Associations Between Premorbid Trajectory-defined Subgroups of Schizophrenia and Clinical and Neuroanatomic Features

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Abstract

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Different trajectories of premorbid functioning in schizophrenia spectrum disorder (SSD) have been associated with differences in clinical presentation and neuroanatomy; however, previous studies have largely focused on IQ-based premorbid cognitive trajectories, which discount non-cognitive domains of functioning and are unable to capture differential slopes of functional trajectories prior to psychosis onset. The present study utilized latent class mixture modeling of Premorbid Adjustment Scale (PAS) data from a multi-site sample of individuals with SSD (n=720), identifying four latent class psychosocial functioning trajectory subgroups. SSD premorbid trajectory groups differed in age of psychosis onset and likelihood of having a narrow schizophrenia or schizophreniform diagnosis versus broader SSD diagnosis. When the SSD-derived latent class model was applied to a larger sample including 253 SSD relatives, 1221 individuals at clinical high risk for psychosis who did not develop a psychotic disorder within 2 years (CHR nonconverters), and 710 controls, premorbid functioning trajectory groups also differed in estimates of current IQ and cannabis use. However, while narrowly defined SSD subjects differed from other diagnostic categories in age-normalized global cortical thickness (CT) and cross-regional CT similarity to idiopathic schizophrenia, there were no significant differences between premorbid trajectory groups on these metrics within SSD nor in the full

sample. Results highlight differences in premorbid functioning and current clinical profile between schizophrenia and other psychotic disorders. These findings additionally suggest weaker associations with current cognition and neuroanatomy for measures of broader premorbid psychosocial functioning compared to premorbid measures narrowly focused on cognition.

Introduction

Schizophrenia spectrum disorders (SSD), including schizophrenia and other psychotic disorders, account for approximately 1.5% of all disease burden (Vos et al., 2020) and over 300 billion dollars in economic burden in the United States per year (Kadakia et al., 2022). Early intervention following first-episode psychosis is associated with improved treatment response and long-term outcome in SSD (Perkins et al., 2005; Wyatt, 1991). However, the treatment of individuals at clinical high risk for psychosis has yet to show a systematic prevention of psychotic disorder transition (Lieberman et al., 2019). Improving our ability to identify high risk individuals, prior to psychosis-onset is therefore an important goal for the field.

Importantly, decreased general functioning often emerges years prior to the onset of psychotic symptoms (Agerbo et al., 2004) and is impacted by altered neurodevelopment and genetic risk associated with SSD (Kochunov et al., 2020; Toulopoulou et al., 2019). This suggests that premorbid impairment may reflect core biological processes associated with the development of SSD and may serve as an important target for preventative care with the potential to detect elevated risk for SSD up to a decade earlier than psychotic symptoms (Kahn & Keefe, 2013). However, premorbid functioning in SSD varies dramatically, with some individuals experiencing very little impairment prior to psychosis onset, and others experiencing serious impairment across social and academic domains (Cole et al. 2012; Horton et al., 2015; Kuo et al., 2023). Some have hypothesized that biologically distinct subgroups within SSD exist and that these subgroups may present with different trajectories of premorbid functioning, as well as other clinical and brain characteristics. In support of this, Dickenson et al. (2020) observed unique polygenic score (PGS) profiles for schizophrenia subgroups defined by reading-

test based estimates of premorbid function versus post-illness cognitive assessments. Specifically, the subgroup defined by significant deterioration in cognitive ability had the highest symptom severity of any subgroup and increased PGS for schizophrenia compared to a cognitively stable subgroup. Additionally, the subgroup defined by early compromised cognition without cognitive decline had lower PGS for education, and higher PGS for ADHD than deteriorated and cognitively stable subgroups. Prior studies have observed differences in grey matter volume in cognitive trajectory-based subgroups in schizophrenia, but results have been mixed, with larger reductions in grey matter volume (GMV) observed in deteriorating subgroups in two studies (Weinberg et al., 2016; Yasuda et al., 2020) and another study finding the largest GMV reductions in a low-functioning cognitive subgroup with no deterioration (Van Rheenen et al., 2017). Thus, more research is needed to clarify the relationship between premorbid trajectory groups and neuroanatomical differences.

Many previous studies of premorbid functioning have focused on cognition, which accounts for less than half of the variance in general functioning (Fett et al., 2011; Kuo et al., 2018). In addition, previous studies have often estimated cognitive trajectories by marking the difference between a reading-based premorbid IQ estimate and a current IQ estimate. This method cannot characterize the timing and slope of potential change in cognitive functioning prior to psychosis onset, which is necessary to identify clinical and neuroanatomical changes associated with functional decline at specific developmental periods. Examining whether there are differences in clinical and brain characteristics using measures of broader premorbid functioning with richer temporal information may help define more specific subgroups of patients with SSD.

Additionally, previous studies examining associations between premorbid cognitive trajectories and brain morphology used regional or whole brain metrics, such as regional and total grey matter volume; however, it is well-established that SSD is associated with widespread changes across the brain. In particular, a seminal study of 4474 schizophrenia patients and 5098 controls by the schizophrenia Enhancing Neuro Imaging Genetics through Meta-Analysis (ENIGMA) working group identified a pattern of cortical thinning across regions in SSD patients compared to controls that was most pronounced in subregions of frontal and temporal cortex, including lateral orbitofrontal cortex and fusiform gyrus (van Erp et al., 2018). SSD patients also displayed surface area reductions compared to controls, with subtler regional differences than for cortical thickness (van Erp et al., 2018). Quantifying the similarity of trajectory-defined subgroups to these average patterns of change in schizophrenia can clarify if trajectory-defined subgroups differ in the extent to which they are characterized by this "typical" pattern of brain change or may have anatomic differences that potentially implicate other biological processes.

Another important biological feature implicated in premorbid cognitive subgroups in schizophrenia are disruptions to brain development during late childhood and early adolescence. Disruptions to normative neurodevelopment are associated with cognitive impairment and the development of mental disorders, including schizophrenia (Bethlehem, Seidlitz, White et al., 2022; Larsen & Luna, 2018). During late childhood and adolescence, synaptic pruning, myelination, and other brain developmental processes refine critical networks in the brain associated with higher-order cognitive abilities (Larsen & Luna, 2018). These neurodevelopmental changes underlie dynamically changing brain metrics during this period, characterized recently in Bethlehem, Seidlitz, White et al. (2022), that benchmarked 123,984 MRI scans to define normative structural changes associated with age and biological sex.

Bethlehem, Seidlitz, White et al. (2022) also developed tools to benchmark individual subjects' MRI metrics within the context of these normative growth curves as centile scores. This offers a powerful tool to examine neuroanatomical differences between premorbid trajectory-defined subgroups using age- and sex- adjusted metrics which account for these nonlinear effects more precisely than traditional, uncorrected MRI metrics.

The present study attempts to address these gaps in our understanding of the relationships between premorbid functioning trajectories, markers of underlying neurobiology, and clinical outcomes. In a large sample of subjects with SSD, premorbid functioning trajectories were estimated using measures of social and academic functioning across multiple timepoints to capture potential changes in general functioning between childhood, early adolescence, and late adolescence. To examine individual-level morphometric similarity to average patterns observed in schizophrenia, regional vulnerability index (RVI) scores were calculated using regional MRI metrics and summary statistics for the average effect size per region in the ENIGMA schizophrenia study (Kochunov et al., 2020; van Erp et al., 2018). Age- and sex-standardized brain centile scores for global cortical thickness, surface area, and grey matter volume were additionally calculated to benchmark individuals in the context of typical neurodevelopmental changes in these metrics. Associations between premorbid functioning trajectories and these novel neuroanatomical metrics were examined. Additionally, associations between premorbid functioning trajectories and the age of psychosis onset, an estimate of current IQ, and the prevalence of a cannabis use disorder were examined. Finally, these analyses were extended to a large sample of subjects without a SSD to investigate the diagnostic specificity of the associations between premorbid functioning trajectories, neuroanatomical metrics, and clinical characteristics.

Methods

Participants

Data from 720 individuals with a schizophrenia spectrum disorder (SSD), 253 first to third degree relatives of individuals with SSD, 1221 individuals at clinical high risk for psychosis who did not develop a psychotic diagnosis (CHR nonconverter) during a monitoring period of up to 2 years, and 710 healthy controls (i.e., without a psychotic disorder) were harmonized across 9 sites of the North American Prodrome Longitudinal Studies (NAPLS 2 and 3) (Addington et al., 2015; Addington et al., 2022) and studies focused on largely recent-onset SSD patients conducted at UCLA: the Adolescent Brain-Behavior Research Clinic (ABBRC) (Eckfeld et al., 2017), Aftercare Program (Nuechterlein et al., 1992), and the UCLA Family Study (Asarnow et al., 2001). SSD participants were included if they had one of the following schizophrenia-spectrum disorder diagnoses: schizophrenia (n=387), schizophreniform (n=131), schizoaffective (n=87), mood disorder with psychotic features (n=23), psychotic disorder not otherwise specified (NOS) (n=84), brief psychotic disorder (n=1), or delusional disorder (n=7), and Premorbid Adjustment Scale (PAS) data. Relatives, CHR nonconverters, and controls were included if PAS data was available along with at least 1 of the following: an estimate of current IQ, a T1-weighted MRI scan that passed quality control procedures, or data on lifetime cannabis use disorder history. Relatives were recruited through the UCLA Family Study or were CHR nonconverters in the NAPLS studies who had a first to third degree relative with SSD (i.e. fulfilling diagnostic criteria for both CHR nonconverters and relatives).

Clinical and Cognitive Data

SSD and other diagnoses were determined using the Kiddie Schedule for Affective Disorders and Schizophrenia (KSADS) (Kaufman et al., 1997) for child-onset subjects in the UCLA Family Study and the Structured Clinical Interview for DSM-IV or DSM-V (SCID) (First et al., 2002) for all other studies. Narrow SSD was defined as a schizophrenia or schizophreniform diagnosis, with broader SSD defined as all other SSD diagnoses (i.e., schizoaffective, mood disorder with psychotic features, psychotic disorder NOS, brief psychotic disorder, delusional disorder). Age of psychosis onset was defined using applicable questions from the KSADS, SCID, or a study-specific question establishing the age when full-blown psychotic symptoms lasted for >1 week. IQ was estimated using subtests from the Wechsler Abbreviated Scale for Intelligence (WASI) (Wechsler, 1999), the Wechsler Adult Intelligence Scale (WAIS) (Wechsler, 1981), or the Measurement and Treatment Research to Improve Cognition in Schizophrenia (MATRICS) Consensus Cognitive Battery (Nuechterlein et al., 2008). For MATRICS battery-based IQ estimates, subtest scores were weighted based on the estimated relationship between MATRICS and WASI scores, calculated from a subset of 191 subjects with both measures (Forsyth et al., 2024). If multiple IQ estimates were available for a given subject, IQ estimates based on comprehensive measures that included both verbal and performance-based subtests were prioritized. For SSD subjects with multiple comprehensive-based IQ estimates, the estimate nearest to psychosis onset was prioritized. Lifetime prevalence and age of onset for a cannabis use disorder was defined via the SCID or KSADS.

MRI Data Processing and Score Generation

T1-weighted MRI data were processed with FreeSurfer (version 7.1.1), a standardized processing pipeline that includes cortical surface reconstruction, registration to the MNI305 atlas, and parcellation of 68 cortical regions (34 bilateral) defined by the Desikan-Killiany Atlas (Fischl et al., 2002; Fischl et al., 2004). Global measures of grey matter volume (GMV), white matter volume (WMV), surface area (SA), and cortical thickness (CT) were extracted for each scan. Regional CT and SA metrics for the 68 cortical regions were also extracted. Quality control (QC) of scans was conducted following the ENIGMA Cortical Quality Control Protocol 2.0 (https://enigma.ini.usc.edu/protocols/imaging-protocols/). CT and SA values for regions that did not pass visual QC were dropped and imputed using the MissForest R package, an iterative nonparametric imputation method that outperforms other imputation methods in the presence of complex interactions and non-linear relations (Stekhoven & Bühlmann, 2012). The ComBat function in the SVA package in R, an empirical Bayes framework, was used to correct all global and regional MRI values for scanner/site-related effects, controlling for diagnostic group, sex, and age (Johnson et al., 2007). Age^2 was included as an additional covariate for global and regional CT correction (Mutlu et al., 2013).

Individual-level regional vulnerability index (RVI) scores for SSD were computed using the RVIpkg package in R (Kochunov et al., 2020). First, regional SA and CT z-scores were calculated for each scan, using the mean and standard deviation across all controls. Next, SSD RVI scores were calculated for each subject as the Pearson's correlation coefficient between z-scores for each region and the average SSD z-score per region derived from the ENIGMA schizophrenia-control meta-analysis, reflecting effect size differences between schizophrenia patients versus controls (van Erp et al., 2018), controlling for age and sex. SSD z-scores per

region were accessed via the ENIGMA Toolbox (https://enigma-toolbox.readthedocs.io/en/latest/pages/04.loadsumstats/index.html).

Individual-subject level centile scores for global CT, SA, and GMV were calculated relative to age- and sex-normative trajectories from the BrainChart program, built upon a reference dataset of over 100,000 MRI scans to calculate a centile score between 0 and 1, accounting for nonlinear age-related trends by sex and site-specific batch effects (Bethlehem, Seidlitz, White et al., 2022). Scans from scanner protocols with fewer than 10 controls were excluded from centiles analyses to allow scanner/protocol effects to be sufficiently accounted for with Combat and during the generation of centile scores.

Premorbid Trajectories of Function

Premorbid function was assessed using the Premorbid Adjustment Scale (PAS) (Cannon-Spoor et al., 1982), a clinician-administered retrospective rating scale of premorbid functioning in childhood (through age 11), early-adolescence (ages 12-15), late-adolescence (ages 16-18), and adulthood (age 19 and above) across five psychosocial domains: sociability and withdrawal, peer relationships, scholastic performance, adaptation to school, and socio-sexual aspects of life. Clinicians derived ratings based on family member and/or subject interview, scoring each domain on a 0-6 range, with 0 denoting the highest level of adjustment and 6 the poorest level of adjustment. Ratings were completed for life periods greater than six months prior to psychosis-onset and when the rater determined that sufficient information was available. The four domains of sociability and withdrawal, peer relationships, scholastic performance, and adaptation to school were selected for a premorbid composite score because of their availability from childhood to late adolescence. At each life period, these ratings were averaged to create a composite score with a possible range of 0-6. Ratings of socio-sexual functioning were not

included in the composite score, as they were not assessed for childhood and early-adolescence. A composite score was not calculated for adulthood, as scholastic performance and adaption to school were not rated for this life period.

Different trajectories of premorbid functioning for SSD subjects were derived using latent class mixture modelling from the lcmm package in R (Proust-Lima et al., 2017). Latent class mixture modeling attempts to identify qualitatively distinct subpopulations in data and departs from other class-generating methods such as clustering analysis by estimating growth factor variances that account for individual differences within latent classes (Bauer & Curran, 2003; Muthén & Muthén, 2000). Models with 1-7 classes were estimated using the PAS composite score, allowing for random intercepts and slopes between classes. Biological sex was included as a covariate in each model to control for previously observed sex differences in premorbid functioning (Schmael et al., 2007; Ventura et al., 2023). The best fitting model was determined using the goodness-of-fit statistics Akaike Information Criterion (AIC), Bayesian Information Criterion (BIC), and Sample Adjusted Bayesian Information Criterion (SABIC), selecting the model with lowest values across all metrics.

Statistical Analyses

SSD Sample

Associations between class membership in the best fitting latent class model and biological sex were first examined using a Type II analysis of variance (ANOVA). An analysis of covariance (ANCOVA) was then used to test the association between class membership and a narrowly defined SSD (i.e., a schizophrenia or schizophreniform diagnosis) versus broader SSD

(i.e., all other psychosis spectrum disorders), covarying for sex. ANCOVA were also used to examine associations between narrow SSD versus broader SSD and age of psychosis onset, current IQ estimates, lifetime history of a cannabis use disorder, and age of cannabis use disorder onset, covarying for sex. The associations between narrow SSD versus broader SSD and CT RVI score, SA RVI score, CT centile score, SA centile score, and GMV centile score were examined using an ANOVA. Sex, age, and scanner site/protocol were not included as covariates in brain metric models, as RVI and centile scores were calculated adjusting for these covariates. Associations were then examined between class membership and age of psychosis onset, current IQ estimate, lifetime prevalence of a cannabis use disorder, and age of cannabis use disorder onset, covarying for sex and narrow versus broader SSD diagnosis using ANCOVA. The model for lifetime prevalence of a cannabis use disorder also included age of cannabis use assessment as a covariate to account for differences in access to cannabis with increasing age. The associations between class membership and CT RVI score, SA RVI score, CT centile score, SA centile score, and GMV centile score were examined using an ANCOVA, covarying for narrow versus broader SSD diagnosis. Two-way interactions between class membership and group-level covariates (i.e., sex and/or narrow vs broader SSD diagnosis) were included in initial models for class membership and each clinical or MRI characteristic and tested for significance using Type III ANCOVA. If all interactions were non-significant, they were removed from the model and associations between class and each metric of interest were re-run and reported as Type II ANCOVA.

For models with significant associations between class membership and clinical characteristics or neuroanatomical metrics of interests, marginal contrasts were obtained with the modelbased package in R for each trajectory group and tested for pairwise differences. To

correct for multiple pairwise comparisons, a standard false-discovery-rate (FDR) correction was applied to pairwise differences using the p_adjust R package, and both nominal and FDR-corrected p-values were reported.

Full Sample

Using the *predictY* function from the lcmm package in R, the best fitting latent class model derived from the SSD subjects was applied to the PAS composite scores for each subject in the full sample, assigning subjects to the class with the highest posterior probability. Differences in assignment to classes between diagnostic category groups was examined using a Pearson's Chi-squared test. Associations between class and biological sex were first examined using a Type II ANOVA. Potential differences between diagnostic category groups in current IQ estimates, lifetime history of a cannabis use disorder, and age of cannabis use disorder onset were first assessed using ANCOVA covarying for sex.

ANCOVA were then used to test associations between class membership in the full sample and current IQ estimate and age of a cannabis use disorder diagnosis, covarying for sex and diagnostic category (i.e., narrow SSD, broader SSD, CHR nonconverter, SSD relative, control). Association between class membership and lifetime prevalence of a cannabis use disorder was investigated, covarying for sex, broad diagnostic category, and age of cannabis use assessment in an ANCOVA.

To establish the sensitivity of RVI and centile scores to diagnostic group differences, a Type II ANOVA was first used to test for potential associations between broad diagnostic category and each brain metric. Associations between class membership and CT RVI score, SA

RVI score, CT centile score, SA centile score, and GMV centile score were then examined using a Type II ANCOVA, covarying for broad diagnostic category.

As above, two-way interactions between class membership and group-level covariates (sex and diagnostic category) were included in initial models for each clinical characteristic and tested for significance using Type III ANCOVA. If interactions were non-significant, associations between class and clinical characteristics were re-run as Type II ANCOVA, excluding interactions. Marginal contrasts per trajectory class were obtained with the modelbased package in R following any significant associations between class membership and clinical or neuroanatomical metrics of interests and tested for pairwise group differences. To correct for multiple pairwise comparisons, a standard FDR correction was applied to pairwise differences using the p_adjust R package, and both nominal and FDR-corrected p-values were reported.

Results

SSD latent-class analysis

Among latent-class models with 1-7 classes (Table 1), the 4-class model had the lowest AIC, BIC, and SABIC and was therefore selected for follow-up analyses. The 4-class model (Figure 1), is characterized by a “stable good” class (n=516, 71.7%) showing high premorbid functioning across childhood and adolescence, a “stable poor” class (n=139, 19.3%) showing impaired premorbid functioning across childhood and adolescence, a “late deteriorating” class

(n=51, 7.1%) showing substantial decline in premorbid functioning between early and late adolescence following low impairment in childhood and early adolescence, and an "early deteriorating" class (n=14, 1.9%) showing premorbid functioning decline in early adolescence with some recovery in late adolescence.

SSD differences in clinical characteristics and neuroanatomical metrics

There was a significant main effect of narrow (i.e., schizophrenia and schizophreniform) versus broader SSD diagnosis on age of psychotic symptom onset, $F(1,666) = 19.41$, $p < 0.001$, due to a 2.3 year later age of psychosis onset overall in narrow versus broader SSD subjects ($p<0.001$) (Figure 2A, Table 2), as well as a significant interaction between narrow versus broader SSD diagnosis and sex, $F(1,666) = 4.15$, $p = 0.04$. Follow-up analyses within each sex indicated that narrow versus broader SSD diagnosis was significantly associated with the age of psychosis onset in both males, $F(1,447) = 6.78$, $p = 0.01$, and females, $F(1,219) = 13.30$, $p < 0.001$; however, this difference was larger in females (narrow SSD mean age = 21.5, SD = 6.5; broader SSD mean age = 18.3, SD = 5.8) than males (narrow SSD mean age = 20.1, SD = 4.5; broader SSD mean age = 18.8, SD = 4.9). Narrow SSD was additionally significantly associated with an estimate of current IQ, $F(1,641) = 6.46$, $p = 0.01$, with follow-up comparisons indicating that narrow SSD subjects had a 3.5 lower current IQ estimate than broader SSD subjects (Figure 2B, Table 2). The narrow SSD by sex interaction was not significant for estimate of current IQ, $F(1,640) = 0.27$, $p = 0.60$. Narrow SSD was not associated with prevalence of a lifetime cannabis use disorder, $F(1,504) = 1.21$, $p = 0.27$ (Table 2), nor with age of cannabis use disorder onset among subjects with a cannabis use disorder history, $F(1,81) = 0.15$, $p = 0.70$ (Table 2). The narrow SSD by sex interaction was not significant with prevalence of a lifetime cannabis use

disorder, $F(1,503) = 3.15$, $p = 0.08$, nor with age of cannabis use disorder onset among subjects with a cannabis use disorder history, $F(1,80) = 0.10$, $p = 0.76$.

Narrow SSD subjects showed significantly higher CT RVI scores, $F(1,341) = 12.78$, $p < 0.001$ (Figure 2C, Table 2), and lower CT centile scores, $F(1,189) = 10.59$, $p = 0.001$ (Figure 2D, Table 2), than broader SSD subjects. There were no significant differences between narrow versus broader SSD in SA RVI, $F(1,341) = 0.03$, $p = 0.86$, GMV centile score, $F(1,189) = 2.38$, $p = 0.12$, or SA centile score, $F(1,189) = 0.02$, $p = 0.90$.

SSD premorbid trajectory class differences in demographic and clinical characteristics

Sex was not significantly associated with class membership, $F(3,716) = 1.05$, $p = 0.79$ (Table 3). Narrow versus broader SSD was significantly associated with class membership, $F(3,715) = 9.19$, $p = 0.03$. Follow-up comparisons suggested that the "stable good" class had a higher proportion of narrow SSD subjects than the "stable poor" class, but this did not survive FDR-correction (uncorrected p=0.015; FDR-adjusted p=0.09; Table 3). The interaction of narrow versus broader SSD and sex was not associated with class membership, $F(3,712) = 1.35$, $p = 0.72$. Class membership was significantly associated with age of psychotic symptom onset, $F(3,664) = 2.68$, $p = 0.04$, with follow-up marginal contrasts analysis indicating that the "stable poor" class's age of psychosis onset was 1.4 years earlier than the "stable good" class (p=0.01, FDR-adjusted p=0.047) (Figure 3A, Table 3). The class by sex interaction was not associated with age of psychotic symptom onset, $F(1,640) = 0.27$, $p = 0.60$. Neither class membership, nor the interaction of class membership and sex were associated with estimate of current IQ, $F(3,638) = 1.24$, $p = 0.30$ and $F(3,635) = 2.29$, $p = 0.08$, respectively (Table 3). Class membership was also not associated with prevalence of a lifetime cannabis use disorder among SSD subjects, $F(3,501) = 1.37$, $p = 0.25$ (Table 3), nor with age of cannabis use disorder onset

among subjects with a cannabis use disorder history, $F(3,78) = 0.12$, $p = 0.94$ (Table 3). The class by sex interaction was not significant for prevalence of a lifetime cannabis use disorder, $F(3,498) = 0.93$, $p = 0.43$, and the interaction was not examined relative to the age of cannabis use disorder due to multicollinearity between sex and class in the resulting model.

SSD premorbid trajectory class differences in neuroanatomical metrics

In models assessing the relationship between class membership and CT RVI, class membership was not significantly associated with CT RVI across narrow and broader SSD subjects, $F(3,335) = 1.76$, $p = 0.15$ (Table 3); however, there was a significant class by narrow versus broader SSD diagnosis interaction for CT RVI, $F(3,335) = 2.96$, $p = 0.03$. Examining the association between class membership and CT RVI for individuals with a narrow SSD diagnosis and for individuals with a broader SSD diagnosis separately did not show significant class differences (narrow SSD $F(3,250)=1.37$, $p=0.25$; broader SSD $F(3,85)=1.55$, $p=0.21$). However, when the association between narrow versus broader SSD diagnosis and CT RVI was examined within each premorbid trajectory class, there were significant group differences for the "stable good", $F(1,252)=4.49$, $p=0.035$,and "late deteriorating" classes, $F(1,19)=12.22$, $p=0.001$, with individuals with a narrow SSD diagnosis showing higher CT RVI compared to individuals with a broader SSD diagnosis within these classes (Figure 3B). For models assessing the relationship between class membership and SA RVI, the main effect of class membership was not significant, $F(3,338) = 1.13$, $p = 0.34$ (Table 3), nor was the interaction between class membership and narrow versus broader SSD diagnosis $F(3,335) = 1.56$, $p = 0.20$.

In models assessing relationships between class membership and CT, SA, and GMV centile scores (Table 3), none of the main effects of class membership nor interactions of class membership by narrow versus broader SSD diagnoses were significant (CT centile score:

$F(3,186) = 2.05$, $p = 0.11$ and $F(3,183) = 1.16$, $p = 0.33$, respectively; SA centile score: $F(3,186) = 0.19$, $p = 0.90$ and $F(3,183) = 1.75$, $p = 0.16$, respectively; GMV centile score: $F(3,186) = 0.96$, $p = 0.41$ and $F(3,183) = 0.81$, $p = 0.49$, respectively).

Premorbid trajectory class membership in full sample

After applying the latent classes derived in the SSD sample to the full sample, there were significant differences in the assignment of individuals from different diagnostic categories between premorbid trajectory classes, $X^2(12, N=2904) = 179.24$, $p < 0.001$ (Table 4). Follow-up analyses of the distribution of individuals per diagnostic group in each trajectory class, considering the average pattern of class assignment across all subjects in the analysis, revealed significant effects for CHR nonconverters and controls. Specifically, CHR nonconverters were over-represented in the "early deteriorating" (n=44, 3.6%, p<0.001, FDR-adjusted p<0.001) and "stable poor" (n=197, 16.1%, p=0.001, FDR-adjusted p=0.01) classes and under-represented in the "stable good" (n=929, 76.1%, p<0.001, FDR-adjusted p<0.001) class. Controls were over-represented in the "stable good" (n=677, 95.4%, p<0.001, FDR-adjusted p<0.001) class and underrepresented in the "stable poor" (n=25, 3.5%, p<0.001, FDR-adjusted p<0.001), "late deteriorating" (n=4, 0.6%, p<0.001, FDR-adjusted p<0.001), and "early deteriorating" (n=4, 0.6%, p=0.001, FDR-adjusted p=0.003) classes. SCZ relatives were not significantly associated with membership to any class (all FDR-adjusted ps > 0.05). The interaction of diagnostic category and sex was not significant for premorbid trajectory class assignment, $X^2(12, N=2904) = 11.14$, $p = 0.52$.

Diagnostic category differences in clinical characteristics and neuroanatomical metrics

Broad diagnostic category was significantly associated with current IQ estimates, $F(4, 2743) = 55.72$, $p < 0.001$ (Figure 5A, Table 5), with follow-up marginal contrasts analysis

indicating that controls had a higher current IQ estimate than CHR nonconverters (p<0.001, FDR-adjusted p-value<0.001), SSD relatives (p<0.001, FDR-adjusted p-value<0.001), narrow SSD (p<0.001, FDR-adjusted p-value<0.001), broader SSD (p<0.001, FDR-adjusted p-value<0.001). CHR nonconverters had higher current IQ estimates than narrow SSD (p<0.001, FDR-adjusted p-value<0.001) and broader SSD (p<0.001, FDR-adjusted p-value<0.001). SSD relatives had higher current IQ estimates than narrow SSD (p<0.001, FDR-adjusted p-value<0.001) and broader SSD (p=0.006, FDR-adjusted p-value=0.01). Finally, narrow SSD subjects had a lower current IQ estimate than broader SSD subjects (p=0.006, FDR-adjusted p-value=0.01). CHR nonconverters and SSD relatives did not differ in current IQ estimate (p=0.40, FDR-adjusted p-value=0.40). The interaction of diagnostic category and sex was not associated with current IQ estimates, $F(4, 2739) = 0.68$, $p = 0.60$.

Diagnostic category was significantly associated with the prevalence of a lifetime cannabis use disorder, controlling for age at assessment and a significant diagnostic by sex interaction, $F(4, 2544) = 5.86$, $p < 0.001$ (Figure 5B, Table 5). Follow-up marginal contrasts analysis indicated that narrow and broader SSD subjects each had a higher prevalence of a lifetime cannabis use disorder than controls (p-values<0.001, FDR-adjusted p-values<0.001), SSD relatives (p-values<0.001, FDR-adjusted p-values <0.001), and CHR nonconverters (SSD Narrow p<0.001, SSD Narrow FDR-adjusted p-value <0.001; broader SSD p=0.01, broader SSD FDR-adjusted p-value=0.02). CHR nonconverters also had a higher prevalence of a lifetime cannabis use disorder than controls (p<0.001, FDR-adjusted p-value<0.001) and SSD relatives (p=0.03, FDR-adjusted p-value=0.03). None of the other pairwise comparisons were significant, ps > 0.05. Controlling for the significant main effect of diagnostic category, the interaction of diagnostic category and sex was significantly associated with the prevalence of a lifetime

cannabis use disorder, $F(4,2544) = 5.20$, $p < 0.001$. Follow-up analyses within each sex indicated that diagnostic category was significantly associated with the prevalence of a lifetime cannabis use disorder in both males, $F(4,1410) = 23.24$, $p < 0.001$, and females, $F(4,1133) = 5.61$, $p < 0.001$; however, male but not female narrow SSD subjects had a higher prevalence of a lifetime cannabis use disorder than CHR nonconverters (males: p<0.001, FDR-adjusted p-value<0.001; females: p=0.42, FDR-adjusted p-value=0.53), and broader SSD subjects (males: p=0.02, FDR-adjusted p-value=0.03; females: p=0.50, FDR-adjusted p-value=0.56) (Figure 6). Male and female narrow SSD had a higher prevalence of a lifetime cannabis use disorder than SSD relatives, but this difference was no longer significant for females after FDR correction (males: p<0.001, FDR-adjusted p-value<0.001; females: p=0.03, FDR-adjusted p-value=0.06).

For subjects with a cannabis use disorder, diagnostic category was also associated with age of the cannabis use disorder onset, $F(4,241) = 5.00$, $p < 0.001$ (Figure 7A, Table 5) with follow-up marginal contrasts analysis indicating that narrow SSD subjects have a 1.7 year later age of cannabis use disorder onset than CHR nonconverters (p<0.001, FDR-adjusted p-value<0.001). There were also trend-level effects, with narrow SSD subjects showing a later age of cannabis use disorder onset than SSD relatives (p=0.03, FDR-adjusted p-value=0.11) and broader SSD subjects showing a later age of cannabis use disorder onset than CHR nonconverters (p=0.03, FDR-adjusted p-value=0.11), but these differences did not survive FDR correction. None of the other pairwise comparisons were significant, ps > 0.05. The diagnostic group by sex interaction was not significant for age of cannabis use disorder onset $F(4,237) = 1.17$, $p = 0.32$.

Diagnostic category was significantly associated with CT RVI, $F(3,1731) = 9.93$, $p < 0.001$, with follow-up marginal contrasts analysis indicating that narrow SSD subjects had higher

CT RVI compared to broader SSD subjects (p<0.001, FDR-adjusted p=0.001), SSD relatives (p<0.001, FDR-adjusted *p*<0.001), CHR nonconverters (p<0.001, FDR-adjusted p<0.001), and controls (p<0.001, FDR-adjusted *p*<0.001) (Figure 7B, Table 5). None of the other pair-wise group comparisons were significant, ps > 0.05. Diagnostic category was not significantly associated with SA RVI, $F(3,1731) = 1.76$, $p = 0.13$ (Table 5).

Diagnostic category was significantly associated with CT centile score, $F(3,1298) = 8.32$, $p < 0.001$, with follow-up contrasts analysis similarly indicating that narrow SSD subjects had lower CT centile scores than broader SSD subjects (p=0.001, FDR-adjusted *p*=0.004), SSD relatives (p=0.002, FDR-adjusted *p*=0.01), CHR nonconverters (p<0.001, FDR-adjusted *p*<0.001), and controls (p<0.001, FDR-adjusted *p*<0.001) (Figure 7C, Table 5). None of the other pairwise comparisons were significant, *p*s > 0.05. Diagnostic category was also significantly associated with GMV centile score, $F(3,1298) = 2.95$, $p = 0.02$, with follow-up marginal contrasts analysis indicating that narrow SSD subjects had significantly lower GMV centile scores than controls (p=0.003, FDR-adjusted *p*=0.03) and CHR nonconverters (p=0.007, FDR-adjusted *p*=0.04) (Figure 7D, Table 5). SSD relatives also tended towards lower GMV centile scores than controls, but this did not survive FDR-correction (*p*=0.04; FDR-adjusted *p*=0.14). None of the other pairwise comparisons were significant, *p*s > 0.05. Diagnostic category was not significantly associated with SA centile score, $F(3,1298) = 0.97$, $p = 0.42$ (Table 5).

Class differences in demographic and clinical characteristics in full sample

As in the analysis of SSD subjects only, sex was not significantly associated with class membership across the full sample, $F(3, 2900) = 3.32$, $p = 0.34$ (Table 4). However, class membership was significantly associated with estimates of current IQ, $F(3, 2740) = 3.72$, $p = 0.01$, with follow-up marginal contrasts analysis indicating that the “stable poor” class had a 2.9

lower current IQ estimate than the "stable good" class (p<0.001, FDR-adjusted p=.005) (Figure 4A, Table 4). The interaction of class membership and sex was not associated with estimates of current IQ, $F(3, 2737) = 1.10$, $p = 0.35$. The interaction of class membership and diagnostic category was not associated with estimates of current IQ, $F(12, 2728) = 1.02$, $p = 0.42$. Class membership was also significantly associated with the prevalence of a lifetime cannabis use disorder, controlling for age at assessment, $F(3,2545) = 3.16$, $p = 0.02$, with follow-up marginal contrasts analysis indicating that the "late deteriorating" class had a higher prevalence of a lifetime cannabis use disorder than the "stable poor" (p=0.002, FDR-adjusted p=0.02) and "stable good" classes (p=0.01, FDR-adjusted p=0.04) (Figure 4B, Table 4). The interaction of class and sex was not associated with the prevalence of a lifetime cannabis use disorder, $F(3,2542) = 2.18$, $p = 0.09$. The interaction of class and diagnostic category was not associated with the prevalence of a lifetime cannabis use disorder, $F(12,2533) = 1.21$, $p = 0.27$. For subjects with a cannabis use disorder, neither class membership, nor the interaction of class and sex were associated with age of the cannabis use disorder onset, $F(3,238) = 0.29$, $p = 0.83$ (Table 4) and $F(3,235) = 0.46$, $p = 0.71$, respectively. The interaction of class and diagnostic category was not examined due to multicollinearity between class and diagnostic category in the resulting model.

Class differences in neuroanatomical metrics in full sample

In models assessing the relationship between class membership and CT RVI, the main effect of class membership was not significant, $F(3,1728) = 0.63$, $p = 0.59$ (Table 4), nor was the interaction between class membership and diagnostic category, $F(12,1716) = 1.14$, $p = 0.32$. For models assessing the relationship between class membership and SA RVI, the main effect of class membership was not significant, $F(3,1728) = 0.17$, $p = 0.92$ (Table 4), nor was the interaction between class membership and diagnostic category, $F(12,1716) = 1.23$, $p = 0.25$.

For models assessing relationships between class membership and CT, SA, and GMV centile scores (Table 4), none of the main effects of class membership nor interactions of class membership by diagnostic category were significant for CT centile score, $F(3,1295) = 1.51$, $p = 0.21$ and $F(12,1283) = 0.70$, $p = 0.76$, respectively; SA centile score, $F(3,1295) = 0.39$, $p = 0.76$ and $F(12,1283) = 1.60$, $p = 0.08$, respectively; or GMV centile score, $F(3,1295) = 1.34$, $p = 0.26$ and $F(12,1283) = 1.18$, $p = 0.29$, respectively.

Discussion

Our study used premorbid functioning data from a large, multi-site sample of individuals with SSD to generate premorbid functioning trajectory subgroups using latent class mixture modeling and examine their associations with clinical and neuroanatomic characteristics. SSD premorbid trajectory groups differed in age of psychosis onset and likelihood of having a narrow schizophrenia or schizophreniform diagnosis versus broader SSD diagnosis. When the SSD-derived latent class model was applied to the full study sample to include subjects without a SSD, premorbid functioning trajectory groups also differed in estimates of current IQ and prevalence of a cannabis use disorder. However, while SSD subjects differed from controls, relatives, and CHR nonconverters in brain metrics reflecting neuroanatomic similarity to the average pattern of alterations observed in schizophrenia and deviance from expected CT or GMV, considering sex and age at MRI scan, there were no significant differences between premorbid trajectory groups on these metrics within SSD nor in our full sample.

Our study's latent class mixture model of best fit consisted of four premorbid functioning trajectory classes. Multiple prior studies using the PAS and latent class mixture modelling (Caqueo-Urízar et al., 2022; Cole et al., 2012; Horton et al., 2015;) or clustering methods (Bechi et al., 2020; Chan et al., 2019) in smaller cohorts of schizophrenia subjects have identified three

premorbid trajectory classes, although one previous k-means clustering study and one prior latent class modeling study similarly identified a four-class model as showing the best fit of the data (Larsen et al., 2004, Kuo et al., 2023). The two largest classes in our model, "stable good" and "stable poor," were common classes observed in previous studies (Bechi et al., 2020; Horton et al., 2015; Kuo et al., 2023). In line with some previous studies (Cole et al., 2012; Joyce et al., 2005), SSD subjects with a "stable poor" trajectory of premorbid function was associated with an earlier onset of psychotic symptoms. As the "stable poor" trajectory was the only class with childhood impairment of functioning, this finding suggests that earlier functional impairment is associated with earlier development of psychotic symptoms. Although the "stable good" group in the full sample showed the highest average current IQ estimates and differed from the "stable poor" group, this difference was not significant in the SSD-only analysis, in contrast to prior studies using IQ-based trajectories of premorbid functioning (Badcock et al., 2005; Dickinson et al., 2020; Leeson et al., 2011; Weickert et al., 2000; Weinberg et al., 2016; Yasuda et al., 2020). As current IQ estimates were used to define trajectories in these previous studies, it is unsurprising that trajectories differed in current IQ estimates in these studies. Interestingly, other premorbid functioning studies utilizing cross-domain PAS scores observed trajectory-based subgroup differences in processing speed remediation, but subgroups did not differ in overall cognitive and verbal learning remediation and current full-scale IQ (Cole et al., 2012; Kuo et al., 2023). Weaker associations between premorbid functional trajectories defined by the PAS and current cognition may reflect the wider psychosocial functional domains assessed by the PAS, which may have weaker associations with neurocognitive functioning. In support of this, previous studies have observed associations between post-psychosis onset neurocognitive

performance and premorbid academic functioning, but not social functioning, defined by the PAS (Barajas et al., 2013; Buonocore et al., 2019; Larsen et al., 2004; Rund et al., 2007).

The "late deteriorating" SSD class, characterized by a significant premorbid functioning decline in late adolescence, was also identified in two prior studies of premorbid functioning trajectories in schizophrenia (Bechi et al., 2020; Larsen et al., 2004). This class was associated with an increased prevalence of a cannabis use disorder in our full sample. Although the cannabis use disorder rate in this class among SSD-only subjects was among the highest, this difference was not significant in the SSD-only analysis, likely due to high rates of cannabis use disorder history in other groups. This suggests that factors other than cannabis use disorder history may differentiate the late deteriorating class from other classes among SSD subjects. Our proportion of "deteriorating" subjects was smaller than that identified in studies using post-psychosis onset estimates of IQ compared to reading-test based estimates of premorbid IQ (43%, Badcock et al., 2005; 44%, Dickenson et al., 2020; 40%, Joyce et al., 2005; 44%, Leeson et al., 2011; 45%, Van Rheenen et al. 2017; 51%, Weickert et al., 2000; 62%, Weinberg et al., 2016; 65%, Yasuda et al., 2020); however, studies of premorbid trajectories using the PAS have reported more varied proportions of subjects assigned to a "deteriorating" group (29%, Bechi et al., 2020; 13%, Cole et al., 2012; 7%, Horton et al., 2015; 45.2%, Kuo et al., 2023). This may suggest that deteriorating groups identified using pre- versus post-psychosis onset IQ methods differentially assign individuals who experience cognitive decline after psychosis onset to a deteriorating trajectory group (see review in Tschentscher et al., 2023), compared to methods that only derive trajectories using premorbid functioning. Alternatively, this could reflect wider variance in functioning across psychosocial domains measured by the PAS compared to narrow cognitive functioning measures (Fett et al., 2011; Kuo et al., 2018).

The “early deteriorating” class in our model of significant decline of premorbid functioning in early adolescence followed by some recovery in late adolescence was not described in previous studies. Individuals who go on to develop schizophrenia commonly diverge from their healthy peers in functioning between childhood and early adolescence (Fuller et al., 2002; Reichenberg et al., 2010; Van Oel et al., 2002), but this deterioration typically continues into late adolescence (Cole et al., 2012; Horton et al., 2015; Kuo et al., 2023). Our “early deteriorating” class represented the smallest subgroup in our sample (n=14, 1.9%), and class membership to this subgroup was not associated with any demographic, clinical, or neuroanatomical features within SSD examined in follow-up analyses. Although speculative, the partial recovery in premorbid functioning between early and late adolescence may be explained by an external factor not measured in the present study, such as an intervention in response to the emergent psychosocial challenges in early adolescence that temporarily restored functioning prior to the onset of psychosis. In our full sample, CHR nonconverters were disproportionately assigned membership to this subgroup, which may indicate that subclinical psychotic symptoms may underlie the change in functioning followed by partial recovery when subthreshold psychotic symptoms did not progress. Taken together, our findings support the developmental trajectory subtypes commonly described in schizophrenia research: a subgroup of individuals with relatively unimpaired functioning until adolescence, a subgroup with stable functional impairment from early in development, and a subgroup with a deterioration of functioning during adolescence (Weickert et al., 2000).

Our premorbid trajectory subgroups did not significantly differ in neuroanatomical similarity to schizophrenia and deviance from expected age- and sex-normalized morphometry, both within SSD and in our full sample. While a significant class-by-SSD-diagnosis interaction

was observed for CT RVI, premorbid trajectory class membership was not associated with CT RVI for narrow or broader SSD diagnoses. Conversely, narrowly defined SSD had a higher CT RVI than broader SSD diagnoses for the "stable good" and "late deteriorating" classes only, which may suggest that neuroanatomical differences between narrowly and broader SSD are only present in subjects with relatively unimpaired premorbid functioning in childhood and early adolescence. Further research is needed to examine if specific diagnoses within narrow and broader SSD differ in class membership and neuroanatomical profile.

Previous studies have observed cortical differences between cognitive subgroups in schizophrenia defined based on pre- versus post-psychosis onset estimates of cognitive functioning (Van Rheenen et al., 2017; Weinberg et al., 2016; Yasuda et al., 2020); however, our study is the first to examine cortical differences between subgroups derived from premorbid functioning. In these prior studies, differences in regional grey matter, total grey matter, and bilateral cortical thickness were observed between cognitive subgroups, but these studies did not examine the holistic pattern of regional cortical differences between subgroups, particularly in the context of average patterns of change associated with schizophrenia (Weinberg et al., 2016; Van Rheenen et al., 2017; Yasuda et al., 2020). Additionally, these previous studies have inconsistently accounted for the linear and nonlinear effects of age and sex on global brain metrics. Our lack of significant differences in CT or SA RVI or GMV, SA, or CT centiles between groups may reflect weaker relationships between brain characteristics in SSD and trajectory groups derived based on broad aspects of premorbid functioning versus trajectory groups based on premorbid versus post-psychosis onset estimates of cognitive-specific function. Alternatively, premorbid trajectory subgroups may be associated with neuroanatomical features

not examined in the present analysis, such as morphometric differences for specific cortical regions, rather than a holistic characterization of all cortical regions.

A narrow definition of schizophrenia spectrum diagnoses, limited to schizophrenia and schizophreniform, was associated with a relatively stable, unimpaired pattern of premorbid functioning, a later age of psychosis onset, and a lower estimate of current IQ than subjects with broader SSD diagnoses (i.e. schizoaffective, mood disorder with psychotic features, psychotic disorder NOS, brief psychotic disorder, delusional disorder). This suggests that narrow SSD diagnoses experience higher levels of premorbid functioning, yet worse performance on cognitive assessments following the onset of full-blown psychotic symptoms, compared to broader SSD diagnoses. This could reflect greater functional impairment post-psychosis onset for schizophrenia and schizophreniform compared to other SSD diagnoses or greater premorbid impairment for non-cognitive domains in broader SSD. However, future research is needed to further investigate schizophrenia spectrum definition differences across domains of premorbid and current functioning.

Narrow SSD was additionally associated with greater neuroanatomical similarity to schizophrenia, specifically in cortical thickness pattern, and greater reductions in age- and sex-normalized total grey matter volume and average cortical thickness than broader SSD diagnoses. Higher RVI score for narrow SSD subjects was consistent with expectations, as RVI was developed from a large sample of patients with a schizophrenia diagnosis (Kochunov et al., 2020; van Erp et al., 2018). One explanation for the reductions in age- and sex-normalized grey matter volume and cortical thickness in narrow SSD may be that individuals with broader SSD diagnoses may vary more in brain structure thanindividuals with schizophrenia and schizophreniform diagnoses. In support of this, previous research has observed robust reductions

in grey matter volume for patients with schizophrenia compared to bipolar disorder with psychotic features, but cortical differences between schizophrenia and schizoaffective or psychotic disorder NOS were less evident (Amann et al., 2016; Ivleva et al., 2012; Kumra et al., 2000). Taken together, cortical thickness-based neuroanatomic features more strongly distinguished schizophrenia and schizophreniform from other schizophrenia spectrum disorders. This is consistent with greater and more regionally specific reductions in cortical thickness for schizophrenia patients than surface area compared to healthy controls (van Erp et al., 2018).

Several limitations to the present study should be considered. First, our study included a sample of subjects with a wider range of SSD diagnoses and varied ages of psychosis onset than many previous studies of premorbid functioning. Given that the PAS assesses functioning through 6 months prior to psychosis onset, subjects with only one or two timepoints may have influenced the groups derived by the latent class model differently than subjects with all three PAS timepoints and/or the assignment of early-onset subjects to trajectory groups may have been less precise. However, the inclusion of subjects with earlier-onset SSD allowed for a more complete characterization of SSD subjects and the inclusion of subjects with broader SSD offered the opportunity to examine associations between premorbid functioning and clinical outcomes and neuroanatomical features across SSD diagnoses. Indeed, individuals with narrow versus broader SSD differed significantly in premorbid functioning, clinical outcomes, and neuroanatomy, suggesting that broader SSD diagnoses present with attenuated differences compared to healthy individuals. Another limitation is that the PAS is a retrospective scale that can be influenced by recall biases, such as anchoring judgments of past functioning with current levels of functioning. While these biases limit the objectivity of the PAS to accurately measure premorbid functioning, the PAS has been shown to predict important clinical outcomes in larger

patient cohorts than would be feasible in longitudinal measures across childhood and adolescence (Cannon-Spoor et al., 1982, Caqueo-Urízar et al., 2022, Schmael et al., 2007). Finally, cognitive and MRI acquisition methods differed across the contributing studies. Harmonizing data across multiple studies was critical to reach an adequate sample size to compare clinical and neuroanatomical characteristics across SSD subgroups; however, this may have added noise to these analyses, despite post-hoc methods to correct for between-study variation. Future studies that prioritize large study cohorts within a study site or utilize shared data with congruent data acquisition and processing methods across study sites will help to clarify the true association between SSD cognition and neuroanatomical features.

In summary, trajectories of premorbid functioning were associated with differential clinical characteristics within SSD, specifically differences in the age of psychosis onset and likelihood of having a narrow versus broader SSD. Deficits in premorbid psychosocial functioning increase the risk of developing SSD and may be less severe in schizophrenia compared to broader psychotic disorders. Premorbid functioning trajectories were not associated with current cognitive ability or MRI-based metrics in the current study, which may suggest a weaker relationship between MRI characteristics and premorbid trajectories of broad psychosocial functioning compared to trajectories of premorbid versus post-psychosis onset cognitive functioning. Future research will examine trajectories of premorbid functioning within a narrowly defined schizophrenia sample and their associations with regional brain morphometry.

Table 1: Latent class model comparison

	Complete	AIC	BIC	SABIC	%class1	%class2	%class3	%class4	%class5	%class6	%class7
Classes											
1	Yes	5466	5517	5482	100	NA	NA	NA	NA	NA	NA
2	Yes	5393	5462	5414	1.9	98.1	NA	NA	NA	NA	NA
3	Yes	5342	5429	5369	1.9	19.4	78.6	NA	NA	NA	NA
4	Yes	5311	5416	5343	1.9	71.7	7.1	19.3	NA	NA	NA
5	No	5336	5460	5374	18.2	20.4	60	1.4	0	NA	NA
6	No	5295	5437	5339	2.1	10.4	13.3	46.5	27.6	0	NA
7	No	5303	5464	5352	30.7	14.2	42.4	2.1	10.7	0	0

Table 2: SSD differences in demographic and clinical characteristics and neuroanatomical metrics

	Narrow SSD *(n=518)*	Broader SSD *(n=202)*	F	p
Sex				
Female	156	87		
Male	362	115		
Diagnosis				
Schizophrenia	387	0		
Schizophreniform	131	0		
Schizoaffective	0	87		
Mood disorder w psychotic features	0	23		
Brief psychotic disorder	0	1		
Psychotic disorder NOS	0	83		
Delusional disorder	0	7		
PAS				
Childhood composite score [Mean *(S.D)*, range: 0-6]	1.5 *(1.1)*	1.7 *(1.1)*		
Early adolescence composite score [Mean *(S.D)*, range: 0-6]	1.8 *(1.1)*	2.2 *(1.1)*		
Late adolescence composite score [Mean *(S.D)*, range: 0-6]	2.1 *(1.2)*	2.2 *(1.2)*		
Clinical Variables				
Age of Psychosis Onset [Mean *(S.D.)*]	20.5 *(5.2)*	18.6 *(5.3)*	19.41	**<0.001**
Current IQ [Mean *(S.D.)*]	98.3 *(15.7)*	102.0 *(15.7)*	6.46	**0.01**
Cannabis use disorder diagnosis [y/n]	104/253	33/142	1.21	0.27
Age of cannabis use diagnosis [Mean *(S.D.)*]	16.6 *(3.0)*	16.2 *(2.4)*	0.15	0.7
Neuroanatomical Metrics				
CT RVI [Mean *(S.D.)*, range: -1-1]	0.10 *(0.23)*	-0.00 (0.25)	12.78	**<0.001**
SA RVI [Mean *(S.D.)*, range: -1-1]	0.04 *(0.20)*	0.03 *(0.20)*	0.03	0.86
CT centile [Mean *(S.D.)*, range: 0-1]	0.35 *(0.27)*	0.50 *(0.34)*	10.59	**0.001**
SA centile [Mean *(S.D.)*, range: 0-1]	0.46 *(0.29)*	0.47 *(0.31)*	0.02	0.9
GMV centile [Mean *(S.D.)*, range: 0-1]	0.44 *(0.28)*	0.50 *(0.29)*	2.38	0.12

Table 3: Schizophrenia-spectrum class differences in demographic and clinical characteristics and neuroanatomical metrics

	Stable good (n=516)	Stable poor (n=139)	Late deteriorating (n=51)	Early deteriorating (n=14)	F	p
Sex					1.1	0.8
Female	174	44	19	6		
Male	342	95	32	8		
SSD Definition [narrow(%)/broader(%)]	383 (74%) / 133 (66%)	89 (17%) / 50 (25%)	39 (8%) / 12 (6%)	7 (1%) / 7 (3%)	9.19	**0.03**
Clinical Variables						
Age of Onset [Mean *(S.D.)*]	20.4 *(5.1)*	18.8 *(6.3)*	19.6 *(2.9)*	20.4 *(6.2)*	2.7	**0.03**
Current IQ [Mean *(S.D.)*]	99.5 *(16.3)*	97.7 *(14.6)*	100 *(13.6)*	105 *(14.7)*	1.2	0.3
Cannabis use disorder diagnosis [Yes *(% of class)*]	103 *(31%)*	19 *(18%)*	11 *(33%)*	4 *(33%)*	1.37	0.25
Age of cannabis use diagnosis [Mean *(S.D.)*]	16.6 *(2.7)*	16.7 *(4.9)*	16 *(1.4)*	16.7 *(1.1)*	0.1	0.9
Neuroanatomical Metrics						
CT RVI [Mean *(S.D.)* , range: -1-1]	0.08 *(0.23)*	0.05 *(0.26)*	0.08 *(0.30)*	0.02 *(0.21)*	1.8	0.2
SA RVI [Mean *(S.D.)* , range: -1-1]	0.04 *(0.20)*	0.02 *(0.18)*	0.02 *(0.20)*	-0.09 (0.25)	1.1	0.3
CT centile [Mean *(S.D.)* , range: 0-1]	0.37 *(0.30)*	0.49 *(0.31)*	0.36 *(0.31)*	0.59 *(0.27)*	2.1	0.1
SA centile [Mean *(S.D.)* , range: 0-1]	0.46 *(0.30)*	0.47 *(0.30)*	0.51 *(0.27)*	0.52 *(0.28)*	0.2	0.9
GMV centile [Mean *(S.D.)* , range: 0-1]	0.44 *(0.29)*	0.50 *(0.28)*	0.44 *(0.23)*	0.66 *(0.17)*	1	0.4

Table 4: Class differences in demographic and clinical characteristics and neuroanatomical metrics in full sample

	Stable good (n=2329)	Stable poor (n=399)	Late deteriorating (n=111)	Early deteriorating (n=65)	F	p
Sex					3.32	0.34
Female	1019	167	50	35		
Male	1310	232	61	30		
Diagnosis					168.13	**<0.001**
SSD Narrow (schizophrenia, schizophreniform)	383	89	39	7		
SSD Broader	133	50	12	7		
Controls	677	25	4	4		
SSD Relatives	207	38	5	3		
CHR Nonconverters	929	197	51	44		
PAS						
Childhood composite score [Mean *(S.D)* , range: 0-6]	1.0 *(0.7)*	3.1 *(0.6)*	0.9 *(0.7)*	0.8 *(0.7)*		
Early adolescence composite score [Mean *(S.D)* , range: 0-6]	1.4 *(0.9)*	2.8 *(1.0)*	1.5 *(1.0)*	3.7 *(0.8)*		
Late adolescence composite score [Mean *(S.D)* , range: 0-6]	1.4 *(1.0)*	2.4 *(1.2)*	3.7 *(0.8)*	2.0 *(1.3)*		
Clinical Variables						
Current IQ [Mean *(S.D.)*]	107 *(15.6)*	102 *(15.5)*	103 *(14.6)*	105 *(16.4)*	3.72	**0.01**
Cannabis use disorder diagnosis [Yes *(% of class)*]	265 *(13%)*	44 *(12%)*	23 *(25%)*	9 *(14%)*	3.16	**0.02**
Age of cannabis use diagnosis [Mean *(S.D.)*]	15.5 *(2.6)*	15.5 *(3.6)*	14.8 *(2.5)*	15.2 *(1.9)*	0.29	0.83
Neuroanatomical Metrics						
CT RVI [Mean *(S.D.)* , range: -1-1]	0.01 *(0.24)*	0.01 *(0.24)*	0.05 *(0.26)*	-0.02 (0.21)	0.63	0.59
SA RVI [Mean *(S.D.)* , range: -1-1]	0.02 *(0.20)*	0.02 *(0.20)*	0.04 *(0.20)*	0.02 *(0.23)*	0.17	0.92
CT centile [Mean *(S.D.)* , range: 0-1]	0.48 *(0.30)*	0.51 *(0.30)*	0.41 *(0.28)*	0.52 *(0.26)*	1.51	0.21
SA centile [Mean *(S.D.)* , range: 0-1]	0.47 *(0.29)*	0.48 *(0.29)*	0.43 *(0.30)*	0.49 *(0.34)*	0.39	0.76
GMV centile [Mean *(S.D.)* , range: 0-1]	0.50 *(0.28)*	0.52 *(0.29)*	0.44 *(0.29)*	0.57 *(0.32)*	1.34	0.26

Table 5: Diagnostic category differences in demographic and clinical characteristics and neuroanatomical metrics

	Narrow SSD (n=518)	Broader SSD (n=202)	SCZ Relative (253)	CHR Nonconverter (1221)	Control (710)	F	p
Sex							
Female	156	87	137	543	348		
Male	362	115	116	678	362		
PAS							
Childhood composite score [Mean *(S.D)* , range: 0-6]	1.5 *(1.1)*	1.7 *(1.1)*	1.3 *(1.0)*	1.5 *(1.0)*	0.8 *(0.7)*		
Early adolescence composite score [Mean *(S.D)* , range: 0-6]	1.8 *(1.1)*	2.2 *(1.1)*	1.5 *(1.0)*	1.9 *(1.1)*	0.8 *(0.7)*		
Late adolescence composite score [Mean *(S.D)* , range: 0-6]	2.1 *(1.2)*	2.2 *(1.2)*	1.5 *(1.1)*	2.0 *(1.2)*	0.8 *(0.7)*		
Clinical Variables							
Current IQ [Mean *(S.D.)*]	98.3 *(15.7)*	102.0 *(15.7)*	106.0 *(17.0)*	107.0 *(15.4)*	111.0 *(13.2)*	55.72	**<0.001**
Cannabis use disorder diagnosis [Yes *(% of class)*]	104 *(29%)*	33 *(19%)*	25 *(10%)*	152 *(12%)*	27 *(6%)*	5.86	**<0.001**
Age of cannabis use diagnosis [Mean *(S.D.)*]	16.6 *(3.0)*	16.2 *(2.4)*	15.0 *(3.6)*	14.8 *(3.4)*	15.8 *(1.8)*	5	**<0.001**
Neuroanatomical Metrics							
CT RVI [Mean *(S.D.)* , range: -1-1]	0.10 *(0.23)*	0.00 *(0.25)*	0.00 *(0.24)*	-0.01 (0.24)	0.01 *(0.24)*	9.93	**<0.001**
SA RVI [Mean *(S.D.)* , range: -1-1]	0.04 *(0.19)*	0.03 *(0.20)*	0.03 *(0.19)*	0.02 *(0.20)*	0.00 *(0.19)*	1.76	0.13
CT centile [Mean *(S.D.)* , range: 0-1]	0.35 *(0.27)*	0.49 *(0.34)*	0.46 *(0.28)*	0.51 *(0.30)*	0.50 *(0.29)*	8.32	**<0.001**
SA centile [Mean *(S.D.)* , range: 0-1]	0.46 *(0.29)*	0.47 *(0.30)*	0.46 *(0.29)*	0.46 *(0.29)*	0.5 *(0.29)*	0.97	0.42
GMV centile [Mean *(S.D.)* , range: 0-1]	0.44 *(0.28)*	0.50 *(0.29)*	0.46 *(0.29)*	0.51 *(0.29)*	0.52 *(0.28)*	2.95	**0.02**

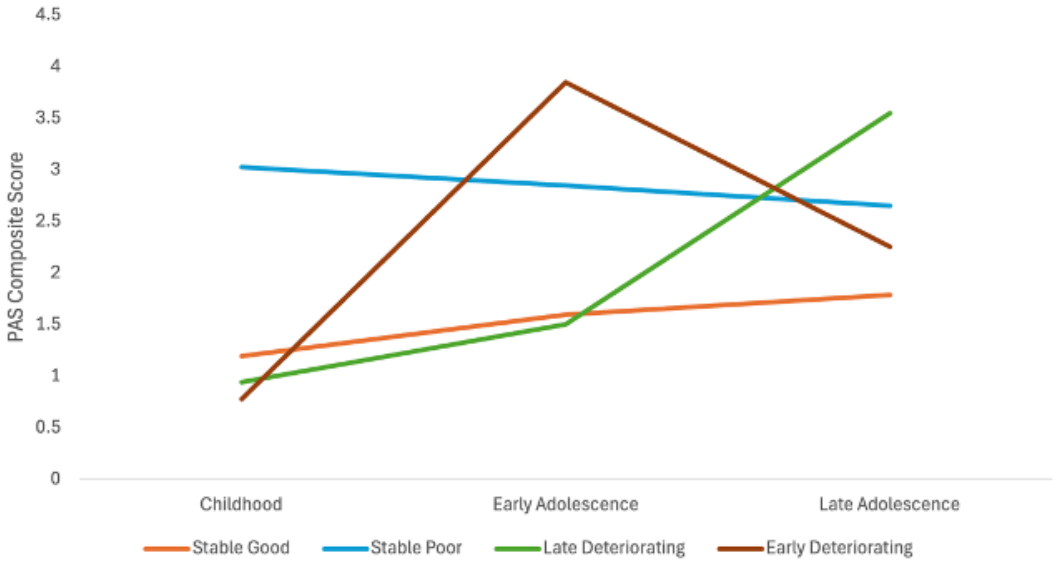

Figure 1: 4-class Premorbid Adjustment Scale (PAS) composite score model.

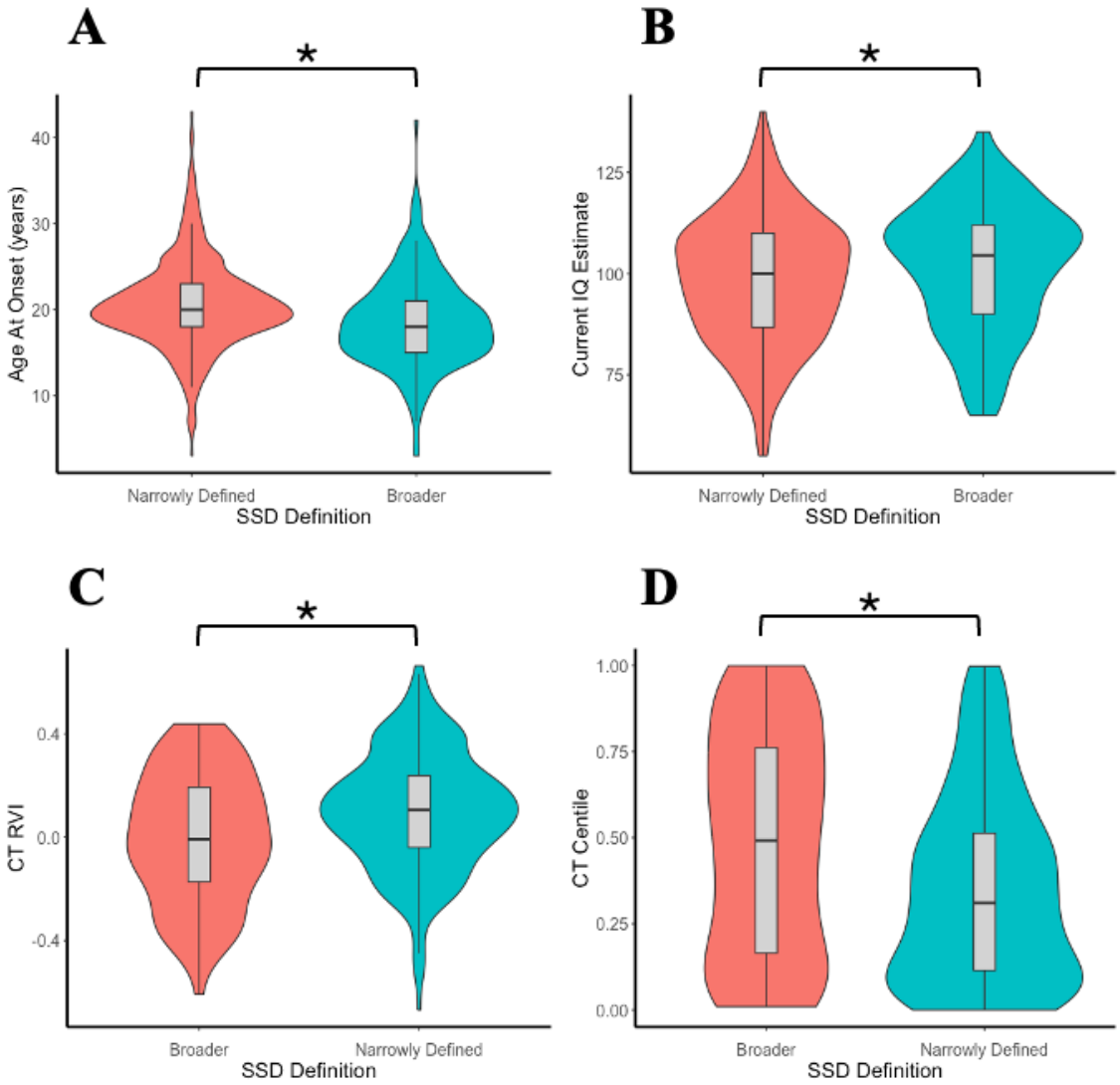

Figure 2. Schizophrenia spectrum disorder (SSD) definition differences in age at psychosis onset (A), current IQ estimate (B), cortical thickness (CT) regional vulnerability index (RVI) (C), and CT centile (D). *$p < 0.05$.

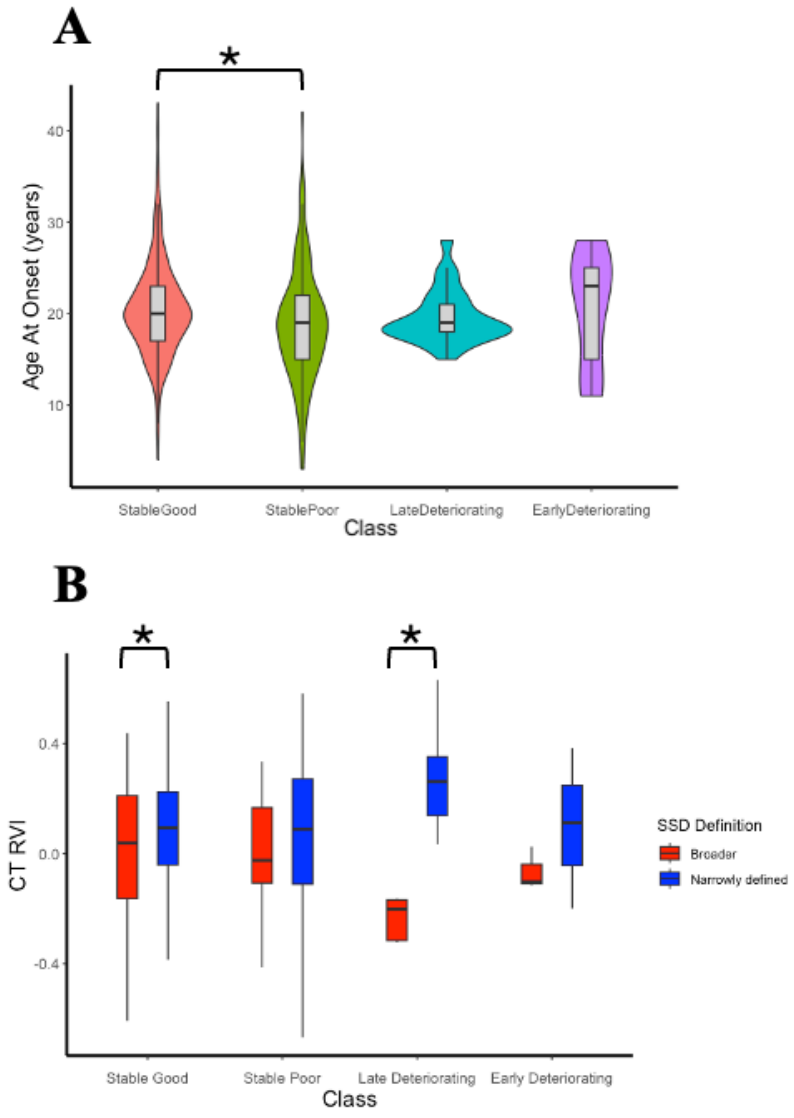

Figure 3. Class differences in age at psychosis onset (A) and class by schizophrenia spectrum disorder (SSD) definition on cortical thickness regional vulnerability index (CT RVI) (B). *$p < 0.05$.

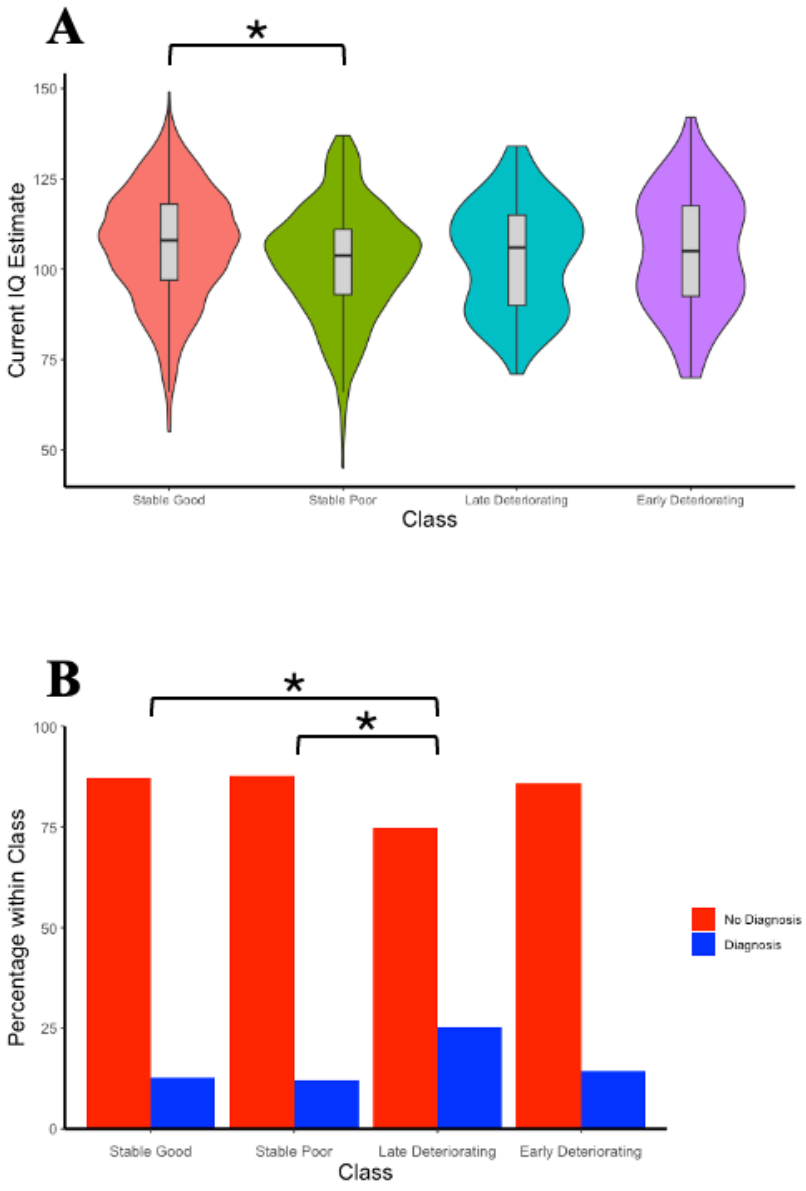

Figure 4. Full sample class differences in current IQ estimate (A) and lifetime cannabis use disorder diagnosis (B).
*$p < 0.05$.

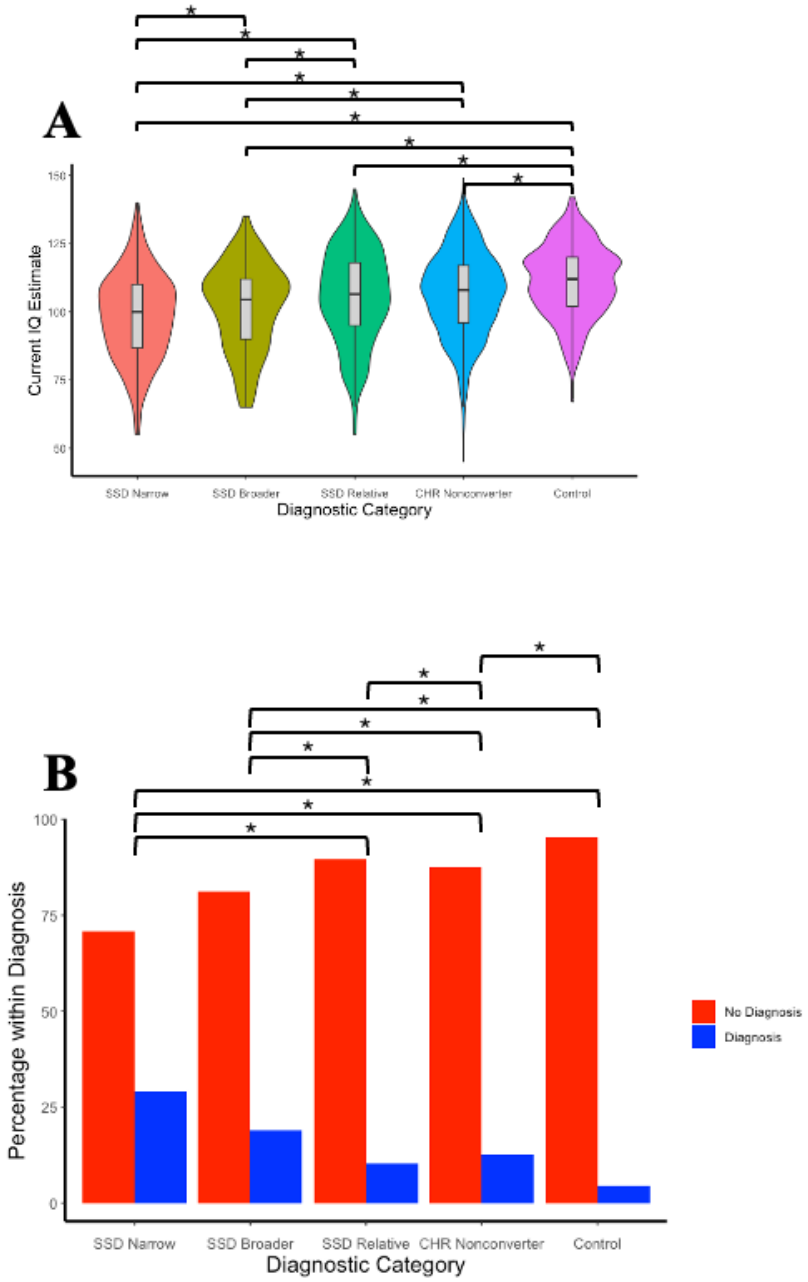

Figure 5. Full sample diagnostic category differences in current IQ estimate (A) and lifetime cannabis use disorder diagnosis (B). *$p < 0.05$.

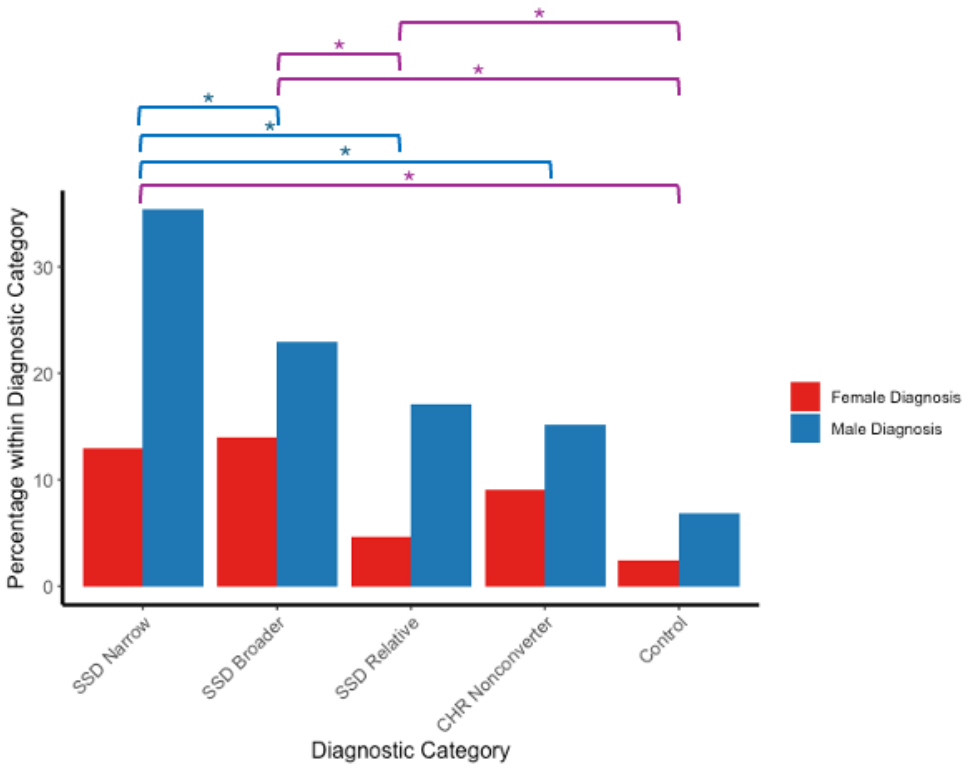

Figure 6. Full sample diagnostic category by sex on lifetime cannabis use disorder diagnosis. Purple bars indicate significant pairwise differences within males and within females. Blue bars indicate significant pairwise differences within males only. *$p < 0.05$.

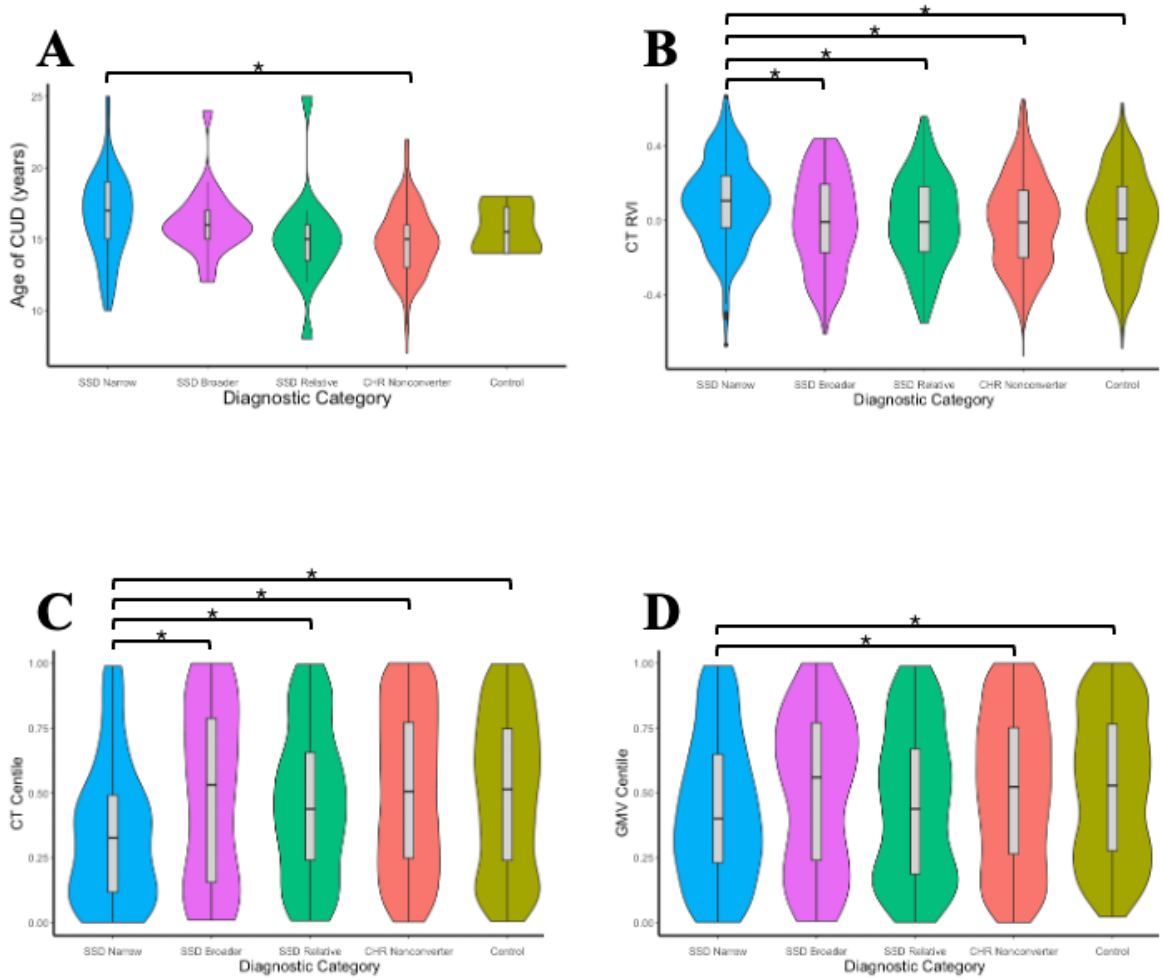

Figure 7. Full sample diagnostic category differences in age of cannabis use disorder (CUD) diagnosis (A), cortical thickness (CT) regional vulnerability index (RVI) (B), CT centile (C), grey matter volume (GMV) centile (D). *$p < 0.05$.

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