HHS Public Access

Author manuscript

Am J Psychiatry. Author manuscript; available in PMC 2020 August 01.

Published in final edited form as:

Am J Psychiatry. 2020 February 01; 177(2): 164–171. doi:10.1176/appi.ajp.2019.18111290.

Characterizing covariant trajectories of individuals at clinical high-risk for psychosis across symptomatic and functional domains

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Abstract

Objective—The outcomes of individuals at clinical high-risk for psychosis are known to be heterogenous, but whether different outcome groups can be ascertained with respect to distinct covariant trajectories across multiple domains of symptoms and functioning is unclear.

Method—Group-based multi-trajectory modeling was applied to longitudinal ratings of four symptom domains (positive, negative, disorganized, general) and general functioning among clinical high-risk subjects in an initial discovery sample (N = 422). An independent sample (N = 133) was used to test replicability.

Results—Three trajectory groups were identified among clinical high-risk individuals in the discovery sample: Group 1 (30%) exhibited substantial improvement across all domains, with half exhibiting positive outcomes for both functioning and positive symptoms; Group 2 (49%) exhibited moderate impairments across domains with approximately one quarter meeting criteria for positive outcomes, and the remaining subjects (Group 3; 22%) exhibited consistent levels of severe impairment across domains and did not experience positive outcomes. These trajectory groups and remission patterns replicated in an independent sample.

Conclusions—Replicable subgroups of help-seeking clinical high-risk cases can be ascertained based on distinctive profiles of change over time in symptoms and functioning. Within each of the three identified subgroups, similar patterns of change (i.e., rapid, moderate, or no improvement) were observed across the four symptom domains and functioning. This consistency of change over time across domains within each subgroup is a novel observation supporting the syndrome consistency of clinical high-risk symptoms and signs. The observed trajectory subgroups are suggestive of different degrees of need for clinical interventions, ranging from minimal/supportive for about one-third of cases to increasingly intensive among the remainder.

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Introduction

The clinical high-risk paradigm was developed in the 1990's as a framework for identifying predictors and mechanisms of onset of psychosis, toward the broader goal of stimulating early detection and intervention programs that could lead to improved long-term outcomes (1). During the intervening years, it has become increasingly apparent that the clinical high-risk syndrome is itself associated with significant burdens, independently of whether it precedes conversion to a psychotic disorder (2). Individuals meeting clinical high-risk criteria are distressed and seeking treatment (3). Although by definition their positive symptoms (i.e., delusions, hallucinations, thought disorder) are at sub-psychotic intensity, these symptoms are nevertheless disruptive and rate-limiting for social and role functioning (4), on average at about the level associated with major depressive disorder with comorbid alcohol abuse (5). Better characterization and quantification of the clinical course and functional outcomes of clinical high-risk individuals is needed to optimize the design and implementation of early detection and intervention programs for young people with and at-risk for psychosis.

Prior work has shown that most "non-converters" continue to experience attenuated positive symptoms for at least two years after first seeking help (6), and functioning tends to remain substantially impaired as well (7–9). Nevertheless, a portion of clinical high-risk individuals experience remission of positive symptoms (10), with some also achieving functional remission (11,12). Among those who do recover, remission of positive symptoms tends to be reached sooner than functional remission (11,13), suggesting that rates of improvement may differ across domains. Recent work has expanded the range of outcomes of interest in the clinical high-risk population to include symptomatic and functional recovery, remission, recurrence, and relapse (14). However, the criteria for such outcomes have been pre-defined rather than discovered in the data. Longitudinal approaches that can ascertain covariant patterns across multiple symptom trajectories over time are needed to capture and quantify the variations in course and outcome among clinical high-risk individuals.

Here we used group-based multi-trajectory modeling, a discovery-oriented statistical approach similar to latent growth class analysis, to characterize the longitudinal trajectories of symptoms in four domains (positive, negative, disorganized, general) as well as general functioning among help-seeking clinical high-risk individuals. We used independent discovery (NAPLS2, $N = 422$) and replication (NAPLS1, $N = 133$) datasets to identify and assess the replicability of trajectory patterns across samples. We also assessed rates of favorable vs unfavorable outcomes for functional and positive symptoms based on pre-specified criteria within the identified trajectory groups to further characterize differences in outcomes among clinical high-risk individuals.

Methods

Participants

NAPLS2—The North American Prodrome Longitudinal Study (NAPLS2) was a consortium study investigating the prodromal phase of psychosis at eight sites (UCLA, Emory, Harvard, Hillside Hospital, UCSD, UNC-Chapel Hill, Calgary, and Yale). Help-

seeking individuals were enrolled if they met criteria for a clinical high-risk syndrome as per the Structured Interview for Prodromal Risk Syndromes (15) or, if 18 or younger, met criteria for schizotypal personality disorder. Other inclusion criteria included age 12–35 years old, no current or lifetime diagnosis of Axis I psychotic disorder (including affective psychoses), IQ > 70, no history of a central nervous system disorder, no substance dependence in the past 6 months, and sub-psychotic symptoms not clearly caused by an Axis I disorder. Recruitment took place between 2008 and 2012, and a total of 764 clinical high-risk individuals participated in the study. Participants were followed for up to 5 visits occurring every 6 months across 2 years or until the point of conversion to psychosis if it occurred earlier (16). Information gathered at each visit included current symptom ratings using the Structured Interview for Prodromal Symptoms (SIPS), current functioning indexed by the Global Assessment of Functioning (GAF) scale, and conversion to psychosis as defined by thresholds on the SIPS. Subjects provided written informed consent after receiving a complete description of the study.

To facilitate quadratic longitudinal modeling, data from a minimum of three visits were required (see online supplement for participant flow chart). Excluded participants who completed two or less visits (N = 340) did not differ significantly from the analytic sample (N = 422) on age, sex, race, or highest parent education level, but were more likely to convert to psychosis (i.e., because most conversions occurred before the 12-month follow-up, which for most subjects represented the third assessment point) (see online supplement). Of the 422 included participants, 193 completed all five assessments, 110 participated in four assessments, and 119 engaged in three assessments. Predominant reasons for study drop-out included: no-show, conversion to psychosis prior to the third visit, and participant unable to be scheduled (see online supplement). Individuals with missing data (i.e., 3 or 4 visits) were more likely to be male (see online supplement). Accounting for dropout and sex in the final trajectory model did not substantially change results (see online supplement).

Some individuals who converted to psychosis completed three or more visits prior to converting (n = 19, 4.5%) and were included in one version of the analyses. Inclusion of these eventual converters supported generalization of results to the population of help-seeking clinical high-risk individuals presenting at baseline, independent of their long-term outcomes. Data from conversion visits were not included because visits were not confined to the regular 6-month assessments. In a secondary version of the analyses, exclusion of converters did not substantially change model parameters (see online supplement).

NAPLS1—As a test of replication, we utilized data from the first phase of the NAPLS consortium (NAPLS1), which combined data collected at the study sites between 1998 and 2005 (17). Clinical high-risk participants met criteria for a prodromal risk syndrome based on the SIPS interview at baseline. Though there was some variability in study design across sites, all included clinical evaluations at 6-month intervals up to 30 months and collected the SIPS and GAF at each visit. To facilitate comparison to NAPLS2, only individuals meeting clinical high-risk criteria were included in the study (N = 510) and data from the 30-month visit were omitted (see online supplement for participant flow chart). Participants who were simultaneously enrolled in medication trials (N = 47) were also excluded (see online

supplement). The NAPLS1 and NAPLS2 samples were completely independent and non-overlapping.

Of the 463 clinical high-risk participants, 133 (28.7%) participated in three or more visits and were included in the analytic sample. Compared to subjects with three or more assessments, individuals who completed one or two visits were more likely to have converted to psychosis in the first 12 months and to have parents who completed high school or less (see online supplement). Of the 133 participants in the analytic sample, 51 completed three assessment visits, 43 completed four visits, and 39 completed all five visits. Dropout was associated with higher baseline GAF scores (see online supplement). Analyses were re-run including dropout and baseline GAF parameters and suggest that group membership of Group 1 may be inflated by 3–5% and Group 2 size may be deflated by a similar amount in final models (see Results and online supplement). No substantial changes in model derivation or parameters were observed when eventual converters *(n* = 19) were excluded (see online supplement).

Symptom and Function Measures

In both NAPLS2 and NAPLS1, current functioning and symptom severity were indexed using GAF and the Scale of Prodromal Symptoms (SOPS) as assessed in semi-structured clinical interviews by trained raters (16,17). GAF scores index impairment in terms of symptoms and functioning across social, work, and school domains, and scores range from 1 to 100. The SOPS is used to assess the severity of symptoms within four domains: Positive, Negative, Disorganized, and General. Each domain consists of 4–6 items and is rated in severity ranging from absent (0) to extreme (6). On the positive scale only, a rating of “3” on any item indicates severity consistent with prodromal criteria, and “6” on any item indicates “severe and psychotic” and connotes conversion to psychosis. To reflect overall impairment, scores were summed for items within each domain to create composite scores (e.g., “sum of severity of positive symptoms”) at each visit. Possible scores ranged from 0 to 24 (Disorganized, General), 25 (Positive), or 36 (Negative). As the study was focused on prodromal symptoms, the lowest possible positive score was “3” at baseline.

Data Analyses

Analyses were conducted in SAS 9.4 using PROC TRAJ (18). Graphs were made in R using ggplot2 (19) and gridExtra (20). Start values were tested in STATA 15 using a macro created by Bobby Jones (personal communication, 4.12.18).

Discovery of symptom and functioning multi-trajectory groups—We used group-based multi-trajectory modeling, a form of latent growth class analysis, to identify common trajectories of symptoms and functioning in NAPLS2. This method is used to approximate the true distribution of trajectories by discovering subgroups of individuals that follow similar patterns of change across time on multiple variables (18). Notably, models simultaneously considered scores for symptom severity across four domains (positive, negative, disorganized, general) and functioning (GAF) at each visit when constructing models and assigning group membership.

To identify the number of distinct, stable trajectories that would be important to represent in multi-trajectory models and check statistical assumptions, models for each dimension were first estimated individually (see online supplement). Model comparison began with estimation of one class and increased in number until model fit indices did not meet recommended thresholds or identify theoretically meaningful trajectories. We examined recommended fit indices: lower absolute value Bayesian information criteria and log likelihood relative to the previous model, posterior probability of assignment to groups > 0.7, group size > 5%, and odds of correct classification > 5. Spaghetti plots of individual data trajectories along with estimated group trajectories were used to visually assess data separation and model fit for final univariate models. Guidelines for reporting on latent trajectory studies were followed (21) (see online supplement). Final univariate and multivariate models were tested with 100 sets of start values to assess the likelihood that global maxima were met.

Assessing pattern replicability and comparing models—The NAPLS1 dataset was used to assess the replicability of multi-trajectory patterns derived in the NAPLS2 dataset. Univariate trajectory models were assessed in the same manner as in NAPLS2 (see online supplement). A multi-trajectory model with the same number of groups and parameters used in NAPLS2 was fit to the NAPLS1 data. Trajectory parameters were compared across samples using bootstrapped confidence intervals for each parameter, created by deriving model parameter estimates from 1000 subsets of 133 individuals (i.e., the size of the NAPLS1 sample) from the NAPLS2 dataset. Replication criteria were met if the NAPLS1 parameter fell within the 95% confidence interval of the bootstrapped NAPLS2 parameter distribution (see online supplement).

Outcomes—In both samples, remission of positive symptoms was defined as the absence of any positive symptoms with a severity rating of 3 or greater at a given visit (22), as per prodromal criteria. The threshold for functional remission was set at a GAF score of 61 (“both mild persistent symptoms and some difficulty in social, work, and school functioning”) (11,23,24) (see online supplement for analyses with a higher functional threshold). The frequency of a variety of outcomes for positive symptom severity and functioning were assessed within each trajectory group: persistent impairment (i.e., remission criteria never met), remission (i.e., remission criteria met at the final visit), recurrence (i.e., remission criteria met but not sustained), recovery (i.e., remission criteria sustained across at least two visits), and relapse (i.e., remission criteria met for two visits followed by recurrence). Outcomes were further grouped into “favorable outcomes” (remission and recovery) and “unfavorable outcomes” (persistent impairment, recurrence, relapse) (14,25). Rates of favorable vs unfavorable outcomes were compared between groups using Wald X^2 tests (two-tailed).

Results

Model Derivation

Among participants in NAPLS2 (N = 422), the mean age at baseline was 18.5 years (SD = 4.3) and 59.2% were male. The sample was predominantly Caucasian (55.9%), 17.1% were

African-American, and 27.0% fell into other categories (e.g., Asian, multiracial). The highest parent education level was high school or below for 17.5% of the sample.

We selected the three-group model because the groups appeared theoretically meaningful and criteria for parameters assessing model fit were exceeded, indicating that groups were stable and distinct from one another (see online supplement). Figure 1 displays the trajectories of each of the three groups across the five assessed domains. The three groups corresponded to: 1) individuals who improved rapidly across functioning and all symptom domains and generally exhibited minimal impairment by the end of the study (Group 1, 29.6%; 2) those who exhibited moderate levels of functional impairment and symptoms across all domains at baseline with some improvement across the study (Group 2, 48.9%); and 3) individuals who exhibited high levels of functional impairment and symptom severity with no improvement (i.e., nonsignificant quadratic and linear parameters) across domains except positive symptom severity (Group 3, 21.5%).

The three derived trajectory groups did not differ significantly on age, sex, race, or mean number of visits (see online supplement). The groups differed significantly on parental education, with Group 2 exhibiting the lowest percentage of parents who completed high school or less (11.3%), followed by Group 3 (20.9%) and Group 1 (25.2%), $\chi^2(2) = 11.27$, $p = .007$.

Rates of favorable outcomes (i.e., remission or sustained recovery) on positive symptom severity and functional impairment also differed significantly across groups (Figure 2, also see online supplement). Within Group 1, over half of participants exhibited favorable outcomes on positive symptom severity or functional remission, and 47% achieved favorable outcomes on both domains. In contrast, approximately one third of Group 2 participants reached favorable outcomes on positive symptom severity and functional outcomes, but few (5%) exhibited favorable outcomes in both domains. Very few participants within Group 3 (13%) achieved favorable outcomes on positive symptom severity, even fewer (5%) exhibited favorable functional outcomes, and less than 1% showed favorable outcomes on both.

Model Validation

Among participants in NAPLS1, the mean age at baseline was 18.0 years (SD = 4.6) and 61.7% were male. The sample was predominantly Caucasian (79.0%), 6.8% were African-American, and 14.3% fell into other categories (e.g., Asian, multiracial). The highest parent education level was high school or below for 12.8% of the sample.

To assess the replicability of trajectory patterns identified in the NAPLS2 sample, a three-group quadratic model was derived and assessed in NAPLS1 ($N = 133$). Criteria for model fit and reliability were met (see online supplement Table 2) and the three derived groups (Figure 3) resembled those derived in NAPLS2, ranging from 1) individuals who improved rapidly across functioning and all symptom domains and generally exhibited minimal impairment by the end of the study (Group 1, 26.7%); 2) those who exhibited moderate levels of functional impairment and symptoms across all domains at baseline with some improvement (Group 2, 54.9%); and 3) individuals who exhibited high levels of functional

impairment and symptom severity with no improvement (i.e., nonsignificant quadratic and linear parameters) across all domains (Group 3, 18.4%). Of note, dropout analyses suggest that Group 1 size estimates may be inflated by 3–5% and Group 2 estimates may be deflated by a similar amount in the final model (see online supplement).

The three derived trajectory groups did not differ significantly on race, parental education, or mean number of visits (see online supplement). The groups differed significantly on age at baseline, with Group 3 exhibiting the lowest mean age (mean=16.55, *SD*=2.85), followed by Group 2 (mean=17.54, *SD*=4.13) and Group 1 (mean=20.01, *SD*=5.77), $F(2) = 5.51$, $p = .005$.

Rates of favorable outcomes on positive symptom severity and functional impairment also differed significantly across groups (Figure 4, also see online supplement). Within Group 1, over three-fourths of participants exhibited favorable outcomes on positive symptom severity or functional remission, and a majority (60%) achieved favorable outcomes on both domains. In contrast, approximately 40–50% of Group 2 participants reached favorable outcomes on positive symptom severity and functional outcomes. Fewer participants within Group 3 achieved favorable outcomes on positive symptom severity (30%), only 3% exhibited favorable functional outcomes, and less than 1% achieved favorable outcomes across both symptoms and functioning.

Model Comparison

To compare the model estimates identified in NAPLS2 and NAPLS1, trajectories from both samples were plotted together (Figure 5) and model parameters were compared using bootstrapped confidence intervals (see online supplement). Differences between NAPLS2 and NAPLS1 trajectory model parameters (two-tailed $p < .05$) were observed for quadratic and slope parameters for Group 2 Positive, Disorganized, and General symptoms (steeper in NAPLS1) and intercepts for Group 2 Positive symptoms (higher in NAPLS2). These findings indicate full statistical replicability for Groups 1 and 3, and partial statistical replicability for Group 2. Despite increased heterogeneity in Group 2 slopes and quadratic terms across samples, the conceptual definition of this group (i.e., moderate improvement across domains, with highest rates during the first 6–12 months of follow-up) was consistent across samples (Figure 5).

Discussion

We identified three trajectory groups of clinical high-risk individuals that captured most variation across outcome dimensions throughout the two-year NAPLS2 study. The patterns of the three trajectory groups broadly replicated statistically and conceptually in the independent NAPLS1 sample, suggesting that the identified groups are reliable and may be generalizable to the broader clinical high-risk population. Of the three identified groups, patterns ranged from substantial improvement with high rates of favorable outcomes to stable impairment across functioning and symptom domains. Group 1 exhibited rapid improvement across all domains, and close to half of the members exhibited favorable outcomes on both functioning and positive symptoms at their last visit. Group 2 demonstrated moderate improvement across symptom and functioning domains, with

approximately a quarter of individuals reaching favorable outcomes on indices of functioning and positive symptoms. In contrast to Groups 1 and 2, Group 3 exhibited consistent levels of moderate to severe impairment in functioning and symptom severity across domains that persisted across the two-year period and generally did not reach any remission criteria.

With knowledge of these profiles, we may be able to develop prediction models using baseline data that could inform needs for treatment. For example, Group 3 would likely require substantial intervention for impairments across functioning and symptom domains, whereas Group 1 may need only short-term support and monitoring and Group 2 may need an intermediate level of support. Post-hoc analyses indicated lower rates of comorbid affective and non-cluster A personality disorders within Group 1 relative to Groups 2 and 3 but did not identify differences between Group 2 and Group 3, indicating that the burden of additional psychopathology does not fully explain differences in severity of impairment (see online supplement). Prediction of outcome profiles in addition to conversion may also improve signal-to-noise in clinical trials, as individuals who will likely remit quickly on the target symptoms (i.e., Group 1) could potentially be excluded. Further assessment of predictors and biological correlates may also yield insight into different mechanistic pathways that contribute to the clinical high-risk phenomenon and could provide a platform for individualized early treatment and intervention.

There are a number of limitations associated with data-driven approaches to trajectory modeling. To facilitate quadratic modeling, only individuals with at least three visits were included in the analytic sample. This approach narrows the interpretation of our findings to help-seeking clinical high-risk individuals who participated in at least a year of follow-up assessments. As many individuals who converted to psychosis did so within the first year of study follow-up (26), these trajectory groups do not capture functional and symptomatic patterns prior to conversion for most converters. However, other prediction approaches have been developed for conversion (3) that are complementary to the present approach, and together these tools capture a wider range of the outcomes of help-seeking clinical high-risk individuals. A second limitation of trajectory modeling, and of longitudinal studies broadly, is the influence of missing data on model parameters. The majority of our participants missed at least one of the four bi-yearly follow-up visits, and we thoroughly assessed the missing at random assumption and potential influence of differential rates of attrition across trajectory groups (see online supplement). The only effect observed was a shift in NAPLS1 group membership sizes of 3–5% for Groups 1 and 2, which we noted in our interpretation of this model. As model selection is influenced by the number of assessments, length of follow-up, and sample size ($N < 200$), different study designs may lead to alternate models. Lastly, trajectory modeling inherently simplifies the variability of individual trajectories within each class. Some individuals may exhibit greater change compared to others within their group, and conclusions about individual outcomes should be approached with caution. Broadly, it is important to keep in mind that the identified trajectories are estimates of common outcome patterns among the help-seeking clinical high-risk population (27).

In summary, we identified three profiles of clinical high-risk longitudinal trajectories indicative of: rapid symptomatic and functional improvement with high rates of positive

outcomes, moderate gains in symptomatic and functional improvement with ongoing need for support, and stable, chronic impairment in symptoms and functioning. These differences in outcomes highlight the need for individualized treatment for this population and the potential for prediction of subgroup outcomes to improve opportunities for early intervention and treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Disclosures and acknowledgements

Tyrone Cannon is a consultant to Boehringer Ingelheim Pharmaceuticals and Lundbeck A/S. No other authors reported potential conflicts of interest.

Supported by grants: This work was supported by NIH grants U01 MH081902 (Cannon), P50 MH066286 (Bearden), U01 MH081857 (Cornblatt), U01 MH82022 (Woods), U01 MH066134 (Addington), U01 MH081944 (Cadenhead), R01, U01 MH066069 (Perkins), R01 MH076989 (Mathalon), U01 MH081928 (Seidman), U01 MH081988 (Walker). Dana Allswede's work was funded by NSF Graduate Research Fellowship (DGE-1122492).

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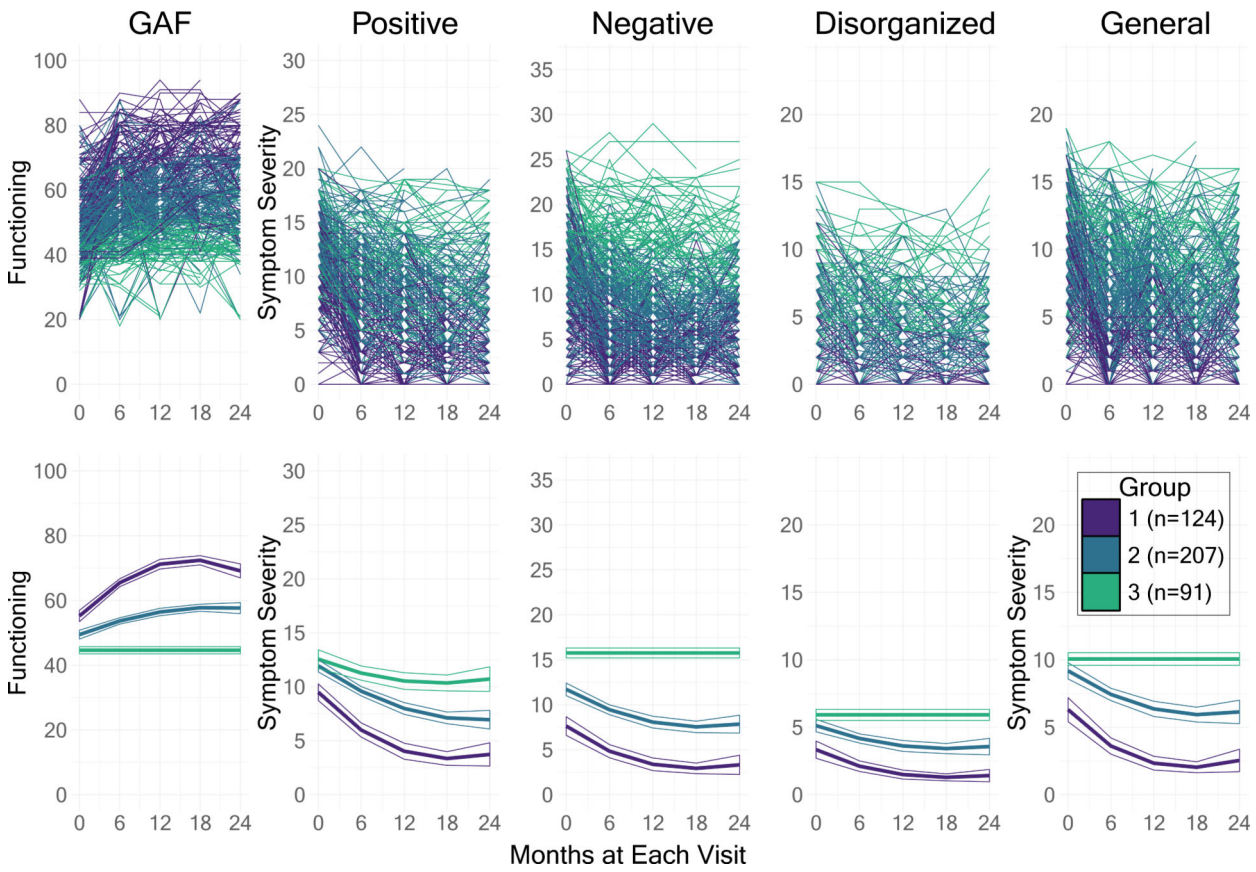

Figure 1.

Individual trajectories and group trajectory estimates for functioning (GAF) and symptom severity across SOPS domains for the three derived groups in NAPLS2 (distinguished by color).

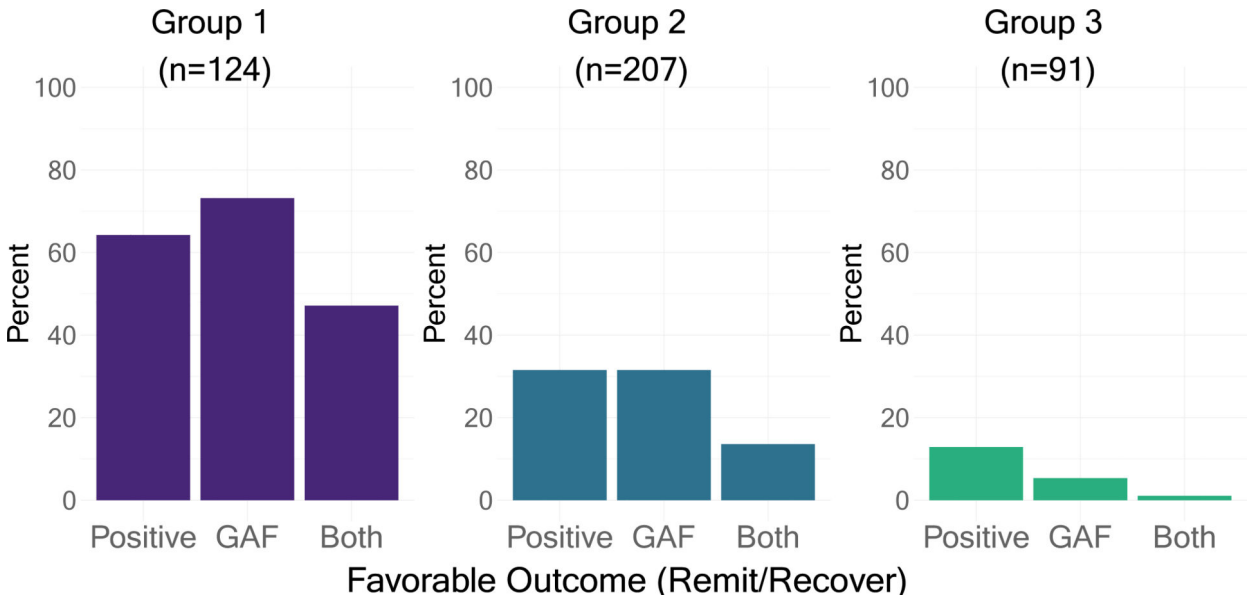

Figure 2.

Percent of individuals in NAPLS2 who exhibited favorable outcomes (i.e., remitted or recovered) on positive symptom severity, functional impairment, or both within each group.

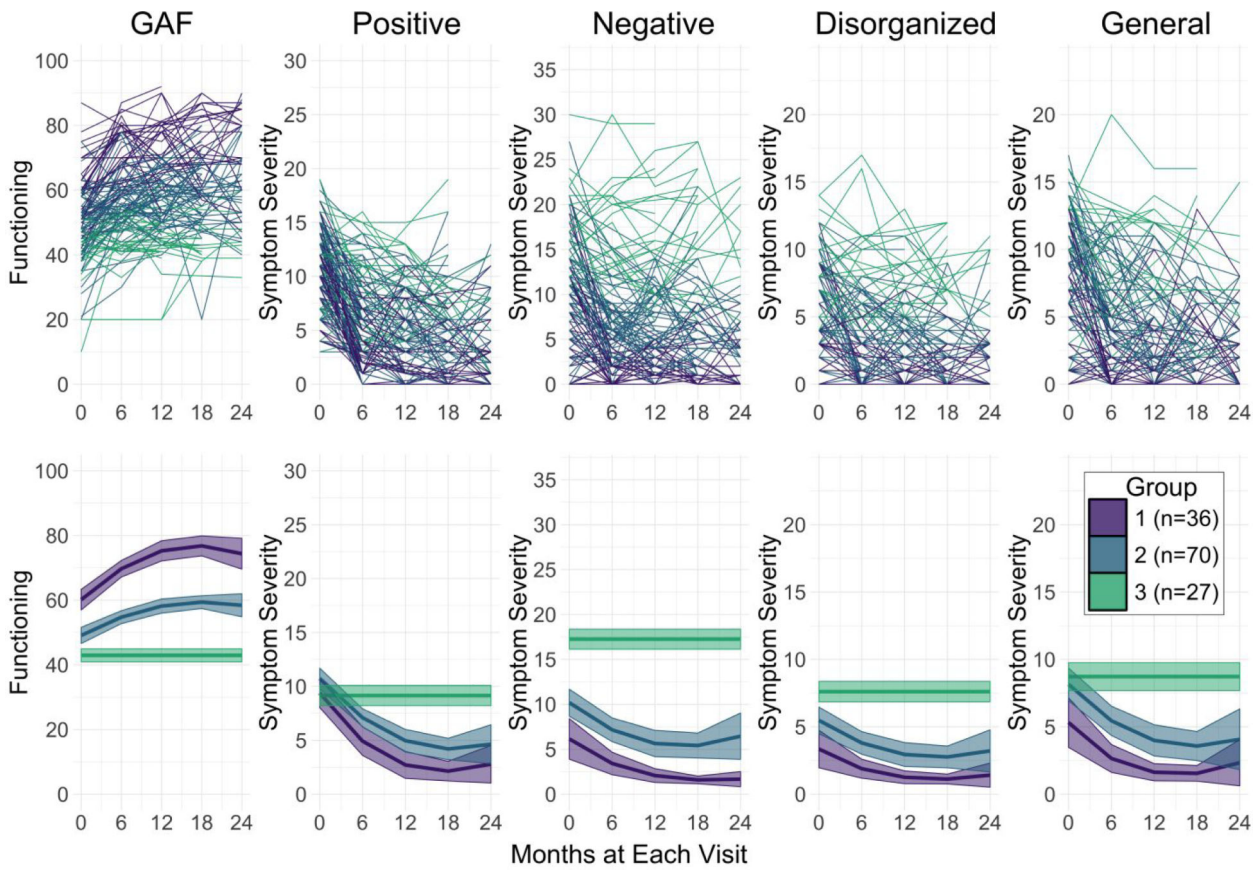

Figure 3.

Individual trajectories and group trajectory estimates for functioning (GAF) and symptom severity across SOPS domains for the three derived groups in NAPLS1 (distinguished by color).

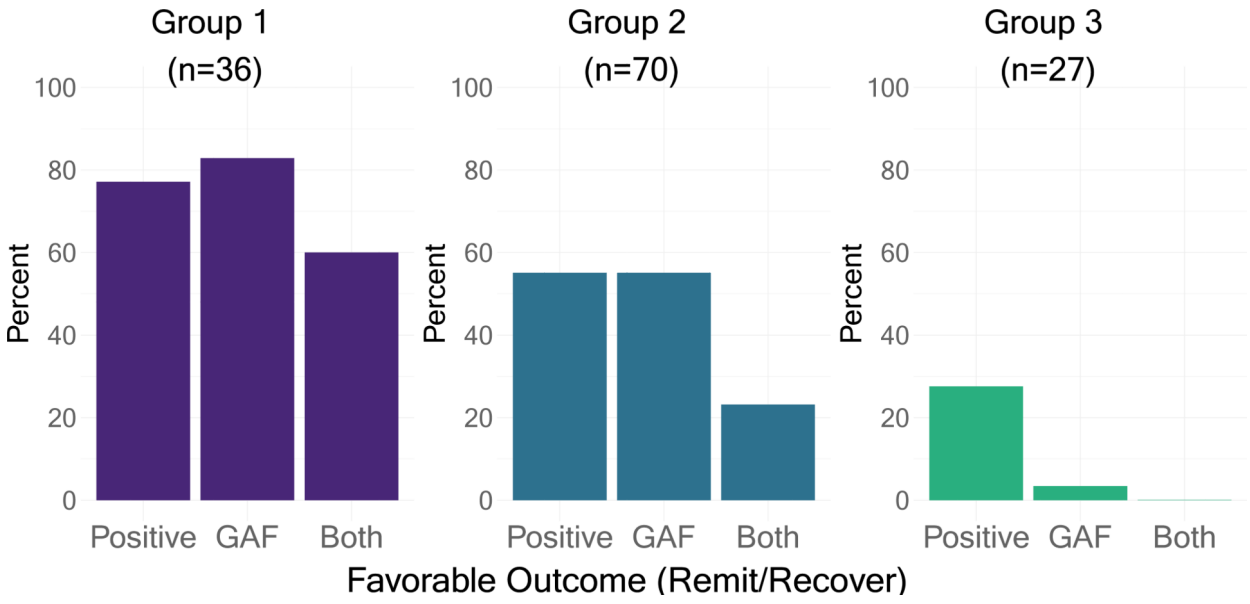

Figure 4.

Percent of individuals in NAPLS1 who exhibited favorable outcomes (i.e., remitted or recovered) on positive symptom severity, functional impairment, or both within each group.

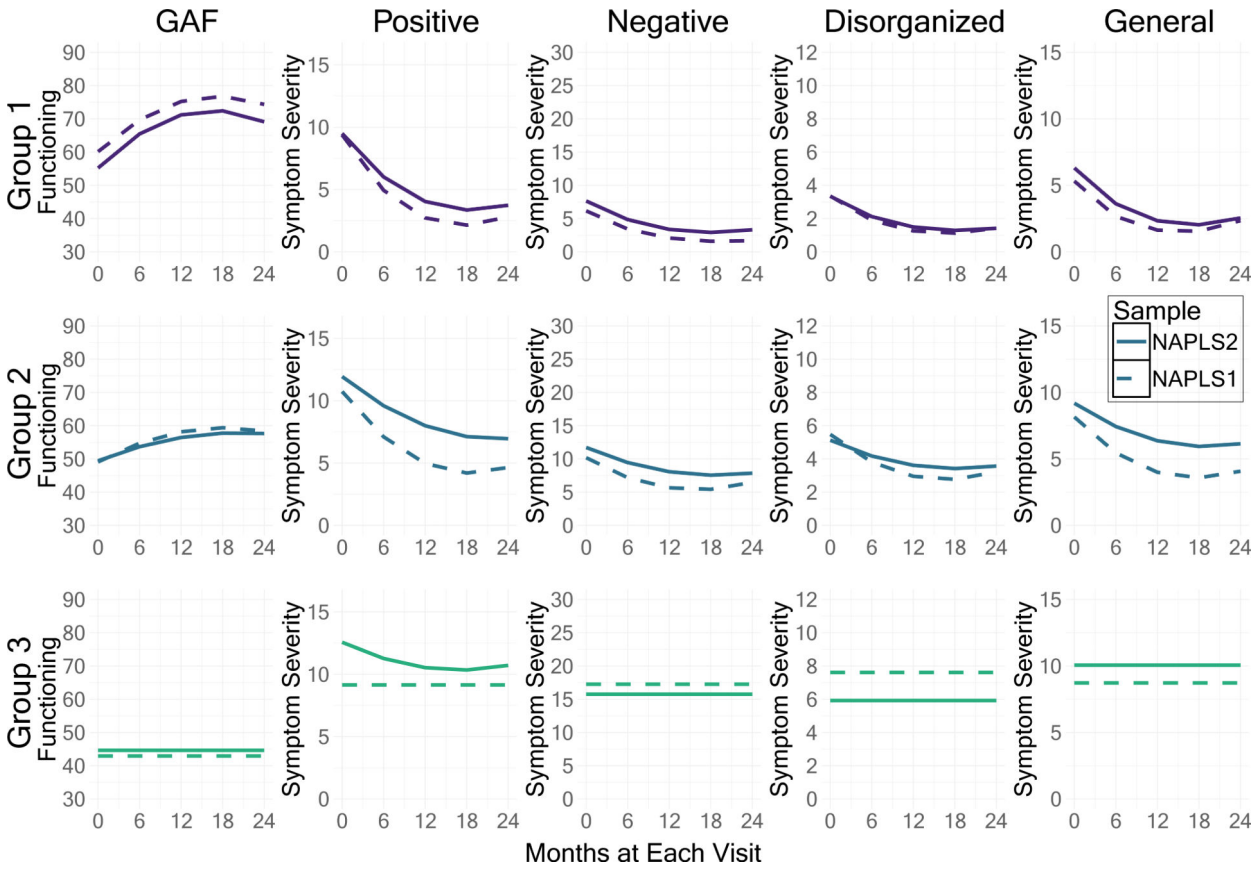

Figure 5.
Group trajectory estimates from NAPLS2 and NAPLS1 for each functioning and symptom domain.