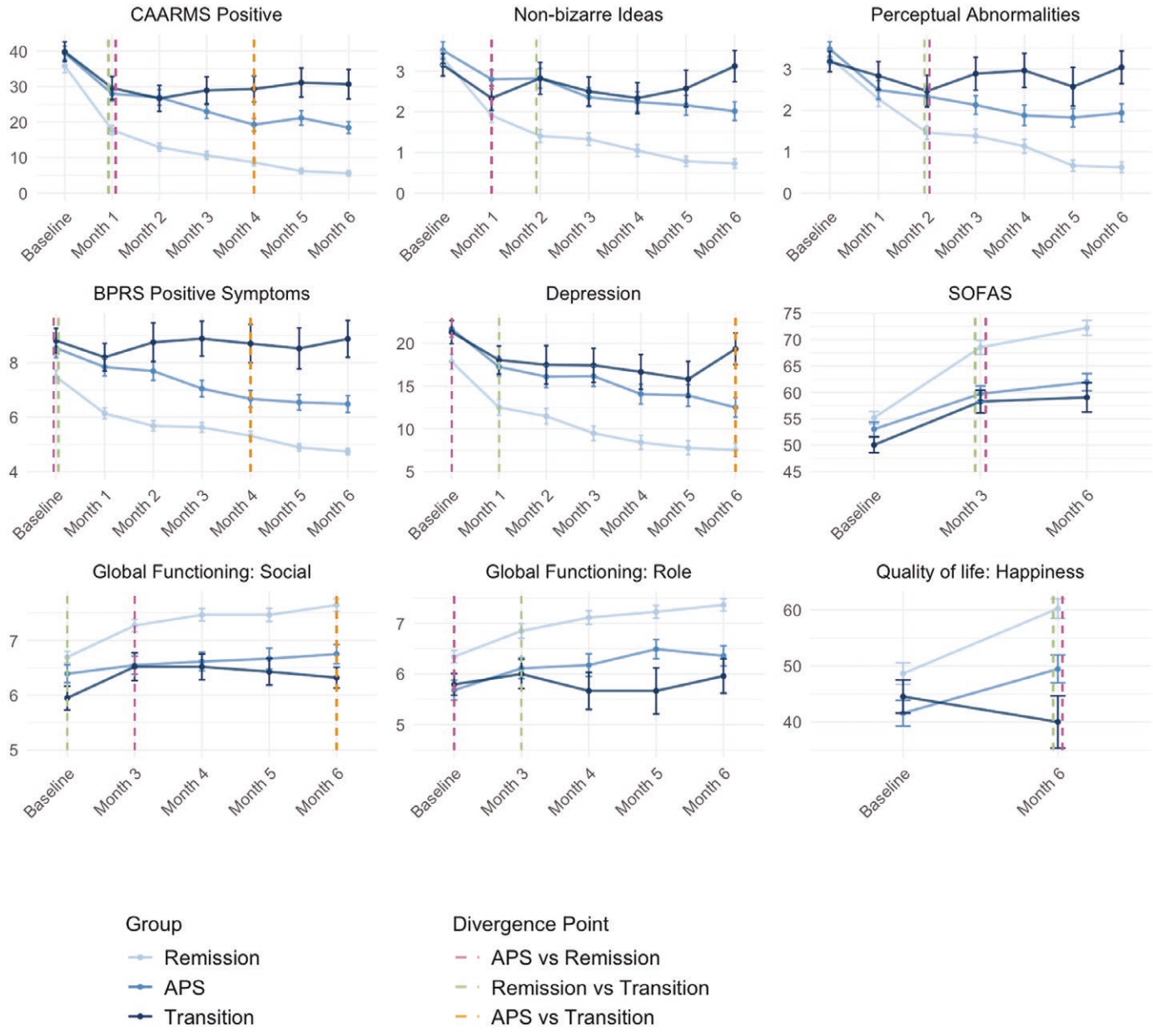


**Figure 2.** Divergence Points for Measures with Group X Time Interactions in the Neurapro Study. Dashed Lines Indicate the Divergence Point for Each Pair of Groups on a Measure. The Divergence Point was Defined as the Timepoint at Which 2 Groups Began to Consistently Differ (ie, *P*-value < .05) on a Measure with No Subsequent Return to Non-Significant Group Differences. Group Differences That Emerged at 6 Months are also Shown for Indicative Purposes.

**Table 2.** Performance Metrics of Predictive Classification Models Using Baseline and 6-Month Data

| Sample | Data | BAC (%) | Sensitivity (%) | Specificity (%) | AUC (CI) |
|---|---|---|---|---|---|
| Discovery (Neurapro) | Baseline | 59.2 | 59.2 | 59.2 | 0.62 (0.54–0.71) |
| | 6-months | 69.6 | 60.5 | 78.6 | 0.79 (0.72–0.86) |
| | Baseline + 6-months | 70.4 | 63.2 | 77.7 | 0.79 (0.72–0.86) |
| External validation (STEP) | Baseline | 64.4 | 67.9 | 60.0 | 0.68 (0.58–0.76) |
| | 6-months | 72.1 | 64.3 | 80.0 | 0.82 (0.76–0.89) |
| | Baseline + 6-months | 73.2 | 67.9 | 78.5 | 0.82 (0.76–0.89) |

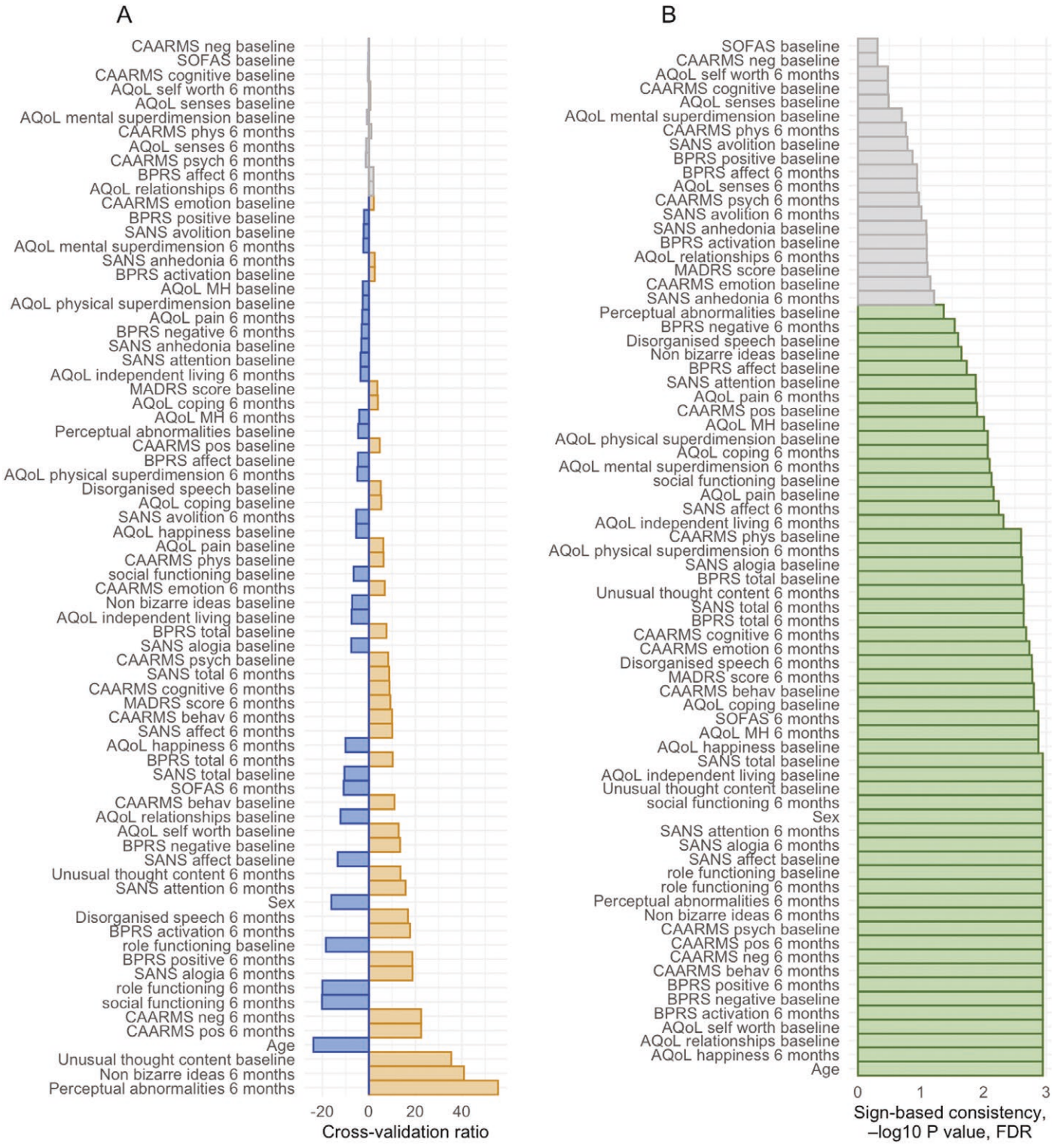


**Figure 3.** The Reliability of Predictors in the Combined Baseline-6-Month Model was Evaluated Using Cross-Validation Ratio Mapping (A) and the Significance of Predictive Features Used by the Model was Assessed by Means of Sign-Based Consistency Mapping (B). Both Visualization Methods are Detailed in Supplementary Materials.

75% overlap APS vs transition; 78% overlap remission vs transition). See Figure S2 and Table S14 for full details.

### *Comparison of Post-transition Outcomes*

Post-transition role but not social functioning was lower in the transition group compared to the remission and persistent APS groups at the 12-month follow-up. Role functioning was lower in the transition group compared to the remission and persistent APS groups at 24-month follow-up, however, social functioning was only lower in the transition group compared to the remission group at this timepoint (Figure S3 and Table S16).

### *Clinical and Functional Trajectories*

Following FDR correction, group-by-time interactions were observed for 12 variables in the STEP sample, with overlap observed across 9 measures between Neurapro and STEP (86% overlap across all measures). See Table S18 and Figure S4 for full details.

### *Supplementary Machine Learning Analyses*

Neither combining samples nor including cognition in the Neurapro analysis improved prediction performance. Full details are provided in supplementary materials.

## Discussion

This study is the first to date to: (1) compare clinical and functional outcomes in UHR individuals with persistent APS compared to both those who later transition and those who achieve sustained remission, (2) investigate the timing of early symptom and functioning divergence between subgroups of UHR individuals, and (3) predict non-remission vs sustained remission of UHR status using baseline and 6-month follow-up data both separately and combined.

Across 2 independent samples, individuals with persistent APS and those who later transitioned to psychosis demonstrated poorer clinical and functional outcomes compared to individuals who remitted from UHR status at 12- and 24-months, with medium to large effect sizes. These group differences were observed over a broad range of symptom measures, including positive, negative, depressive, and basic symptoms, as well as general psychopathology and multiple measures of social and occupational functioning and quality of life. Indeed, individuals with persistent APS much more closely resembled individuals who later transitioned to psychosis than those who achieved UHR remission at both 12- and 24-months. Non-psychotic diagnoses were high across all 3 groups, but the persistent APS and transition groups had significantly higher rates of depression compared to the remission group at 24 months. Consistency of these findings across samples was highest when comparing the persistent APS and transition groups to those who remitted, although consistency was very high across all groups at 24 months, highlighting the external validity of the findings. Finally, differences in functioning between those with persistent APS and those who transitioned were largely not observed until the post-transition assessment. While these findings are suggestive of a drop in functioning post-transition, it is interesting to note that post-transition functioning in the transition group was similar to baseline functioning in the persistent APS group. As such, it is possible that poor functioning is associated with periods of clinical instability, such as symptom onset or exacerbation, rather than with transition specifically.

Poor outcomes in the persistent APS group highlight that outcomes beyond transition to psychosis need to be considered in UHR populations, both in clinical and research settings. In particular, the persistence of psychotic symptoms, even at a "subthreshold" level, may be an important indicator of poor outcomes in UHR individuals regardless of their transition status. Current guidelines for the treatment of early psychosis clearly indicate different intervention pathways for UHR and first-episode psychosis stages, with longer and more intensive treatment recommended for FEP.[44–46] While these guidelines are necessary to prevent overtreatment and overmedication of UHR individuals who are unlikely to go on to develop full-threshold psychosis (42% and 51% of participants in the current study samples), they fail to recognize that individuals with APS lasting months or years may require more extended, intensive clinical care beyond that what is currently provided. Although many UHR services offer care for 12 months or longer,[16] this is not universally the case and UHR patients are increasingly being seen in primary care services, where the tenure of care may be shorter.[47] Thus, basing intervention decisions solely on a transition/non-transition binary may result in a large proportion of UHR individuals not receiving the required level of care. This issue is only likely to be exacerbated by the development and application of risk calculators that focus solely on the transition to the exclusion of other possible outcomes.[39,48,49] Thus, there is a critical need for research approaches that focus on identifying possible biomarkers for persistent APS and the development of new treatment approaches that specifically target this population.

Consistent with previous studies,[6,7] the current study observed few baseline differences between individuals who experienced persistent APS and those who achieved sustained remission at follow-up. Furthermore, the persistent APS and transition groups also demonstrated a very high degree of similarity in terms of their baseline symptoms and functioning. However, we were able to identify several measures on which the outcome groups diverged within the first 6 months of the study. Namely, differences in positive and depressive symptoms, quality

of life, and functioning began to appear between those who remitted and both the persistent APS and transition groups within the first 3 months of follow-up. Conversely, differences in trajectories between the persistent APS group and the transitioned group were identified on fewer measures and, when they could be identified, they occurred later in follow-up (months 4 or 6). Early divergence in trajectories across measures between those who remit and those who do not suggest that monitoring a patient's progress on these measures over a relatively short period of time may provide an indication of their likely clinical outcome. Importantly, in the current study, we observed that individuals who achieved sustained remission showed relatively rapid improvements in both symptoms and functioning across several measures, whereas these improvements were attenuated in those with persistent APS and those who transitioned. Thus, failure to show early improvement may be an important clinical indicator of later poor outcomes in UHR individuals and suggests the need for change of treatment approach. Furthermore, later divergence between the transition and persistent APS groups indicates that differentiating outcomes of these groups based on the unfolding clinical picture may be more challenging and not apparent until later in the follow-up period.

Given the observed divergence in clinical and functioning trajectories between groups within the first 6 months of the study, we performed exploratory machine learning analyses to determine whether clinical outcomes could be predicted using data from baseline, 6-month follow-up, or combined baseline, and 6-month data. Consistent with the minimal baseline differences observed between outcome groups, we found that accurate prediction of outcome using baseline data alone was not possible. These findings are consistent with a recent study predicting remission vs non-remission in the North American Prodrome Longitudinal Study (NAPLS) using baseline data, which achieved an AUC of 0.66 and incorrectly predicted almost half of individuals not achieving remission to be in the sustained remission group.[50] However, in the current study, prediction accuracy improved substantially when 6-month follow-up or combined baseline and 6-month follow-up data were used, with an AUC of 0.82 in both instances in the external validation sample. In the combined model, the most stable predictors of non-remission were perceptual abnormalities, non-bizarre ideas, total positive symptoms at the 6-month follow-up, and unusual thought content at baseline. Conversely, stable predictors of sustained remission included measures of social and role functioning at the 6-month follow-up, as well as age and sex measured at baseline.

Together, our findings indicate that, while predicting an individual's likelihood of non-remission (i.e., persistence of APS or transition to psychosis) at baseline is challenging, combining baseline and early follow-up data can substantially improve risk estimates. This is consistent with the dynamic nature of early psychopathology,[10] and highlights the importance of longitudinal monitoring of symptoms and functioning at-risk individuals. These findings also have important clinical implications: namely, that using longitudinal information would allow clinicians to dynamically update risk predictions following a period of care, and adapt intervention strategies accordingly. If symptomatic and functional improvement is not evident in the early months of treatment this may be a red flag that the treatment approach needs to be modified to avoid the persistence or deterioration of attenuated psychotic symptoms. In the current study, the 6-month follow-up was selected as the earliest timepoint where assessments in our discovery and validation samples overlapped. However, future studies with multiple early follow-up timepoints, such as the Accelerating Medicines Partnership Schizophrenia study,[51] would be well-positioned to explore whether prediction can be enhanced by incorporating even earlier follow-up data.

### Limitations

The current study should be considered in the context of several limitations. First, the maximum follow-up period for participants across both samples was 2 years. This may not be sufficient to capture final clinical outcomes for all UHR individuals as previous studies found that around 20% of transitions occurred beyond 2-year follow-up.[52] Thus, the ability to predict outcomes using baseline and/or 6-month data may increase with longer follow-up periods. Loss of participants over the follow-up period was also higher in the transition group compared to the persistent APS and remission groups, particularly at 24 months. Studies that follow transitioned participants for longer periods are therefore required to fully tease apart potential group differences between individuals with persistent APS and those who transition in the medium-to-long term. Second, both study samples were drawn from clinical trials rather than observational studies. While a recent meta-analysis did not find differences in transition rates between cohort studies and clinical trials,[53] it is unclear whether participation in a clinical trial may have unique impacts on outcomes in UHR populations. However, while it was not possible to examine treatment-related differences in outcomes in the STEP study due to the complex design, there were no differences in outcome status between those who received omega-3 fatty acids vs placebo in the Neurapro study. Finally, sample sizes were relatively small for prediction purposes. However, SVMs are well-suited for smaller datasets due to their reliance on support vectors, regularization to prevent overfitting, and ability to handle high-dimensional data.[54–56] Moreover, the consistency of external validation results with discovery findings further supports the robustness and generalizability of the model, even with a limited sample size.

## Conclusions

Overall, this study supports previous research in highlighting the importance of considering not just transition but also the persistence of APS as both a key outcome in UHR studies and as an indicator necessitating more intensive and prolonged intervention in clinical settings.[7,8] Our findings also demonstrate that UHR individuals who achieve sustained remission begin to diverge quite rapidly from those who transition or experience persistent APS across several symptom and functioning domains. Conversely, those with persistent APS and those who transitioned demonstrated similar trajectories to those who later transitioned, particularly on functioning measures. When individuals with persistent APS and those who transitioned were combined into a non-remission group, we found that prediction of non-remission vs sustained remission using baseline data was challenging, however, the addition of 6-month follow-up data substantially improved prediction accuracy. As such, our results highlight the essential role of longitudinal data in designing personalized care and enhancing the accuracy of risk prediction models in UHR populations.

## Supplementary material

Supplementary material is available at https://academic.oup.com/schizophreniabulletin/.

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## Conflict of Interest

Nelson, Hickie, Yung, and Amminger have received National Health and Medical Research Council (NHMRC) funding. No other conflicts were reported. McGorry reported grants from the National Institute of Mental Health during the conduct of the study; in addition, McGorry had a patent for AU 2015203289 issued, a patent for US 9884034 issued, a patent for US 15/844444 issued, and a patent for CA 2773031 issued; and he has received past unrestricted grant funding from Janssen-Cilag, AstraZeneca, Eli Lilly, Novartis, and Pfizer, and honoraria for consultancy and teaching from Janssen-Cilag, Eli Lilly, Pfizer, AstraZeneca, Roche, Bristol Meyers Squibb, and Lundbeck. He has received grant funding from the Colonial Foundation, the National Health and Medical Research Council of Australia, Australian Research Council, NARSAD, the Stanley Foundation, NIH, the Wellcome Trust, and the Australian and Victorian governments. Yuen reported grants from National Institutes of Health during the conduct of the study. Spark reported grants from National Institute of Health during the conduct of the study. Niendam reported grants from National Institute of Health during the conduct of the study; and owning shares in and being a founder and board member of Safari Health, Inc., outside the submitted work.

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