CHILDREN, ADOLESCENTS AND FAMILIES WITH SEVERE MENTAL ILLNESS: TOWARDS A COMPREHENSIVE EARLY IDENTIFICATION OF RISK

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EDITORIAL
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Editorial: Children, Adolescents and Families With Severe Mental Illness: Toward a Comprehensive Early Identification of Risk

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Editorial on the Research Topic

Children, Adolescents and Families With Severe Mental Illness: Toward a Comprehensive Early Identification of Risk

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Serious Mental Illnesses (SMI), such as depressive, bipolar, and psychotic disorders, often start in childhood and adolescence, are the leading cause of disability in young people and tend to cause life-long disability (1–4). SMI are commonly considered to originate from multiple, unfavorable and developmentally relevant gene-environment interactions; yet, the cause (or, more plausibly, the diachronic constellation of determinants and precipitating factors) of the SMI in an individual patient is usually unknown (5). Among epidemiological predictors, family disposition and early onset of mental problems are well-established predictors of SMI, in particular, when combined (6, 7). Furthermore, having a family member suffering from SMI profoundly affects family dynamics, e.g., by increasing expressed emotions, or by decreasing the patient's ability to support other family members while simultaneously increasing his or her need for their support (8, 9). On a converging line, it has been recently confirmed that, for example, preventive interventions targeting the offspring of parents with SMI have tangible prognostic impact both in terms of reduced incidence of mental illness in children and attenuation of internalizing symptoms (10, 11). However, within the framework of the early detection of psychosis, a positive family history of psychosis even in combination with a recent drop in functioning was an insufficient predictor of a conversion to first-episode psychosis by itself when compared to symptom-based risk criteria (12–14). Thus, contemporary clinical applied research on the early detection of SMI, even in its most developmentally-oriented branches, typically emphasizes an indicated approach based on subtle psychopathological antecedents (e.g., attenuated positive symptoms and basic symptoms [BS] as included in Clinical High Risk [CHR] criteria, anomalous subjective experiences, and schizotypal traits) (15) while the best strategy to incorporate evidence-based, transgenerational familial risk features still warrants more research (14, 16). Therefore, addressing the need of care and developing suitable early identification strategies for familial or genetic high-risk, and other young vulnerable groups is essential (11, 16–23).

In light of the above, this Research Topic aimed to disentangle some of the complexities in the field of children, adolescents and families with SMI, to advance knowledge on young people and families suffering from or being at risk of developing SMI and set the stage toward a comprehensive early identification of risk for SMI in children and adolescents (16, 20, 22, 23).

CLINICAL HIGH-RISK STATE FOR PSYCHOSIS AND FAMILIAL VULNERABILITY: THE MANIFOLD INTERSECTION OF RISK

Nine papers in this Research Topic broadly addressed a clinical high-risk state (CHR) of psychosis in children and adolescents mainly by ultra-high risk (UHR) but also by basic symptom criteria (12, 13). Based on reports of high rates of personality disorders in adult UHR samples, Boldrini et al. examined personality traits in a 13–19-year-old Italian UHR sample (n = 58). Their results indicate that avoidant interpersonal strategies, impaired mentalization, and difficulties in emotional regulation might be important treatment targets to prevent both personality disorder and psychosis. Walger et al. examined the prevalence and the age effect of 14 criteria-relevant basic symptoms on clinical and functional patterns in a UHR sample (N = 261, age 15–40 yrs.). Results showed the high prevalence of basic symptoms (BS) in UHR and confirmed an age effect in BS and, thus, the earlier assumed link between presence of BS and brain maturation processes.

Poletti, Azzali, et al. investigated the prevalence of SMI in family members of distinct clinical subgroups of adolescents (n = 147; non-UHR vs. UHR vs. first-episode psychosis). Interestingly, results showed that more than 60% UHR had any broader family history of SMI, approximately a third of them by at least one first-degree relative. These results confirm the importance of within-family risk factors in UHR adolescents, suggesting the crucial need of their early detection. Consistently with the latter study, a clinical-conceptual perspective paper by Poletti, Gebhardt, et al. aimed to disentangle the complex intertwine of intergenerational risk factors that contribute to the risk of developing SMI in offspring, taking schizophrenia spectrum disorders as paradigmatic example.

In line with the UHR approach, Hartmann et al. offer initial insights on a broader, more agnostic approach to risk identification-to better capture the diffuse nature of emerging psychopathology, its developmental nuances and the multiplicity of potential exit syndromes other than psychosis (e.g., mania, severe depression, and personality disorder). Such extended approach, termed clinical high at-risk mental state [CHARMS (24)], might empower current opportunities for early risk inception, targeted early intervention and prevention strategies. On a complementary side, Kang-Yi et al. adopt an original angle to illuminate a widely neglected topic, that is the multitude of psychiatric diagnoses and related treatment that precede the recognition of schizophrenia in adolescents between 9 and 17 years (n = 1,459). The study confirmed earlier findings of multiple diagnoses and treatments initiated prior to, overall indicating a considerable need of care even in the prolonged help-seeking phase before the first and often delayed diagnosis of schizophrenia.

In a more basic research approach, Di Lorenzo et al. investigated the differences in auditory mismatch negativity (MMN) parameters in a 9–18-year-old sample of subjects with autism spectrum disorder (n = 37) with or without UHR by attenuated psychotic symptoms. The group with both conditions demonstrated a negative correlation between the severity of autistic symptoms and the MMN latency, although aberrations MMN amplitude and latency in the whole group were independent of concurrent attenuated psychotic symptoms. Büetiger et al. investigated the neural correlates of depersonalization and derealization through MRI in a mixed clinical sample of help-seeking individuals (CHR n = 97; clinical controls n = 91 and first-episode psychosis n = 29. Against the background of frequently depersonalization and derealization symptoms are frequent in CHR subjects, this study gives preliminary evidences that there may be divergent pathophysiological mechanisms leading to a final common pathway with similar psychopathological symptoms. Johnsen et al. conducted a systematic review on functional magnetic resonance imaging (fMRI) studies which examined task-related brain activity in young individual at familial high-risk for schizophrenia or bipolar disorder. Nineteen studies were selected. While the low number of studies and the substantial heterogeneity of employed methodological approaches impedes definite conclusions, all together these studies provide evidence for an altered brain processing of emotions in young individuals at familial high-risk for bipolar disorder.

DEPRESSIVE AND OBSESSIVE FEATURES IN DEVELOPMENTAL YEARS

Four papers focus on depressiveness or obsessive-compulsivity in children and adolescents. Studying depression, sleep disorders and inflammatory factors in a 15–18-year-old mixed community-outpatient US sample (n = 92), Reddy et al. reported that one potential pathway between depressive symptoms and sleep disturbances in adolescents may be through an elevated tumor necrosis factor.

Two Chinese studies provided further support of an association between screen/internet use and depressiveness. In a large 10–15-year-old student sample (n = 14,500), Xu et al. showed that the consumption of fast food and sugar-sweetened beverages partially mediate the association between screen time and depressive symptoms by chain mediating effects. Furthermore, in a 11–15-year-old smaller student sample (n = 522), Chi et al. reported that a less positive youth development mediates the association between Internet addiction and depression, and that well-developed mindfulness can alleviate the negative effect of Internet addiction or a low level of psychological resources on depression.

Finally, Novara et al. present the validation of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) in a sample of children with OCD (n = 53) and Tourette Syndrome and TIC (n = 14). Their study indicates that a two-factor model of obsessions and compulsions represent appropriate measures for evaluating and monitoring the management of children with OCD.

EMPOWERING MENTAL HEALTH CARE PROVISION IN CHILDREN AND ADOLESCENTS

Five papers focussed on both general and specific aspects of mental health care provision in children and adolescents. Focussing on need for mental health care in unaccompanied refugee adolescents (n = 561) in Germany, Hanewald et al. reported relevant mental complaints in a 43.6% of the sample. The rates were affected by origin, age and sex, and substantiate the need for early detection of mental complaints and appropriate mental health care for at least every second unaccompanied refugee minor. In a Danish register study of children of psychiatric patients (N = 376) referred to child protection services, Ranning et al. found that only one third of children received support within 1 year after referrals from psychiatry, within an average of 3 months. Their results suggest that children of psychiatric patients represent an underserved population of children at risk for mental disorder. In a school setting study led in Spain, Romero-Ayuso et al. validated and tested (n = 103 teachers and n = 536 children) the potential usefulness of a questionnaire (EPYFEI-Escolar) aimed at determining academic needs and difficulties of children aged 3–11 yrs old. The results suggest the usefulness of this tool and shows that it can also be used to plan intervention programs in the school environment according to the needs of each child and school.

Capitalzing on an ongoing Norwegian innovative research project for child and adolescent mental health disorders, i.e., the Individualized Digital DEcision Assist System, Røst et al. present a model to adapt and harness technological advancements such as computerized Clinical Decision Support Systems, to support practitioners in providing evidence-based care in child and adolescent mental health services.

Finally, given the increased risk of mental disorders in children with a positive family history of SMI, Wiegand-Grefe et al. discuss the architecture of a family-based intervention program for children of mentally ill parents (CHIMPs) whose overall scheme consists of a two-group randomized controlled multicenter trial of soft-psychosocial intervention involving families with mentally ill parents and their children aged 3–19 years.

INTERGENERATIONAL RISK IN OTHER PSYCHOPATHOLOGICAL SPECTRA: AUTISM, 22Q11.2 DELETION SYNDROME, AND NON-SUICIDAL SELF-INJURY

Three papers addressed intergenerational risk features in relevant, adjacent areas of psychopathology, such as autism-spectrum disorder (ASD), psychopathological expressions of 22q11.2 deletion syndrome, and non-suicidal self-injury (NSSI). Coelho and Conceição investigated whether parental perceptions of the disorder could contribute to a better outcome prediction of children with ASD (n = 55). Together, the findings of this study suggest that parents' concerns should be taken into account when planning a therapeutic intervention for ASD. Sandini et al. focused on the 22q11.2 deletion syndrome (aka DiGeorge syndrome and velocardiofacial syndrome), which is characterized by an extended and highly variable psychiatric phenotype across subjects (including schizophrenia, anxiety disorders, mood disorders, and Attention Deficit Hyperactivity Disorder) to look for bi-directional interactions of parental anxious-depressive features and offspring psychopathology. The results confirm an intergenerational association between high levels of parental anxiety and depression and increased psychopathology in offspring for both internalizing and externalizing symptoms. Fu et al. focus on the wide domain of non-suicidal self-injury through a qualitative research design and specifically explore parents' attitudes toward and perceptions of adolescents who have engaged in such behaviors. The study highlights important neglected aspects of the broader non-suicidal self-injury behavior impact on the family, in particular that parents suffer great emotional stress and often lack the knowledge about non-suicidal self-injury and its treatment.

CONCLUSION

Overall, we believe that this Research Topic on "Children, Adolescents and Families with Severe Mental Illness: Toward a Comprehensive Early Identification of Risk" that will be continued as a Community Series provides a comprehensive rationale for rethinking a new wave of broad, family-sensitive approaches to better understand the determinants of SMI in children and adolescents and preventing mental ill-health.

AUTHOR CONTRIBUTIONS

AR, FS-L, and MA contributed substantially to the development of this special issue in the conceptual planning as well as in the reviewing and editing of the included papers. Similarly, they jointly contributed to the preparation and review of the editorial manuscript. All authors contributed to the article and approved the submitted version.

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Internet Addiction and Depression in Chinese Adolescents: A Moderated Mediation Model

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Research has revealed that Internet addiction is a risk factor for adolescents' development of depressive symptoms, although the underlying mechanisms are largely unknown. The present study examines the mediating role of positive youth development and the moderating role of mindfulness to determine the association between Internet addiction and depression. A sample of 522 Chinese adolescents completed measures related to Internet addiction, positive youth development, mindfulness, depression, and their background information, for which the results reveal that positive youth development mediates the relation between Internet addiction and depression. Moreover, the associations between both Internet addiction and depression as well as positive youth development and depression are moderated by mindfulness. These two effects were stronger for adolescents with low mindfulness than for those with high mindfulness. The present study contributes to a more thorough understanding of how and when Internet addiction increases the risk of depression in adolescents, suggesting that Internet addiction may affect adolescent depression through positive youth development and that mindfulness can alleviate the negative effect of Internet addiction or a low level of psychological resources on depression. The implications for research and practice are finally discussed.

Keywords: internet addiction, depression, positive youth development, mindfulness, Chinese adolescents

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INTRODUCTION

The Internet has introduced significant convenience to our lives, although it has also brought about a serious mental health problem: Internet addiction, which is defined as an individual's inability to control his/her use of the Internet (1, 2). Internet addiction may cause various psychological and behavioral problems in an individual's life, including academic failure (3), sleeplessness (4), loneliness (5), and interpersonal relationship conflicts (6), among others. In recent years, depression has emerged as another prevalent and severe psychological problem in adolescents. Depression may negatively influence adolescents in various ways, including their achievement of poor interpersonal relationships, a low quality of life, academic failure, and even suicide (7–9). The relationships between Internet addiction and depression among adolescents are especially important because they are harmful (10), and evidence suggests that Internet addiction and depression are strongly correlated (11). For example, a study of 34 diverse high schools in Western Australia (12) found that Internet addiction (e.g., social networking sites addiction) may lead to depression, while a study of six Asian

countries (13) determined that Internet addiction may positively predict depression in adolescents aged twelve to eighteen years.

Despite previous study findings that claim Internet addiction may be strongly related to depression, the underlying mediating mechanism (i.e., how Internet addiction influences depression) and moderating mechanism (i.e., when Internet addiction is related to depression, or the difference in the degree of Internet addiction related to depression among different groups) remain unclear, especially among Chinese adolescents. Regarding Internet addiction and depression in Chinese adolescents, reports have found that the prevalence of Internet addiction among adolescents aged eleven to eighteen years in China was between 2.4% and 18.2% (4, 14), while the prevalence of depression was about 30% among adolescents aged twelve to nineteen years (15). These serious problems are attracting considerable attention from society and mandating that research urgently explore the underlying mechanisms of Internet addiction and depression among Chinese adolescents. Therefore, the present study constructs a moderated mediation model to examine the mediating role of positive youth development and the moderating role of mindfulness in the relation between Internet addiction and depression in Chinese adolescents. The findings promote an understanding of how and when Internet addiction is associated with depression in adolescents so as to provide effective prevention and intervention strategies against Internet addiction and depression among this group.

Positive Youth Development as a Mediator

The development assets theory suggests that the occurrence of problem behaviors may be attributed to a lack of positive psychological resources, such as positive youth development features (e.g., self-efficacy and resilience) (16). Psychological resources may be weakened by adversity, difficulties, and stress from environmental and personal perceptions (17–20). When these positive resources are absent, individuals no longer have the ability to adapt to their situations and are thus unable to rid themselves of the adverse effects of negative influence, which may further yield externalized and internalized problems (21, 22). Positive youth development, which integrates multiple psychological resources, refers to the individual's potential in terms of talent, strength, interest, ambition, and so forth rather than one's lack of abilities (23). Based on the positive youth development perspective, Catalano et al. (24) proposed a model comprising the following fifteen constructs: bonding, resilience, social competence, emotional competence, cognitive competence, behavioral competence, moral competence, self-determination, self-efficacy, spirituality, beliefs in the future, clear and positive identity, recognition for positive behavior, prosocial involvement, and prosocial norms. This model, which has been implemented by researchers in Western countries for youth development research, inspired Shek and Sun (25) to develop the Chinese Positive Youth Development Scale (CPYDS), which has been widely employed in the Chinese context (26, 27).

An increasing number of empirical studies demonstrate that positive youth development features may help prevent/reduce various externalized and internalized problems among adolescents (24, 28). Further, positive youth development constructs (e.g., positive identity and cognitive–behavioral competence) mediate the correlation between adversity (e.g., childhood maltreatment) and adolescent depression (28). Regarding Internet addiction and depression, researchers stress that Internet addiction can undermine adolescents' offline activities by, for instance, influencing grade declines and poor parent–child and peer relationships, thus forcing them to experience stress (29). On the other hand, being tempted by the network and resisting the temptation to control themselves also force adolescents to experience stress. These stressors may result in their loss of psychological resources (e.g., self-efficacy) and increase their risk of developing mental health problems (e.g., depression) (30). Studies demonstrate that Internet addiction and depression are strongly associated with positive youth development; for example, Shek and Yu (31) found that positive youth development is negatively related to Internet addiction among adolescents aged ten to eighteen years in Hong Kong. Studies have also found that positive youth development negatively predicts depression (32, 33). Based on the development assets theory and previous research, we hypothesized that positive youth development mediates the relationship between Internet addiction and depression (Hypothesis 1).

Mindfulness as a Moderator

Mindfulness refers to the state of being aware of the present reality or current experience in an accepting or non-judgmental way (34, 35). Some researchers believe mindfulness can be defined as a psychological trait that refers to an individual's tendency to be mindful in one's daily life (34, 36, 37); in other words, mindfulness may be simultaneously regarded as both a state and a trait. Previous studies have determined that mindfulness can be wielded as a protective factor during an individual's positive development (38, 39). For example, Chen et al. (40) and Meiklejohn et al. (41) consistently find that mindfulness can promote adolescents' mental health by, for instance, improving their resilience and emotional competence (e.g., emotional adjustment skills).

Although Internet addiction can negatively affect adolescents, this influence may vary according to age, gender, and personal traits (42, 43). We are interested in whether or not Internet addiction influences mental health differently among individuals with different levels of mindfulness. According to the re-perceiving model of mindfulness, mindfulness can help people re-perceive moment-by-moment experiences with greater objectivity and awareness, rid themselves of automatic behavioral and emotional patterns, and facilitate their adaptive responses to negative stimulation (44). Therefore, researchers suggest that mindfulness may play a risk-buffer role and alleviate the negative effects of risk factors on mental health (39, 45–47). Previous studies demonstrate that higher levels of mindfulness may simplify an individual's development of the ability to re-perceive and subsequently reduce psychological distress as well as the effects of adversity or stress on one's psychological health (48, 49). For example, mindfulness can

weaken the impact of psychological distress on emotional eating behaviors (50) as well as alleviate the impact of bullying on mental resilience and depression (47).

These studies further determined a stronger relation between psychological vulnerability and mental health problems for individuals who possess lower mindfulness (45–47, 50, 51). Regarding the moderating effects of Internet addiction and mental health, research has determined that mindfulness may contribute toward alleviating the negative effects of Internet addiction (e.g., mobile phone addiction) on mental health (52). For example, mindfulness moderates the relation between mobile phone addiction and sleep disturbance, and this effect is weaker in individuals with higher levels of mindfulness (46, 53). Another study suggests that the effect of mobile phone addiction on depression is moderated by mindfulness, wherein the impact is stronger among adolescents with lower levels of mindfulness (51). Thus, in the present study, one may reasonably expect mindfulness to act as an important protective factor that moderates the link between Internet addiction and positive youth development (Hypothesis 2), the link between Internet addiction and depression (Hypothesis 3), and the link between positive youth development and depression (Hypothesis 4).

The Present Study

In summary, the present study examines the mechanisms underlying the association between Internet addiction and depression in adolescents as well as explores the mediating effect of positive youth development and the moderating effect of mindfulness. According to Hayes (54), regarding the combination of mediation and moderation models, if positive youth development mediates the association between Internet addiction and depression and mindfulness moderates the relation between Internet addiction and depression, the mediating effect of positive youth development is then moderated by mindfulness, and the moderated mediation model may be therein constructed. In this model, positive youth development acts as a mediator (i.e., how Internet addiction is associated with depression) while mindfulness acts as a moderator (i.e., when the relation between Internet addiction and depression is stronger) in the relationship between Internet addiction and depression. The proposed moderated mediation model is presented in **Figure 1** below.

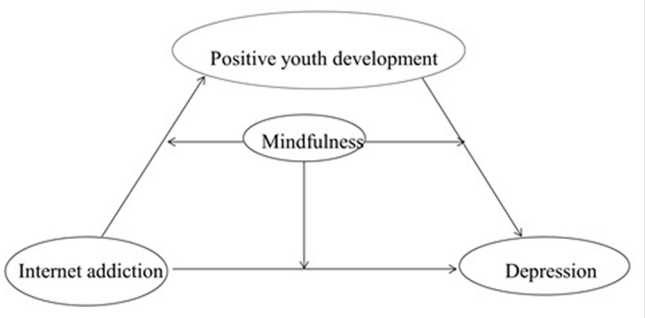

FIGURE 1 | Conceptual model.

METHOD

Participants and Procedure

A total of 532 adolescents from two public middle schools in China participated in our survey, of which 522 (98.12%) completed valid questionnaires. The participants comprised 298 male students and 221 female students. Three participants declined to report their gender, while three declined to report their age; the participants' mean age was 12.33 (SD age = 0.56, range = 11–15). Two trained psychology graduate students administered the survey; one introduced the study's purpose, while the other helped maintain order. During the roughly twenty-five survey, students were required to sit separately, to remain quiet, and to not engage in discussion. The study and data collection procedure received approval from the administration committees of the surveyed colleges and universities as well as the Human Research Ethics Committee of Shenzhen University.

Measurements

Internet Addiction

Internet addiction was measured using Young and De Abreu's (55) ten-item Internet addiction test. The participants rated these items by answering "yes" or "no" according to whether or not they had experienced the according Internet addiction in the past year. A person was classified as having an "Internet addiction" if he/she expressed four or more of the listed behaviors. The test achieved good reliability and validity in prior studies (33); in this study, the Cronbach's α for Internet addiction was 0.82.

Depression

Depression was assessed using the Chinese version of the Center for Epidemiologic Studies Depression Scale (CES-D), which has been tested with Chinese adolescents and has reached good reliability and validity (56). The scale comprises twenty items, each of which was answered on a four-point scale (0 = never, 3 = always) wherein higher values indicate more severe depressive symptoms. The total depression score was divided by 16 points, 15 points, and less than 15 points for no depressive symptoms and 16 points or more for depressive symptoms. In this study, the Cronbach's α for the CES-D was 0.87.

Positive Youth Development

Chinese Positive Youth Development Scale was compiled by Shek and Sun (25) in the Chinese culture context to examine adolescents' fifteen positive psychological qualities (e.g., resilience, self-efficacy, emotional competence, cognitive competence) by scoring their responses on a scale ranging from 1–6 (1 = strongly disagree, 6 = strongly agree). The total score is averaged by items to form a scale score, with higher scores reflecting a higher level of positive psychological qualities. This scale is widely applied and has reached good reliability and validity in prior research (57). In this study, the Cronbach's α for positive youth development was 0.97.

Mindfulness

Mindfulness was measured using the ten-item Child and Adolescent Mindfulness Measure (CAMM) (58), which has been

implemented with Chinese adolescents and has reached good reliability and validity (59). This measure was scored on a scale ranging from 0–4 (0 = never true, 4 = always true). All items were scored in reverse, with higher scores indicating a higher tendency to be mindful in everyday life. In this study, the Cronbach's α for the CAMM was 0.88.

Statistical Analysis

In this study, to maximize statistical power, replacement values for missing data were first estimated using the expectation-maximization algorithm as implemented in SPSS 22.0. Descriptive statistics and a bivariate correlation analysis were secondly conducted. Third, the mediation model (model 4) and the moderated mediation model (model 59) were then tested by using the SPSS macro PROCESS. Why we choose SPSS macro PROCESS rather than SEM program is based on following considerations. Firstly, SPSS is still one of most popular tools used by researchers in psychology and psychiatry (many other fields as well), although new data analysis tools (e.g., Mplus) appear (60). Further, the SPSS macro PROCESS introduced by Hayes (54) has been widely utilized to test complex models of the observed variables, such as the moderated mediation model and the mediated moderation model (e.g., 46, 60, 61). One of advantages of SPSS macro PROCESS is that may offer the Johnson Neyman method of visualizing the interaction effect by generating a series of plots that can be later assembled into a diagram/graph. The diagram depicts the conditional effect of X (focal predictor) on Y (dependent variable), as a function of M (moderator variable). The moderating effects may clearly be probed using the regions of significance in accordance to the Johnson-Neyman technique (54). The bootstrapping method was applied to test for the effects' significance so as to obtain robust standard errors for parameter estimation (54). Specifically, this method produced 95% bias-corrected confidence intervals for these effects from 1,000 resamples of the data; confidence intervals that do not contain zero indicate effects that are significant.

RESULTS

Preliminary Analyses

The results of the descriptive statistics (mean and SD) and correlation analysis are presented in **Table 1**. In this study, the prevalence rates of Internet addiction and depression among adolescents were about 20.44% and 28.16%, respectively. Internet addiction was negatively correlated with mindfulness and positive youth development although positively correlated with depression. Positive youth development was negatively correlated with depression and positively correlated with mindfulness, while mindfulness was negatively correlated with depression.

Testing for the Mediation Model

To test the mediation model, we applied model 4 in model templates for the SPSS for SPSS (http://www.afhayes.com), as is suggested by Hayes (54). As can be perceived from **Table 2**, Internet addiction is positively associated with depression in the mediator's absence ($\beta = 0.46$, $p < 0.001$), while Internet addiction is negatively associated with positive youth development

TABLE 1 | Descriptive statistics and inter-correlations between variables.

Variable	Not addicted/ depressive	Addicted/ depressive	M	SD	1	2	3	4
	n (%)	*n* (%)						
1. IA	327(79.56%)	84(20.44%)	1.54	2.18	–			
2. PYD	–	–	5.01	0.72	–0.33**	–		
3. Mindfulness	–	–	27.40	8.14	–0.39**	0.31**	–	
4. Depression	375(71.84%)	147(28.16%)	12.42	9.21	0.42**	–0.50**	–0.49**	–

*N = 522, IA, internet addiction; PYD = positive youth development, **p < 0.01.*

TABLE 2 | Mediation analysis.

Outcome variables	Independent variables	*B*	*SE*	*t*	*p*
Depression	Constant	0.0001	0.04	0.0001	1.00
	Internet addiction	0.46***	0.04	10.42	<0.001
PYD	Constant	0.0001	0.04	0.0001	1.00
	Internet addiction	–0.33***	0.04	–8.09	<0.001
Depression	Constant	0.0001	0.04	0.0001	1.00
	Internet addiction	0.28***	0.04	7.32	<0.001
	PYD	–0.40***	0.04	–10.37	<0.001

*N = 522, bootstrap sample size = 5000; all data is standardized, the beta values are standardized coefficients, thus they can be compared to determine the relative strength of different variables in the model; ***p < 0.001.*

(β = −0.33, p < 0.001). Moreover, when Internet addiction is controlled for, positive youth development is negatively correlated with depression (β = −0.40, p < 0.001), while when positive youth development is controlled for, the relationship between Internet addiction and depression is significantly positively (β = 0.28, p < 0.001). Finally, to test the mediation model, the bias-corrected percentile bootstrap method was conducted, and the present study generated 5,000 bootstrapping samples from the standardized data (N = 522) *via* random sampling. As can be observed in **Table 3**, the indirect effect of positive youth development was 0.13 (95% CI = [0.09, 0.18]); the empirical 95% confidence interval did not overlap with zero, which means the mediation effect was significantly. Further, the mediation effect accounted for 32.21% of the total effect of the relationship between Internet addiction and depression. Therefore, positive youth development mediates the association between Internet addiction and depression, and Hypothesis 1 is thereby supported.

Testing for the Moderated Mediation Model

To test the mediation model, we applied model 59 in model templates for the SPSS for SPSS (http://www.afhayes.com), as is suggested by Hayes (54). The results are displayed in **Table 4**, wherein the mediator variable model that predicts positive youth development indicates that Internet addiction is negatively associated with positive youth development (β = −0.27, p < 0.001), mindfulness is positively associated with positive youth development (β = 0.20, p < 0.001), and the interaction between Internet addiction and mindfulness is not significant (β = −0.02, p > 0.05); thus, hypothesis 2 is not supported. As can be seen from the dependent variable model that predicts depression, Internet addiction is positively correlated with depression (β = 0.12, p < 0.01), while the interaction between Internet addiction and mindfulness is negatively correlated with depression (β = −0.08, p < 0.05). Therefore, mindfulness moderates the relationship between Internet addiction and depression, and hypothesis 3 is thereby supported. In addition, positive youth development is negatively correlated with depression (β = −0.33, p < 0.001), while the interaction between positive youth development and mindfulness is negatively correlated with depression (β = 0.15, p < 0.001); namely, mindfulness moderates the relationship between positive youth development and depression, and hypothesis 4 is thereby supported.

These results indicate that the relationships between both Internet addiction and depression as well as positive youth development and depression are moderated by mindfulness (see **Figures 2** and **3**). To more thoroughly understand the moderating effect of mindfulness, **Figure 2** describes the relationship between Internet addiction and depression at two levels of mindfulness (i.e., 1 SD below the mean and 1 SD above the mean). In addition, as can be observed from the conditional direct effect analysis in **Table 4**, the effect of Internet addiction on depression was observed when mindfulness was moderated to low (β = 0.20, p < 0.001), although not when mindfulness was high (β = 0.05, p > 0.05). Furthermore, to more thoroughly understand the moderating effect of mindfulness, **Figure 3** describes the relationship between positive youth development and depression at two levels of mindfulness (i.e., 1 SD below the mean and 1 SD above the mean). In addition, as can be seen from the conditional indirect effect analysis in **Table 4**, the effect of Internet addiction on depression was observed when mindfulness was moderated to low (β = 0.12, p < 0.001) as well as when mindfulness was high (β = 0.05, p < 0.05). In other words, positive youth development significantly predicted depression in adolescent group with low mindfulness, while among those with high mindfulness, positive youth development had a significant, but weaker prediction on depression.

TABLE 3 | Bootstrapping indirect effect and 95% confidence interval (CI) for the mediation model.

Indirect path	Estimated effect	95% CI		Ratio to total effect on depression
		LL	UL	
Internet addiction→ PYD→ depression	0.13	0.09	0.18	32.21%

N = 522, bootstrap sample size = 5000, LL, low limit; CI, confidence interval; UL, upper limit; all data is standardized.

DISCUSSION

In the present study, we constructed a moderated mediation model to analyze the mechanism underlying the association between Internet addiction and depression among Chinese adolescents. The results reveal that positive youth development plays the role of mediator and mindfulness plays the role of moderator in the relations between Internet addiction and depression and between positive youth development and depression; these two correlations are stronger for individuals with low mindfulness than for those with high mindfulness. These findings contribute to a more thorough understanding of how and when Internet addiction is associated with depression.

Specifically, we found that positive youth development mediates the relation between Internet addiction and depression. This result coincides with previous studies concerning the relationship between Internet addiction and positive youth development (11, 62) and the relationship between positive youth development and depression (32, 63–65). Researchers suggest that the displacement of offline social interaction *via* online social communication may lead to emotional disorders, such as depressive symptoms (66). For example, adolescents who engage in more online social activities may be more inclined to experience conflict with their parents and peers, social interaction withdrawal in real life, and a decline in their ability to regulate their emotions (67, 68). In other words, Internet addiction can deprive young people of forming real-world social relationships due to the excessive amount of time they spend online (13). These situations may reduce adolescents'

TABLE 4 | Conditional process analysis.

	β	*SE*	*t*	*p*
Mediator variable model for predicting PYD				
Constant	−0.01	0. 04	−0.18	0.86
Internet addiction	−0.27***	0.05	−5.57	<0.001
Mindfulness	0.20***	0.04	4.57	<0.001
Internet addiction x Mindfulness	−0.02	0.04	−0.55	0.58
Dependent variable model for predicting depression				
Constant	−0.07	0.04	−2.07	0.04
Internet addiction	0.12**	0.04	3.02	<0.01
Positive youth development	−0.33***	0.04	−9.13	<0.001
Mindfulness	−0.31***	0.04	−8.43	<0.001
Internet addiction x Mindfulness	−0.08*	0.03	−2.24	<0.05
Positive youth development x Mindfulness	0.15***	0.04	4.11	<0.001
	B	*SE*	*LLCI*	*ULCI*
Conditional direct effect analysis at values of the moderator				
M − 1SD	0.20***	0.04	0.11	0.28
M	0.12***	0.04	0.04	0.20
M + 1SD	0.05	0.06	−0.07	0.17
	B	*Boot SE*	*Boot LLCI*	*Boot ULCI*
Conditional indirect effect analysis at values of the moderator				
M − 1SD	0.12	0.03	0.06	0.18
M	0.09	0.03	0.04	0.14
M + 1SD	0.05	0.03	0.01	0.12

*N = 522, bootstrap sample size = 5000, LL, low limit; CI, confidence interval; UL, upper limit; all data is standardized, the beta values are standardized coefficients, thus they can be compared to determine the relative strength of different variables in the model; *p < 0.05, **p < 0.01, ***p < 0.001.*

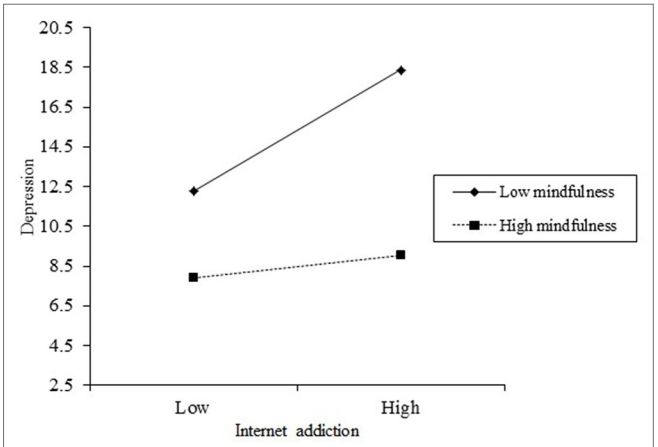

FIGURE 2 | The moderating role of mindfulness in the relation between Internet addiction and depression. The moderating effect is graphed for two levels of mindfulness: (1) low mindfulness (1 SD below the mean) and (2) high mindfulness (1 SD above the mean).

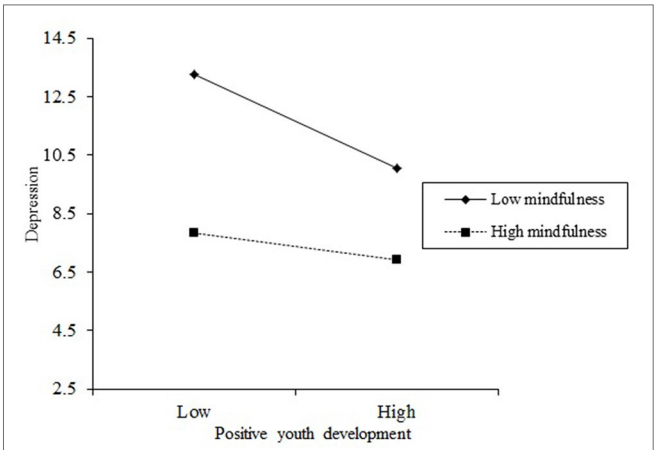

FIGURE 3 | The moderating role of mindfulness in the relation between positive youth development and depression. The moderating effect is graphed for two levels of mindfulness: (1) low mindfulness (1 SD below the mean) and (2) high mindfulness (1 SD above the mean).

psychological strengths, such as their social, cognitive, and emotional competence, which may further intensify their withdrawal, avoidance, and negative feelings and consequently increase their risk of experiencing depressive symptoms (e.g., hopelessness and sadness) (69, 70).

In addition, we found that the direct link between Internet addiction and depression and the indirect effect of Internet addiction and depression through positive youth development are moderated by mindfulness. These two effects are stronger among adolescents with low mindfulness than those with high mindfulness, and these findings coincide with previous studies that attest to the risk buffer and protective function of mindfulness (45, 46, 48).

Firstly, the moderating effect of mindfulness in the relationship between Internet addiction and depression may be explained from the risk-buffer function of mindfulness; namely, the negative effects of Internet addiction may be buffered by mindfulness. Internet addiction is a risk factor not only for mental

health (e.g., anxiety and sleep disturbances) (46, 51), but also for social maladjustment (e.g., poor academic performance and interpersonal problems) (71, 72). These stressors are likely to lead to adolescents' psychological vulnerabilities, such as rumination as well as the refusal to accept and participate in real life, which may further lead to negative emotional experiences and increase their risk of developing depressive symptoms (73). Mindfulness refers to the state of being aware of the present reality or current experience in an accepting or non-judgmental way (34, 35), which may help adolescents rid themselves of rumination and enjoy their current lives and further reduce their likelihood of becoming depressed (74). By echoing the risk-buffer effect of mindfulness, the present study reports that Internet addiction negatively affects adolescents with low mindfulness more strongly than adolescents with high mindfulness. Thereby, adolescents with high levels of mindfulness may have a relatively greater capacity for ridding themselves of rumination and accepting the status quo, which in turn may reduce their risk of experiencing depression than those with low levels of mindfulness.

Second, the moderating effect of mindfulness in the relationship between positive youth development and depression may be explained from antagonistic interactions hypothesis of protective–protective model (75). Positive youth development (76, 77) and mindfulness (47, 45) are two protective factors that significantly contribute to mental health, for instance, by reducing an individual's likelihood of experiencing depression; however, the effect of positive youth development on depression did not strengthen as mindfulness increased in our study, which is a result similar to those of previous studies that construct the moderated mediation model (45, 78). One explanation for this finding may be that mindfulness produces many positive effects on adolescent development, and adolescents with high mindfulness have fewer mental problems (e.g., depression). Thus, positive youth development does not express more positive effects for adolescents with high mindfulness. This finding may additionally indicate that positive youth development and mindfulness, as the two protective factors, may mutually compensate such as individual resource factors can buffer or weaken the adverse effects of risk factors. That is, highly positive youth development exhibits a stronger positive impact, while lowly positive youth development exhibits a stronger negative impact in adolescents with low mindfulness but not in adolescents with high mindfulness. Thus, adolescents with low mindfulness may rid themselves of negative impacts if they have highly positive youth development, and adolescents with lowly positive youth development may avoid negative impacts if they have high mindfulness.

Moreover, we did not find that mindfulness moderates the association between Internet addiction and positive youth development. This finding may imply that adolescents with either low or high mindfulness may be influenced by the negative effects of Internet addiction, which would more or less weaken their social and psychological competences. These findings are consistent with previous studies, thus confirming the adverse effects of Internet addiction on adolescents' psychological resources (11, 45, 51, 62). Although adolescents' psychosocial abilities are inevitably weakened by Internet addiction, the present study's optimistic results assert that mindfulness may indeed alleviate or protect them from slipping into worse situations (e.g., depression). The findings may further imply that improving adolescents' mindfulness may effectively alleviate the negative influence of Internet addiction on mental health.

LIMITATIONS AND IMPLICATIONS

The current study has several limitations. Firstly, the study utilized a cross-sectional research design that failed to prove causality between Internet addiction and depression. For this reason, future studies might wish to apply a longitudinal research design. Second, as the study was conducted in two secondary schools in Shenzhen, caution is urged in terms of the findings' generalizability. Future studies may expand the survey's scope by including a national scope. Finally, positive youth development includes four second-order constructs (i.e., prosocial attributes, positive identity, cognitive–behavioral competence, and general positive youth development qualities) (79), and we solely utilized the overall score of positive youth development as a mediator variable. Future research may attempt to respectively analyze the mediating effects of the four second-order constructs in the correlation between Internet addiction and depression.

Despite these limitations, the study has significant theoretical and practical implications. Firstly, the study tested the mediating role of positive youth development and the moderating role of mindfulness in the relationship between Internet addiction and depression, thus contributing toward a more thorough understanding of how and when Internet addiction is associated with depression in adolescents. The results suggest that parents and educators should help adolescents learn how to use the Internet responsibly. Educators may also wish to focus on helping adolescents increase their positive youth development traits (e.g., resilience, self-efficacy, and self-esteem) and mindfulness skills. These two aspects may promote adolescents' adoption of positive coping strategies that enable them to deal with the negative impacts of Internet addiction. Previous studies reveal that positive youth development and adolescent mindfulness can be increased through training, such as Positive Adolescent Training through Holistic Social Programmes (80) and Mindfulness Based Cognitive Stress Reduction (81, 82). Therefore, according to previous studies, educators may wish to implement courses and activities that aim to improve positive youth development and mindfulness in an effort to reduce the negative impacts of Internet addiction on adolescents.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

Ethical review and approval was not required for the study on human participants in accordance with the local legislation and institutional

requirements. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

XCi and XL designed experiments, carried out experiments, conducted the statistical analysis and wrote the manuscript. TG, MW and XCe conducted data collection work and the double statistical analysis. XCe critically reviewed and revised the manuscript. All authors contributed to and have approved the final manuscript.

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Different Patterns of Mental Health Problems in Unaccompanied Refugee Minors (URM): A Sequential Mixed Method Study

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Unaccompanied refugee minors (URM) represent one of the most vulnerable refugee groups due to their young age, developmental status, and insufficient coping strategies. Clinical observations indicate that the frequency of mental health problems varies between different URM subgroups. In the present research project, clinical interviews as a source of qualitative data were combined with quantitative psychometric information in a mixed-method approach in order to study the patterns of mental health problems in 561 URM from four different language groups (Arabic, Farsi, Somali, and Tigrinya) immediately after arrival in the host country (Germany). Qualitative analysis obtained as differentiating categories "language, countries of origin, age, and gender"; quantitatively, the Refugee Health Screener (RHS-15) was applied. According to the positive screening results, the highest number of mental complaints was returned by children and adolescents speaking Farsi (65.9%) and Somali (65.8%). They were followed by URM speaking Arabic (49.4%) and Tigrinya (43.3%). The results were influenced not only by origin, but also by age (with higher burden among older Farsi-speaking URM) and gender (with higher burden among male URM). Although the prevalences in URM subgroups differ, the observed high rates of positive screening results in our sample of URM from Germany substantiate the need for early detection of mental complaints and appropriate mental health care for at least every second URM.

Keywords: unaccompanied refugee minors, trauma, mental disorders, screening, Refugee Health Screener (RHS-15), children and adolescents

INTRODUCTION

Unaccompanied refugee minors (URM) are distinctly different from other refugee groups because of their younger age, earlier psychosocial development stage, and deprivation from parental or any other adult's care. URM therefore constitute a vulnerable subgroup with a special need for protection. Accordingly, the reception directive of the European Parliament and the Council of

Europe from 2013 obliges member states to take special account of particularly vulnerable refugees (1).

Like all minors, URM are more dependent on adult care at a younger age than close to adulthood. The lack of emotional, physical, financial, and emotional parental support both during (pre-)migration and the post-migration period has been demonstrated to significantly increase the risk of developing mental health problems in URM (2–6). Accordingly, Bean et al. (7) reported higher levels of traumatic stress symptoms in URM compared to adolescent refugees who had arrived with their parents. Before fleeing from their country of origin, URM often face social upheaval and chaos in their region. They experience threats regarding their own safety and/or the safety of a family member or a close person; they may witness or become engaged in violence, e.g. witnessing murders, mass killings, or having combat experience, affecting their moral perspectives (3, 8).

During migration, URM are frequently endangered, forced to survive often dubious transitional placements and face uncertainty about the future. The migration process can take much longer than expected, with different steps, interruptions, and times of detention. Adolescents from Afghanistan, for example, often stay in Iran or decide to move on to Europe at a later stage. Migrants from Somalia and Eritrea are frequently held hostage during their routes through Sudan and Libya, and families back home are forced to pay ransom. Many are killed and others suffer torture, violence, and sexual abuse. The final step on their way to Europe by boat also involves multiple threats and the risk of perishing or witnessing others drowning in the sea.

URM undergo these complex migration journeys at a young age amid important stages of psychological development and without the protection of adult minders. Such journeys will often take months or even years. Traumatic events during flight are likely to have devastating effects on URM's basic trust in the ability of adults to care for them. The latter include sexual exploitation and violence even after arrival in the host country (8–12). Yet the ability of children and adolescents to withstand external stress depends to a large extent on the emotional state of their minders. It has been reported that the separation of children from their parents may have a greater impact on the mental health of children than acts of war (13, 14).

The next stage of the migration process—arrival in the country of destination—may equally involve potentially stressful and harmful aspects.

Despite the experience/hope of having found a refuge in a safe place, the latter includes feelings of loss towards their homeland as well as distance from family and peers. In some cases, successful migrants even experience feelings of "survivor guilt" caused by the fact of being still alive while close persons were injured or killed (15). Frequently, the families left behind expect support with pursuing their own migration plans, financial aid by remittances or at least efforts towards reimbursement of money invested for smugglers and/or ransom. Added to this, the urge to cope with a new environment arises immediately upon being confronted with an unknown social and cultural world with a foreign language and, importantly, administrative demands regarding asylum procedures which are often difficult to fathom. The psychological impact of detention and human rights restrictions in the context of migration policies has been reported widely (12, 16–18), especially in the case of traumatized refugees.

The described complex of problems may place additional psychological strains on migrants (19–21), particularly on single children and adolescent URM without emotional protection, support, or security provided by family members (4, 22).

Concerning mental illness related to such psychosocial stressors, Jenssen et al. (3) reported that 54% of 93 URM in the care of the State Child Protection Services in Norway suffered clinically relevant posttraumatic stress symptoms, 30% showed anxiety symptoms, and 20% displayed symptoms of depression. Furthermore, the UMR in this study had experienced 5.5 stressful life events on average (e.g. death of a loved one, drastic changes in the family, separation from family against will, war or armed military conflict, experience of physical violence or witnessing of physical abuse), showing a significantly positive correlation with posttraumatic stress, anxiety symptoms as well as symptoms of depression. Vervliet et al. (23) assessed the mental health of 307 URM upon arrival in their host countries (Norway and Belgium). They found a high number of traumatic experiences in URM, e.g. death of a loved one, physical maltreatment and the experience of being in danger. Duncan (24) reported high rates of symptoms of posttraumatic stress disorder (PTSD) in 168 Sudanese refugee children in a Kenyan refugee camp, with almost 75% of them suffering from moderate to severe symptoms. In more detail, Derluyn et al. (25) mentioned that URM girls displayed more anxiety symptoms, emotional problems, and higher avoidance scores than boys, while boys had more difficulties with exhibiting prosocial behavior than girls. Moreover, sexual abuse was more frequent among unaccompanied minors compared with refugee minors with families. Within the group of URM, girls were especially prone to sexual abuse (26), Vervliet et al. (23) reported that in a cohort of 307 URM, upon arrival in Norway and Belgium high scores were found for anxiety (38 percentage points), depression (44 percentage points), and PTSD (53 percentage points). Regarding the severity of PTSD and depression symptoms, impairments in mental health were significantly associated with the accumulation of traumatic events and the lack of refugee status (3, 20). More specifically, four domains of traumatic events, namely abuse of human rights, lack of basic necessities, traumatic loss, and separation from others, were associated with symptom severity (27).

Taken together, recent studies have highlighted that the heightened risk of developing mental health problems in URM is due to multiple factors, such as high numbers and the extent of traumatic experiences in the country of origin and during flight, gender, and post-migration factors (9, 23, 28–30).

In 2016, 36,000 URM reached Germany seeking asylum (31). In Germany, upon arrival URM are distributed to different regions according to an administrative algorithm. Giessen, a small university town in the federal state of Hesse in central Germany, is host to one of the largest and most longstanding reception centers for refugees in Germany. Hence, the number of URM arriving here is particularly high.

The described high vulnerability and high rates of PTSD, depression, and anxiety disorders in URM identified in clinical trials were in line with our clinical observations within the first routine medical examination of the URM in Giessen. However, we also noticed recurrent variations of complaints within the different URM subgroups. In order to analyze these clinical observations and derive an overarching multidisciplinary explanatory approach based on clinical observation and enriched by these experiences, we applied a *mixed-method research design* (32, 33) to identify the differentiating factors influencing the mental health issues within the URM cohort during clinical routine. As an overarching goal we tried to implement a valid and economical procedure within the first medical examination. This was done related to the reception directive of the European Parliament and the Council of Europe form 2013, that obliges member states to take special account of particularly vulnerable refugees (European Parliament, European Council 2013). Against this obligation, in Germany up to now no standardized procedure has been established.

METHODS

Our research approach starting from clinical experiences corresponds to a mixed-method research design which combines elements of qualitative and quantitative research approaches (34). Specifically, we used an explanatory sequential mixed design: In the first step, we collected *qualitative* data by conducting narrative biographical interviews of UMR within the medical examinations. These semi-structured and problem-centred interviews (35, 36) with "anker-points" related to, among others, biography, family, education and reasons for flight took about 45–60 min.

Our strategy to analyze the qualitative data/interviews was a hermeneutic one. Aim of this procedure is to define supra-individual categories by clustering the narratives on common themes. This is conducted by a five-step approach: 1. Paraphrasing the contents of the narrative interviews. 2. Assigning the obtained paraphrases to themes/headlines according to a biographical interview guide. 3. Collecting interviews with similar content and unifying the headlines 4. Conceptualizing: similarities and diversity are formulated in terms of theoretical information and empirical knowledge. This step translates the original terminology into scientific words. 5. Theoretical generalization: relating the results to theories and supposed relations (37).

In doing so, we subsequently analyzed the obtained material and observed significant differences in the living conditions for UMR and the descriptions of mental health complaints across the different countries of origin. To systematize the findings, we formed inductively distinct categories.

In the second step, we used the RHS-15 as a *quantitative* measure to test the initial qualitative results of group differences in mental health problems. Target criteria of the Refugee Health Screener (RHS-15), developed by Hollifield et al. (38), are symptoms of depression, anxiety, PTSD, and physical concomitants as well as the subjective self-efficacy of the interviewed persons. The RHS-15 was derived from the most commonly mentioned complaints of refugees that have been documented in literature. To avoid potential harm triggered by answering the RHS-15, it doesn't ask about any names or details of specific traumatic experiences. The questionnaire lists 14 Likert-scaled questions and an additional visual analog scale ("distress thermometer"). Based on a sum score >11 of the items 1–13 and/or a distress >5, the screening result is evaluated as "positive". This evaluation strategy was derived from the results of the validation studies by Hollifield et al. (38). The overall procedure appears to be economical and easy to apply in large-scale screening of the mental health status of refugees (39). Cultural sensitivity and equivalence of the different language versions of RHS-15 have been shown (40). Within a German refugee sample, the different language versions of the RHS-15 showed excellent internal consistencies with Cronbach's α ranging from .91 to .93, and good convergent and predictive validity (41). The practicability and efficiency of the RHS-15 have been demonstrated in previous studies (39).

The total scores of the RHS-15 (RHS_{total}) representing the severity of symptoms (items 1 to 13) were not distributed normally, as indicated by the Shapiro-Wilk-Test (for all items $p < .001$). Therefore, the data were quantitatively analyzed for significant group differences with nonparametric tests (Kruskal-Wallis-Test, Mann-Whitney-Test). In addition, Spearman correlations were applied to assess covariations with age. Given the skewed distribution of the data, we decided to report the medians and the 0.25 resp. 0.75 quartiles. All calculations were performed with IBM SPSS-Statistics 24 software.

In the final step, we integrated the two data spheres of qualitative and quantitative results and discussed them by adding objective country-specific information from public databases in order to provide an in-depth explanation for our findings.

Study Cohorts

The URM were initially admitted to a central reception facility for refugees operated by the German state of Hesse and then eventually referred to the youth welfare office. Within the first week of their arrival, a general practitioner (GP) is assigned to conduct the initial medical examination and provide medical care in accordance with The Asylum Seekers Benefits Act and the Infection Protection Law. This physical examination was supplemented by medical history, dental status, blood tests, a stool sample, and chest X-ray. In order to additionally assess the mental status of the UMR during the initial examination, the responsible GPs extended the mandatory physical examination to include a psychological assessment and employed the RHS-15 screening supported by interpreters. The RHS-15 survey was voluntary. The resulting data helped to provide a more complete assessment of the young persons' health status and were made available to improve psychosocial care in shelters provided by the welfare organization responsible.

The total study cohort consisted of 561 URM from 4 different language groups (Arabic, Farsi, Somali, and Tigrinya) attending their first medical examination from 2015–2017. They represented various countries of origin: the majority of URM spoke Farsi (39.8%) and originated mainly from Afghanistan. They were

TABLE 1 | Sample characteristics relating to language resp. land of origin (Arabic = Syria; Farsi = Afghanistan; Somali = Somalia; Tigrinya = Eritrea).

Language	Arabic	Farsi	Somali	Tigrinya
Gender				
Male (n, %)	74 (87.1)	189 (90.9)	53 (72.6)	74 (47.1)
Female (n, %)	11 (12.9)	19 (9.1)	20 (27.4)	83 (52.9)
Age (mean, SD)	17.89 (1.07)	17.68 (1.17)	17.79 (0.91)	17.74 (0.80)

followed by Tigrinya speakers from Eritrea (30.0%). Arabic speakers (16.3%), mainly from Syria, Iraq, Algeria, and Morocco, came next. The smallest language cohort were Somali speakers from Somalia (14.0%). The study sample was found to be representative with regional distribution of origin of the major groups of URM in Hesse in 2016 (42). The mean age of the children and adolescents was 17.7 years (SD=1.01), ranging from 14 to 19 years. 124 of them were female (23.7%) and 366 were male (76.3%). See **Table 1**.

Subjects were excluded from further analysis if more than one item from the RHS-15 was missing (n=13), or if information about age or gender (n=25) was not available (total exclusion=6.77%). If only one item was missing, the missing value was imputed from the mean value of the specific item within the corresponding language group (6 item values). Overall, this left 523 URM for the final statistical analysis.

At the time of arrival in Germany, all participants were under the age of 18 years and had all migrated without being accompanied by any adult person older than 18 years of age. At the time of the study, some URM were already 18 or 19 years old due to the time interval between arrival in Germany and the onset of the study.

After receiving a positive decision from the ethics committee of the medical faculty of Justus-Liebig-University Giessen, the collected data were evaluated scientifically *post hoc*.

RESULTS

Analysis of the Qualitative Data

As a result of the qualitative analysis, we identified relevant content differences determined by the supraordinate category "land of origin" representing the different impacts of long-lasting social and political conditions on vulnerability and resilience for mental health. The specific context factors relating to the global historical-political situation were evaluated by comparing the narratives with in-depth country-specific enquiries acquired from the UNICEF or UNHCR databases and related to the current literature in the field. To illustrate our conclusions, we subsequently present four illustrative biographical case reports of interviewed URMs with these origins.

As we conducted a post-hoc analysis, the case reports were taken from the records of the medical examinations. All personal information contained therein (e.g. names, exact places of action) was changed or edited out to exclude the identification of the participants.

In general, by means of the medical examinations, we obtained the impression that the Somali- and Farsi-speaking refugees might suffer most from mental health complaints. Somalia has had a long-term history of warfare and combat, especially in the southern regions. In the narratives of the Somali URM, the impact of the al-Shabaab militia as well as rivalries and blood feuds between clans were reported to have affected the lives of the parents and families of the URM before they had left the country. The parental generation of the URM had to live under unstable and traumatic living conditions for many years, accounting for an insufficient development of resilience factors within the next generation. As data presented by the UNICEF/UNESCO Institute for Statistics in 2015 demonstrated, in Somalia less than every fifth child will receive the opportunity to attend a primary school (43). The same holds true for Farsi-speaking URM. The greatest share of them in our cohort came from Afghanistan. Decades of warfare within the country have increased the risk for transgenerational traumatization (8, 44). Many of the Afghans who had fled to Iran were forced to live a socially marginalized life there. Despite speaking the same language (Dari, Farsi), Afghans living in Iran are discriminated against because of their specific dialect and are subsequently often segregated. Frequently, there are no opportunities for these children to regularly attend schools. In 2011, 47% of the 15 to 24-year-olds were able to read (45). Amongst URM in Iran, child labor is a common feature. In order to survive, segregated children and adolescents are forced to work in leather factories, in the construction industry and brickworks. In Germany, adult asylum seekers from Afghanistan have a fairly small chance of success in the asylum procedure and/or have to endure uncertainty until a final decision concerning their asylum application has been made.

URM Guuleed - Somalia

Guuleed is a 15-year-old male from Somalia. His father died during the war. Guuleed lived with his mother in a village outside Mogadishu. As the oldest of four siblings, he helped his family and relatives on the small family farm. G. attended the religious school Madrasa for one year. The family experienced the presence of the Al Shabaab militia as a constant threat, and there were repeated violent attacks on villagers. At the age of 14, Guuleed escaped from Somalia via Sudan and the Sahara. He spent three months in prison in Libya, and three days on a boat on the Mediterranean Sea prior to his arrival in Italy, with onward journeys to Switzerland and finally Germany. The clinical examination found persistent hepatitis B as well as an infection with Lambliasis. The RHS-15 was positive. In the care group, he withdraws, does not speak much, and preferred to play football all day long. He was transferred to a special youth welfare facility which takes care of adolescents suffering from traumatic disorders.

URM Ramin – Afghanistan

Ramin is a 14-year-old male from Afghanistan. He had to flee from Afghanistan with his mother and siblings at the age of three after the Taliban murdered his father. Ramin grew up in difficult conditions in Iran, did not attend school and received no health care. At the age of 14, he came to Germany without his family from Iran via Turkey and the Balkan route. Prior to his arrival in Germany, he was located in France. In Germany, he was taken

into custody by the youth welfare office and lived in a youth welfare institution. Again and again, he displayed aggressive breakthroughs requiring psychiatric treatment. He had stomach problems and a plethora of functional complaints. He reported heavy mental burden in the RHS-15. Ramin learned to speak German quickly, obtained a high school diploma, and started vocational training. After a significant reduction in his medical drug intake, he was engaged as a youth representative for his firm, finished with a good final grades, and received support with behavioral therapy. To begin with, he had a scarcity of mental resources, but ultimately he was able to achieve a moderate level of stability with the help of external structures (school, training, medical support).

In contrast with a higher proportion of complaints among Somali and Afghan URM, children and adolescents from Eritrea and Syria seemed to report fewer mental complaints. In Eritrea, sporadic battles used to occur on the border with Ethiopia, but there was no civil war going on in the country. Regular schooling is commonly available, with a 93% literacy rate for citizens aged 15 to 24 reported in 2015 (45). Nevertheless, the government is autocratic and political tensions between government supporters and opposition groups as well as human rights violations have been widely reported. Attempts to escape compulsory military service are a frequent cause of migration and flight (46, 47).

Most of the Arabic-speaking URM are refugees from Syria. In Syria, mandatory education is provided for nine years. The literacy rate for adolescents over the age of 15 in 2013 was approximately 96% (45). Prior to the onset of the civil war in 2011, the country had low crime rates and comparatively stable living conditions.

URM from Eritrea and Syria were thus only temporarily exposed to distressing events and conditions of threat. Before the onset of the civil war, young people in Syria had the chance to grow up in a comparatively stable society, with a well-developed health and education system. The social environment offered opportunities to develop resources and resilience within a—relatively to Afghanistan and Somalia—quite stable framework, with positive features of education, social support, and stable family structures. In addition, refugees from Syria and Eritrea have better prospects for remaining in Germany, unlike refugees from Afghanistan and Somalia. The expected chances of success in the asylum procedure after reaching adulthood also seem to have an impact on the mental health of URM.

URM Kidane - Eritrea

Kidane is a 15-year-old- male from Eritrea. His father is in prison; an older sister lives in Ethiopia. Kidane lived with relatives in Asmara. He liked to play football and ride a bike and attended school in Eritrea for 7 years. There was an increasing threat of being conscripted for military service and he was afraid because his father is in prison. After fleeing the county, he spent 2 years on the way from Eritrea to Germany without any contact with his parents during this time. He suffered a car accident while in the Sahara. Later, Kidane spent 5 months in prison in Libya, where he was frequently beaten and his right collar bone was broken. He underwent surgery in Switzerland. At the clinical examination in Germany he was found to be underweight. Scabies scars and amoebae in his stool were found. The RHS-15 was negative. Kidane integrated well into the care group and was transferred to a youth welfare facility. He wanted to continue to attend school and get an education. He wants to support his relatives in Eritrea financially as soon as possible.

URM Elvedin - Syria

Elvedin is a 16-year-old male from Syria. In his home country, Elevedin went to school for 8 years. During the civil war, he witnessed explosions and attacks with helicopters and planes. He left his home with his family and lived in a camp in Syria. Then, Kidane left Syria with his uncle, but without his parents. Subsequently, he lost his uncle in Turkey. Kidane had only sporadic contact with his parents via cell phone and was very worried. It took him 6 weeks to travel from Syria to Germany. In Austria he was imprisoned for one week. Finally, an attempt to cross the border to Germany was successful. No physical abnormalities were found and the RHS-15 was negative. He hopes to learn German and attended school as quickly as possible. Kidane intends to study computer science, his greatest wish is to live with his parents in Germany in the future.

These short case vignettes exemplify the domains we identified as distinct factors contributing to the mental health status of URM within the narrative interviews. Firstly, we found similarities between the narratives of the Somali-Afghanistan cohorts and the Eritrean-Syrian cohorts of URM. The analysis of these patterns resulted in the constitution of different categories to explain the observed differences in mental health of the URM subgroups. As mentioned above, this framework is based on political-historical and psycho-social factors determining the living conditions of the URM in their homeland and makes it possible to identify and contrast the facets of URM's individual experiences and their impact on child development. In addition to the category "land of origin", the qualitative analysis of the narratives revealed that the factors "age" and "sex" further contributed to the variance in the URM's mental health. This is in line with the empirical findings described in the sections above.

Analysis of the Quantitative Data: Refugee Health Screener (RHS-15)

In order to quantify the qualitatively determined different patterns in mental health complaints, we ascertained the extent of mental health complaints in the study sample using the RHS-15 and analyzed the results related to the category factors "land of origin, age and sex".

The internal consistency of the RHS-15 was high with a Cronbach's α=.895. As a global outcome, we found that 43.6% of the study participants were rated as "positive" in the RHS-15. This implies that this share is highly likely to be suffering from at least one mental disorder (**Figure 1**).

With regard to the different languages/versions of the RHS-15, URM speaking Farsi (65.9%) and Somali (65.8%) showed the most frequently positive screening results, followed by Arabic (49.4%) and Tigrinya (43.3%) speakers. Upon differentiating the number of symptoms (RHS_{total}) with Kruskal-Wallis-Tests, we

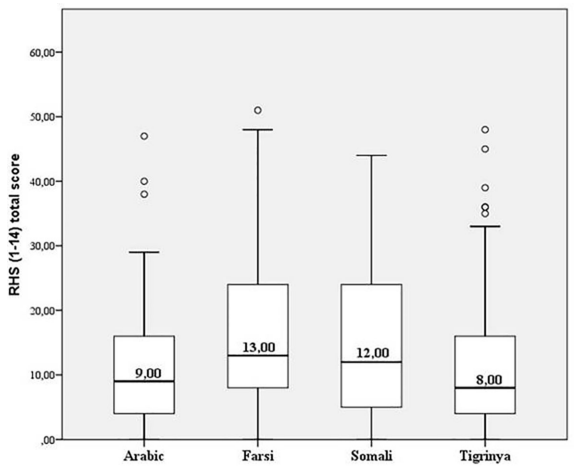

FIGURE 1 | Distribution of symptom load (Median of RHS total scores) relating to language resp. country of origin (Arabic = Syria; Farsi = Afghanistan; Somali = Somalia; Tigrinya = Eritrea). The boxes represent the ranges from the 0.25-quantile to the 0.75-quantile.

found a significant difference between the language cohorts (n=523; H(3)=31,528; p < .001). Pair-wise comparisons revealed significant differences between Tigrinya-Somali (H=58,674; p=.036), Tigrinya-Farsi (H=82.574; p=.000) and Farsi-Arabic (H=71.104; p=.002) (cf. **Figure 1**)

A significant association between age and degree of mental impairment was only found in Farsi-speaking URM (Spearman correlation: r =.152, p =.028) with older URM expressing more mental complaints than younger URM.

In general, male URM (n = 399; RHS_{total}: Median= 10, 0.25 quantile (RHS-total)= 4, 0.75 quantile (RHS-total)=20; positive RHS-15 = 58.9%) were found to carry a higher burden of symptoms and more positive screening results compared to female URM (n = 124; Median= 5.5, 0.25 quantile (RHS-total) = 2, 0.75 quantile (RHS-total)=16; positive RHS-15 = 48.4%; Mann-Whitney-Test U=29995.00; p=.000).

DISCUSSION

URM are particularly at risk of mental health problems (9, 23, 28–30). During the first medical examinations of UMR, we observed qualitative differences between sample subgroups, mainly corresponding to land of origin, sex, and age. To address these differences, a valid screening procedure assessing mental impairment and trauma-associated symptoms of URM was applied and implemented within the routine (first line) examination by a GP. The RHS-15 was chosen because of its high sensitivity and simple mode of application (38). Without, however, specifying this in detail, the implementation of the RHS-15 in this context has proven its feasibility analogous to a prior study and is therefore recommended for wider use (39).

As an alarming result, almost half of the 523 URM included in the study (46.9%) returned a positive screening result, indicating that positively screened URM may suffer from at least one of the most common mental disorders, which are mainly expected to be PTSD, depression, and anxiety. The proportion of study participants rated as "positive" is comparable to the observations of Jakobsen et al. (48) and Derluyn & Broekaert (49). Jakobsen et al. (48) reported that 41.9% of unaccompanied asylum-seeking adolescents in Norway, mainly originating from Afghanistan and Somalia, had symptoms suggestive of at least one psychiatric disorder, mostly PTSD, major depressive disorder, agoraphobia, or general anxiety disorder. In the same way, Derluyn & Broekaert (49) highlighted that 37 to 47% of URM exhibited symptoms of PTSD, depressive disorder, or anxiety. Not least, in comparison to the general population, the observed substantially higher rates of indications for psychiatric disorders and mental health problems in refugee minors is in line with the results of a recently systematic review by Kien et al. (50), who found up to a third suffering from depression or anxiety and up to half being affected by PTSD. The authors of the review also stated a high heterogeneity of point prevalences, which may be influenced by the different traumatizing experiences in the home country or during migration and diverse challenges or problems in the host country.

Differences Between Language Cohorts

In our study sample, significantly different patterns of mental health in URM were found depending on the language cohort: Somali and Farsi speakers reported much more mental strain and had higher positive screening results in the RHS-15 compared to Arabic and Tigrinya speakers. This finding points to the influence of origin on the extent of mental distress reported by URM upon arrival in Germany. In addition to the individual traumatic experiences, war-related reduced, or missed schooling specific to the different countries of origin, interruption of schooling during flight followed by higher demands due to lower language skills in asylum countries all contributed to huge levels of further migration stress (51, 52). Furthermore, as children's social adjustment and self-worth are mainly predicted by the quality of peer relationships, positive experiences in school, and leisure time were shown to be sufficiently protective factors in overcoming and processing of migration trauma.

Influence of Age and Gender

A positive correlation between age and symptoms has already been reported by Bean et al. (53). Our study supports this finding for Farsi-speaking minors. One possible explanation for the age-effect could be that older minors may have experienced a higher number of traumatic life events. Another possible reason for the increase in mental symptoms with age in Germany could be the fear of deportation from Germany back to the respective countries of origin once the age of maturity is reached. Unlike European passport holders, among refugees, reaching the age of eighteen is not associated with more liberties, but rather with more fears. At present, deportations of URM before that age are prohibited in Germany. Repatriation is only permitted if family members, other legally entitled persons or a suitable host institution in the country of origin can provide proof of a safe and responsible environment. In a host of cases, reaching adulthood will also mean the end of youth welfare support. Former URM may be moved to a

community shelter for asylum seekers of mixed backgrounds and legal custody will also end. In the worst case, reaching adulthood could mean mandatory deportation without legal protection.

Data on gender differences have provided controversial results. Sourander (6) found no gender differences in the frequency of psychiatric symptoms in URM. Seglem et al. (54) reported more depressive symptoms in female than in male URM, albeit the effect size was low. The meta-analysis by Huemer et al. (28) emphasized that female gender increases vulnerability for the onset of mental health problems in URM. In the latter study, female URM appear to be more prone to be victims of sexual violence. In our study, a higher symptom burden and more positive screening results were found in male adolescents than female adolescents. A possible explanation for the diversity of gender effects found in different studies may be the heterogeneity of the studied samples. The relation between the frequency of stressful life events and the occurrence of mental disorders could be an essential factor. Some studies reported an overall higher incidence of negative or traumatizing life events (e.g. familial changes, death of a loved one, war or armed conflict, physical maltreatment, sexual violation) in male URM than in female URM. In addition, higher PTSD scores in male URM than in female URM were reported in some of the studies (9, 10, 23, 53). Another reason may have been that the type and frequency of traumatic experiences were not systematically recorded in our study because there was concern that these factors could have re-traumatized the URM during the RHS-15 screening. Until further standardized studies concerning gender differences are available, the interpretation of data in this field will have to be interpreted in a prudent manner.

LIMITATIONS

The RHS-15 is a screening tool for easy and widespread use. The screening is to be understood as a first measure to detect mental suffering in UMR and cannot replace a valid diagnostic by a child/adolescent psychiatrist. Implementing a screening procedure within the first medical examination should therefore be understood as a feasible first step embedded in a broader concept for support. Although it covers the most common mental health complaints on a symptomatic level, it cannot replace elaborated diagnostic classification. Although the RHS-15 has proven good predictive values for detecting the relevant symptoms (41), another aspect to be kept in mind is a possible overestimation of symptom frequency by using a questionnaire-based self-report-screener, which sometimes is extreme. For instance, Engelhardt et al. (55) showed that PTSD rates in veterans from clinical diagnostic interview were 41% lower than estimates obtained by self-report questionnaire. A positive screening result will, however, increase awareness of mental problems and therefore increase the chance that more essential steps will be undertaken as a consequence.

As a measure of caution, it must be pointed out that more specific psychopathological symptoms—such as psychosis and effects of a poor physical constitution—are beyond the scope of the RHS-15 and should be derived from the general practitioner's findings.

The representatives of obtained group differences are limited due to the RHS-15 assessment in the four language versions—although about 77% of the Afghans speak Farsi—the results cannot be generalized to all URM stemming from Afghanistan. The type and frequency of traumatic experiences should be systematically recorded in further studies to provide a better understanding of the obtained group differences.

Another potential bias could be the stage and long-term perspective of the individual asylum procedures. An earlier study conducted by our group demonstrated that the results of the RHS-15 were different between refugee groups immediately after arrival compared to those with a longer duration of residence in the country (39). Moreover, in the present study primarily factors that increased vulnerability were examined. URM were examined shortly after arriving in Germany and of course the migration process was not yet completed this point. Post-migration factors fostering resilience were not the subject of the study, although they can counterbalance vulnerability factors (56). Favorable post-migration factors such as social and professional support, education, religion, acculturation strategies, and hope may contribute to the fact that refugees can be both vulnerable and resilient at the same time and therefore can adapt well despite unfavorable starting conditions (57, 58). This duality should be given more attention in further studies.

CONCLUSION

We performed an analysis of the current mental health condition in URM and related the findings to factors we extracted from the obtained interviews. In this last section we focus on the combined results of the qualitative and quantitative data.

Different non-trauma-related factors determine the risk of developing trauma disorders: origin, age, and gender can represent risk factors for the occurrence of post-traumatic disorders in URM. In particular, the situation in the country of origin before the occurrence of individual stress from trauma or flight seems to influence the subsequent coping options after flight. Longer substantial instabilities in the country of origin, associated with social stress factors and less school education, seem to influence individual resilience.

The alarming prevalences of mental health complaints identified substantiate the particular vulnerability of UMR. They highlight the need for adequate child and youth psychotherapy because it is known that untreated mental health problems such as PTSD might lead to chronic courses of disease (59) and severe behavioral problems (7). As other studies have previously underlined, early symptom detection is of critical importance in order to provide timely psychosocial intervention among URM in the form of a stepped care approach (60), comprising e.g. physical safety, adequate residential settings, and educational opportunities.

In our procedure, positive screening results during the first medical examination were therefore directly reported to the youth welfare office, paving the way suitable care and housing to be allocated. In some cases, however, the URM were relocated to other federal states after their initial medical examination and

it remained unclear to what extent the need for special protection was considered in the further course of their cases.

Although capacities for psychiatric and psychotherapeutic treatment are still lacking, the attestation of a status of particular vulnerability could help to initialize preliminary stabilizing measures or psychoeducational elements. The provision of early treatment helps to prevent aggravation and continuation of emotional problems (61).

Suffering from mental disorders at a vulnerable stage of life such as adolescence can give rise to severe development difficulties, resulting in obstacles hindering social integration, problems of bonding capacity and competency in relationships as well as chronic courses of disease. Our results indicate that in addition to age and gender, the land of origin representing different historical-political and social developmental conditions moderates the extent of mental complaints and must be borne in mind when assessing URM.

Still, there is a lot of work to be done. The found factors influencing mental health of URM are not the only ones that are of crucial importance for URM´s health in the long run. Beside the conditions in the country of origin, the demanding act of migration itself, social and legal conditions, ethnic affiliation, discrimination in the host country, social support, and possibilities to have access to health care institutions are momentous for further health development (62). Further studies should focus similarly on pre-departure factors, occurrences on the escape-route as well as on post migration stressors. Lifespan perspective and prospective studies can enable a better understanding of the effectiveness of coping strategies and resilience factors (57).

It is crucial to manage the challenge of integration in order to prevent larger societal problems, as less integration has the potential to increase the risk of developing a mental illness. Therefore, early detection of URM at risk for developing mental impairments is an essential preventive measure to avoid later undesirable development in connection with higher costs and poorer integration. On the other hand, predominantly post-flight stressors on children and adolescents might favor negative outcomes and denying URM´s needs can lead to further societal and economic costs along with a lack of integrations actions (57).

The implementation of a screening procedure can therefore be considered "profitable" from an economic point of view. Health care costs, procedural difficulties and duration of proceedings can be reduced, while non- or inappropriate treatment might lead to a chronic course of stress reactions or even suicidal ideation (5).

In view of this, the early detection of mental health problems after arrival is especially important for both the URM and the host county. It enables adequate support during the vulnerable transition period from adolescence to adulthood as well as a successful transition to an integrated life in a new culture and society (60).

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding authors.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the ethics committee of the medical faculty of Justus-Liebig-University Giessen. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

BH: Principal investigator and main author. MK: Transcultural expertise. WF: Data collection. JP-K: Statistical processing of the data. EH: Supporting the study design and the interpretation of the results. TT: Supporting the study design and the interpretation of the results. BB: Statistical and methodological support. BG: study design and editing the manuscript. CM: study design and editing the manuscript. MS: Principal investigator and main author.

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Association Between Screen Time, Fast Foods, Sugar-Sweetened Beverages and Depressive Symptoms in Chinese Adolescents

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Objective: Although previous studies have shown that screen time (ST), fast foods (FFs) and sugar-sweetened beverages (SSBs) consumption are associated with depressive symptoms in adolescents, research on these associations in Chinese adolescents is scarce. This study aimed to examine the association between ST, FFs, SSBs and depressive symptoms in Chinese adolescents, and explore the mediating effects of FFs and SSBs in the association between ST and depressive symptoms.

Methods: This school-based nationwide survey was carried out among 14,500 students in four provinces of China. *The Children's Depression Inventory* was used to assess the participants' depressive symptoms. ST, FFs and SSBs consumption was measured by a self-reported questionnaire. The Bayesian multiple mediation model was used to analyze the mediation effect.

Results: ST, FFs and SSBs, were more likely to be associated with depressive symptoms, and *ORs* (*95%CI*) was 1.075 (1.036–1.116), 1.062 (1.046–1.078) and 1.140 (1.115–1.166), after we adjusted for sociodemographic variables. Additionally, in Bayesian multiple mediation model, direct effect, mediating effect, total effect, the ratio of mediating effect to total effect was 0.125, 0.034, 0.159, and 0.214, respectively. All path coefficients of the three mediation paths are statistically significant ($p < 0.05$).

Conclusions: Our study demonstrates that ST, FFs and SSBs consumption are associated with depressive symptoms in Chinese adolescents. It is likely that FFs and SSBs partially mediate the association between ST and depressive symptoms by chain-mediating effects.

Keywords: depressive symptoms, screen time, dietary behavior, association, adolescent

INTRODUCTION

The World Health Organization previously reported that more than 300 million people worldwide suffer from depression (1). It was hypothesized that depression would be the main cause of the global burden of disease by 2030 (2). Worldwide prevalence rate suggests that there is approximately 11.00% of depression among adolescent (3), and the rate increases with age (4). A study based on the structured diagnostic interview of DSM-IV-TR reports that the prevalence of depression in German adolescent was 27.3% (5). The positive rates of depressive symptoms among adolescents in China, Japan and France were 44.3, 22.0 and 12.6%, respectively (6–8). Moreover, the positive rate of depressive symptoms in adolescents in developing countries may be higher, compared with developed countries. For instance, a study involving three countries shows that the positive rate of depression among adolescents in India is higher than that in Australians and Americans (9). Notably, severe depression can contribute to suicide, and suicide is the second cause of death in people aged 15–29 (1). Depression has been identified as one of the important factors influencing the health of adolescents (10). Thus, the American Academy of Pediatrics recommended that adolescents should be screened for depressive symptoms at least once a year (10). Likewise, the World Health Assembly calls for the prevention and treatment of mental illnesses such as depression at the national level (1).

Approximately 50.0% of children and adolescents spend more than 2 h a day on the screen (11). For example, about 45.0% of adolescents aged 15–19 of Moroccan watch TV for more than 2 h per day, and 38.0% of them use computers at the same time (12). Recent evidence suggests a link between ST and adolescent depression (4, 13), and clear dose–response relationships were observed (14). A Chinese study indicates that watching TV on weekdays for more than 2 h is associated with an increased risk of depression for boys (OR = 1.33, 95%CI: 1.02–1.73) and girls (OR = 1.62, 95%CI: 1.19–2.21) (13). Besides, video games (β = 0.13, p <0.001) and computer use (β = 0.17, p <0.001) for a long time are associated with more severe depressive symptoms in Canadian adolescents (15).

There are growing interests in the association between dietary behavior and depression (16, 17). Several considerable researches suggest that consumption of highly processed foods (e.g., FFs, sweet foods, fried foods, processed meat, etc.) are associated with depression (18, 19), but not vice versa, healthy foods (e.g., fruits, vegetables, nuts, whole grains, etc.) are negatively correlated with depression (20–22). Of interest, adolescents consume more FFs and SSBs in the context of the globalization (23, 24). Approximately 45.4 and 19.6% of adolescent aged 15–19 consume SSBs and FFs more than three times a week (12). Also, the previous study suggests that frequent consumption of FFs and SSBs may be more strongly associated with depression in adolescents (7, 25–27). Notably, a nationwide survey of 65,212 adolescents in South Korea shows that unhealthy dietary consumption was positively correlated with perceived stress and depressive symptoms (17).

Although potential associations were described above, there are also some inconsistent research findings. For instance, a study has found no explicitly association between TV time and adolescent depressive symptoms (15). And more studies have reported Western dietary patterns are not associated with depressive symptoms in adolescents (28, 29), and healthy dietary consumption cannot predict adult depression (10, 30). Furthermore, to our knowledge, previous studies have rarely analyzed the association between ST, FFs, SSBs and depressive symptoms, few have concerned about the intermediary mechanism of this association. Based on the results of the reviews mentioned above, we hypothesized that there might be mediating effects of FFs and SSBs in the association between ST and depressive symptoms in adolescents. In this study, we used data of cross-sectional investigation from China to analyze the mediation model.

MATERIALS AND METHODS

Participants

This school-based nationwide questionnaire survey was carried out among middle school students aged 10–20 years (14.9 ± 1.8) from 32 middle schools in four provinces of China (Shenzhen, Guangdong Province; Zhengzhou, Henan Province; Nanchang, Jiangxi Province; Guiyang, Guizhou Province) from November 2017 to January 2018. Some 15,486 students were surveyed, and 871 (5.6%) adolescents rejected to participate in the survey. A total of 14,615 (94.4%) questionnaires were completed, and 14,500 (99.2%) questionnaires were analyzed, including 7,347 (50.7%) boys and 7,153 (49.3%) girls. Moreover, there were 6,881 (47.5%) rural residents and 7,619 (52.5%) urban residents. The distribution of other sociodemographic variables is shown in **Table 1**.

Procedures

Participants were selected by cluster and the stratified multistage sampling method. As well, research areas were selected according to China's geographical distribution, economic development level and cooperation with our research team. Next, four urban and four rural middle schools in each area were randomly sampled, and 400 students were surveyed of each school, including all grades. Students were gathered in the classroom to complete the questionnaire in about 30 minutes. Notably, teachers maintain order in the classroom to ensure that students complete the questionnaire independently and do not discuss the content of investigation each other. The principles of anonymity, confidentiality and voluntariness are strictly followed in our study. Participants and their guardians provide informed consent, and students can withdraw from the study at any time. This study was approved by the Ethics Committee of Anhui Medical University (batch number: 20140087). The detailed survey information can be found in our previous article (31).

Sociodemographic Variables

Gender, age, grade, residence, father's education level, mother's education level, the only child in the family or not, the number of

TABLE 1 | The positive rate of depressive symptoms in Chinese adolescents of stratified by gender (%).

Variables		Male(n = 7,347)				Female (n = 7,153)			
		N	Depressive symptoms (%)	χ^2	*p*	N	Depressive symptoms (%)	χ^2	*p*
Age(year)	10–15	4,230	1,233 (29.1)	0.447	0.504	4,557	1,250 (27.4)	10.127	0.001
	16–20	3,117	931 (29.9)			2,596	804 (31.0)		
Grade	1	1,133	270 (23.8)	26.294	<0.001	1,291	288 (22.3)	25.802	<0.001
	2	1,210	301 (24.9)			1,206	310 (25.7)		
	3	1,194	336 (28.1)			1,213	312 (25.7)		
	4	1,189	372 (31.3)			1,244	377 (30.3)		
	5	1,220	374 (30.7)			1,198	347 (29.0)		
	6	1,401	388 (27.7)			1,001	277 (27.7)		
Residence	Rural	3,443	1,034 (30.0)	16.377	<0.001	3,438	948 (27.6)	2.49	0.115
	City	3,904	1,007 (25.8)			3,715	963 (25.9)		
The only child in the family	Yes	2,767	762 (27.5)	0.129	0.720	1,902	477 (25.1)	3.547	0.060
	No	4,580	1,279 (27.9)			5,251	1,434 (27.3)		
Boarding school	Yes	3,506	911 (26.0)	10.782	0.001	3,324	883 (26.6)	0.073	0.787
	No	3,841	1,130 (29.4)			3,829	1,028 (26.8)		
Father's education level★	Illiteracy	281	111 (39.5)	77.578	<0.001	283	104 (36.7)	43.422	<0.001
	Elementary school	663	226 (34.1)			788	216 (27.4)		
	Secondary school	2,333	668 (28.6)			2,373	674 (28.4)		
	High school	2,146	556 (25.9)			1,974	481 (24.4)		
	The university	1,832	433 (23.6)			1,647	397 (24.1)		
Mother's education level•	Illiteracy	561	193 (34.4)	67.46	<0.001	608	210 (34.5)	50.5	<0.001
	Elementary school	996	303 (30.4)			1,004	294 (29.3)		
	Secondary school	2,266	628 (27.7)			2,398	637 (26.6)		
	High school	1,980	534 (27.0)			1,806	438 (24.3)		
	The university	1,461	336 (23.0)			1,274	301 (23.6)		
Self-perceived socioeconomic status	Worse	832	310 (37.3)			698	294 (42.1)	179.643	<0.001
	Poor	334	165 (49.4)	148.276	<0.001	175	92 (52.6)		
	Medium	4,821	1,232 (25.6)			5,189	1,298 (25.0)		
	Good	241	83 (34.4)			172	51 (29.7)		
	Better	1,119	251 (22.4)			919	176 (19.2)		
The number of close friend	0	291	182 (62.5)	319.523	<0.001	146	88 (60.3)	254.791	<0.001
	1–2	1,355	524 (38.7)			1,744	650 (37.3)		
	3–5	2,846	720 (25.3)			3,305	804 (24.3)		
	≥6	2,855	615 (21.5)			1,958	369 (18.8)		

★*There are 180 adolescents (92 male students, 88 female students) without fathers.*
•*There are 146 adolescents (83 male students, 63 female students) without mothers.*
Values in parentheses represent the positive rate of depressive symptoms.

close friends, boarding school, self-perceived socioeconomic status were included as covariates.

Depressive Symptoms Assessment

The Children's Depression Inventory (CDI) was used to assess depressive symptoms in adolescents (32). CDI is a self-report internationally popular scale consisting of 27 items for assessing depressive symptoms in children and adolescents (33). Each item consists of three sentences, such as "I feel sad at times", "I often feel sad" and "I always feel sad", which is assigned a score from 0 to 2. The total score ranges from 0 to 54, with a higher score being attributed to the most depressive state. The total score of 19 was determined as a threshold for assessing depressive symptoms according to the scale norm. Namely, a total score of 19 or more was assessed as a positive depressive symptom. In contrast, a total score of less than 19 was assessed as a negative depressive symptom. Additionally, its widespread use confirmed that CDI has good reliability and validity, and the Cronbach α was 0.87 in another study (34).

Screen Time Assessment

ST was measured by two questions: asking students to report the amount of time (hour) spent watching television, using computer and smartphone during weekdays (from Monday to Friday) and on week-ends (from Saturday to Sunday). For instance, how many hours do you spend watching television, using a computer and smartphone during weekdays in the latest week? How many hours do you spend watching television, using computer and smartphone on week-ends in the latest week? There are seven options for each question as follows: 1, 0 h; 2, < 1 h; 3, 1–2 h; 4, 2–3 h; 5, 3–4 h; 6, 4–5 h; 7, ≥5 h, which is assigned a score from 0 to 6. For the analysis, the weekly ST was calculated by adding the scores of the two items together, with the higher score being attributed to the longer ST.

FFs and SSBs Consumption Assessment

Five kinds of FFs and five kinds of SSBs consumption were investigated in this study. FFs include Western-style FFs (e.g., McDonald's, etc.), Chinese FFs (e.g., Shaxian snacks, etc.),

takeaway FFs (e.g., Meituan takeaways, etc.), foods brought from the school cafeteria and those brought from off-campus restaurant packed in a disposable fast food box or plastic bags. Also, SSBs include carbonated drinks (e.g., Sprite, etc.), fruit and vegetable juice drinks (e.g., fruit orange, etc.), tea drinks (e.g., iced black tea, etc.), energy drinks (e.g., Red Bull, etc.), and dairy beverages (e.g., milk tea, etc.). The self-reported food frequency questionnaire (FFQ) was used to assess the consumption of FFs and SSBs in the last week. For example, how many times have you eaten Western-style FFs in the last week (e.g., McDonald's, etc.)? How many bottles of energy drinks do you drink every day in the last week (e.g., Red Bull, etc.)? Four options per question (1, never; 2, 1–2 times/1 bottle; 3, 3–4 times/2–3 bottles; 4, ≥5 times/≥4 bottles) were assigned a score from 0 to 3. The total score for FFs and SSBs was calculated by the scores of five kinds of FFs and five kinds of SSBs, respectively, with the higher score being attributed to the higher frequency consumption. In the present survey, the Cronbach α of FFQ was 0.77.

Statistical Analyses

The database was created by EpiData 3.0. Statistical analyses were performed with Mplus (Mplus Version 7.4) and SPSS 23.0 (SPSS Inc, Chicago, IL). Measurement data is expressed as (mean ± SD). Analytical methods included descriptive statistical analysis, the chi-squared test, common method biases test, logistic regression model, and Bayesian mediation model. Normality test, common method biases test and logistic regression analysis were performed in SPSS software. Participants' depressive symptom scores were converted into binary classification variables based on a positively defined cut-off value (≥19). Then, the chi-square test was used to compare the positive rates of depressive symptoms among adolescents with different demographic characteristics. The common method biases test was performed by Harman single factor test, which is an exploratory factor analysis with no factor rotation and no specified the number of extraction factors. Additionally, we used logistic regression model to analyze the association of ST, FFs and SSBs with depressive symptoms. ST, FFs and SSBs were continuous variables, and depressive symptoms were binary variables in a model. ST, FFs and SSBs were independent variables, and depressive symptoms were dependent variables. Two models were constructed: Model 1 unadjusted variables, and Model 2 adjusted demographic variables. We calculated the odds ratios (*OR*s) and 95% confidence intervals (95% *CI*s) in the logistic regression model.

The mediation effect analysis was performed by Bayesian mediation model, and the Markov chain Monte Carlo (MCMC) method was used for parameter estimation in Mplus software (35, 36). Model convergence was tested by Bayesian posterior parameter distributions plots, trace plots and Bayesian autocorrelation plots. Meanwhile, Bayesian posterior predictive checking using the chi-square test, and the *P* value was obtained by the chi-square value likelihood ratio test of the hypothesis model and the free estimation model. Besides, the model was evaluated by scatter plots and distribution plots of Bayesian posterior predictive checking (PPC) (37, 38). Mediation model indicators (e.g., direct effect, mediating effect, total effect, the ratio of mediating effect to total effect, the ratio of mediating effect and direct effect, mediating effect through mediating variables) were calculated to determine the critical mediation variables and paths. Particularly, we used structural equation model to analyze the mediating effects as a sensitivity analysis (39). Parameter estimation was performed with maximum likelihood, and path coefficient test was performed with the Bootstrap method (40, 41). The significant level was $\alpha = 0.05$.

RESULTS

Sociodemographic Variables and Positive Rate of Depressive Symptoms in Adolescents

Table 1 shows the positive rates of depressive symptoms in adolescents with different sociodemographic variables. 27.3% (3,952/14,500) adolescents were diagnosed with positive depressive symptoms in the total study population. The positive rates of depressive symptoms were statistically different in sociodemographic variables of stratified by gender ($P < 0.05$) except different ages and whether the only child in the family of male ($P > 0.05$), and different residences, whether boarding school and whether the only child in the family of female ($P > 0.05$).

Common Method Biases Test

Eight common factors with characteristic root greater than one were extracted in exploratory factor analysis, and 15.26% (< 40%) variance was explained by the first common factor (42). The results show that the common method biases were not significant, and the correlation among variables is credible in our study.

Correlation Analysis

Table 2 shows the significant association between the positive rate of depressive symptoms, ST, FFs and SSBs in the logistic

TABLE 2 | Association between the positive rate of depressive symptoms, ST, FFs and SSBs.

Model▲	Variables	B	S.E.	Wald	*P*	*OR*	95% C.I.
Model 1	ST score	0.071	0.007	119.003	<0.001	1.074	1.060–1.088
	FFs score	0.060	0.007	66.901	<0.001	1.062	1.046–1.077
	SSBs score	0.112	0.010	122.001	<0.001	1.119	1.097–1.141
Model 2	ST score	0.072	0.019	14.436	<0.001	1.075	1.036–1.116
	FFs score	0.060	0.008	58.564	<0.001	1.062	1.046–1.078
	SSBs score	0.131	0.011	137.403	<0.001	1.140	1.115–1.166

▲ *Model 1, unadjusted variable. Model 2, adjusted for sociodemographic variables.*

regression model ($P < 0.01$). More significant associations were observed after adjusting for sociodemographic variables ($P < 0.01$), and the *OR*s values of the ST, FFs and SSBs were 1.075 (95% CI:1.036–1.116), 1.062 (95%CI:1.046–1.078), and 1.140 (95% CI:1.115–1.166), respectively.

Mediating Effect Analysis

Table 3 shows the mediating effects of FFs and SSBs in the association between ST and depressive symptoms in adolescents. Notably, the direct effect of ST on depressive symptoms was 0.125; the total mediating effect is 0.034; the total effect was 0.159. The ratio of direct effect to total effect, mediating effect to total effect and mediating effect to direct effect was 0.786, 0.214 and 0.272, respectively. The mediating effect through FFs and SSBs was 0.033 and 0.010. Also, this mediation model has three mediation paths as follows: ST → FFs → Depressive symptoms, ST → SSBs → Depressive symptoms and ST → FFs → SSBs → Depressive symptoms. The ratio of the mediating effects of these three paths to the total mediating effect was 70.6, 5.9, and 23.5%, respectively, and the path coefficient tests were statistically significant (p <0.001). Furthermore, sensitivity analysis shows that the estimated path coefficients are consistent in the structural equation model and the Bayesian model. However, the total mediating effect value increased by 0.001, and the path coefficient from ST to SSBs was not statistically significant.

Figures 1–3 show the evaluation of parameter convergence in Bayesian model. **Figure 1** shows the Bayesian posterior parameter distributions. The posterior distribution is close to normal distribution in Bayesian posterior parameter

TABLE 3 | Mediating effects of FFs and SSBs in the association between ST and depressive symptoms in adolescents.

Effects	Paths	Bayesian model			Structural equation model		
		Estimate	*Posterior S.D.*	*95%* C.I.	Estimate	*S.E.*	*95%* C.I.
Direct	F1 → F4	0.125**	0.008	0.109–0.141	0.125**	0.009	0.107–0.142
	F2 → F4	0.112**	0.009	0.094–0.129	0.112**	0.009	0.094–0.129
	F3 → F4	0.092**	0.009	0.074–0.109	0.092**	0.010	0.072–0.110
	F1 → F2	0.219**	0.008	0.204–0.235	0.219**	0.009	0.202–0.238
	F1 → F3	0.018*	0.008	0.002–0.033	0.018	0.010	–0.001–0.036
	F2 → F3	0.419**	0.007	0.405–0.433	0.419**	0.012	0.397–0.442
Indirect	F1 → F2 → F4	0.024**	0.002	0.020–0.029	0.024**	0.002	0.020–0.029
	F1 → F3 → F4	0.002**	0.001	0.000–0.003	0.002**	0.001	0.000–0.003
	F1 → F2 →F3 →F4	0.008**	0.001	0.006–0.010	0.008**	0.001	0.007–0.010
	F1 → F4	0.034**	0.002	0.030–0.039	0.035**	0.003	0.030–0.039

$^{**}p < 0.001$; $^{*}p < 0.05$.

F1: Screen time; F2: Fast foods; F3: Sugar-sweetened beverages; F4: Depressive symptoms.

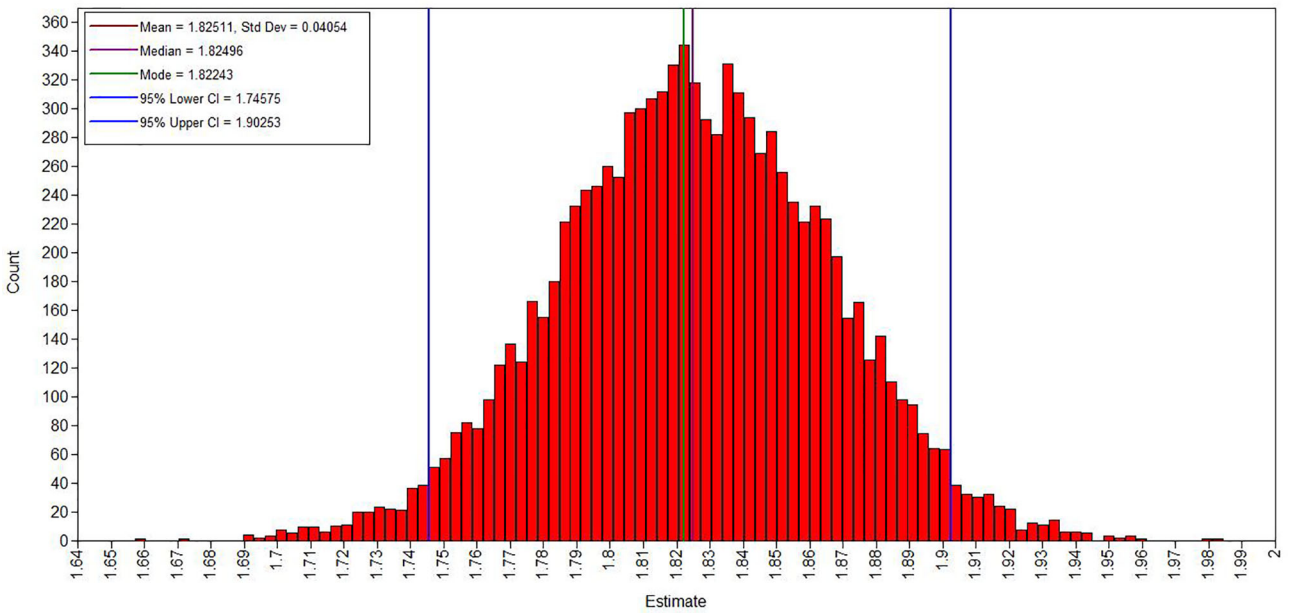

FIGURE 1 | Bayesian posterior parameter distributions.

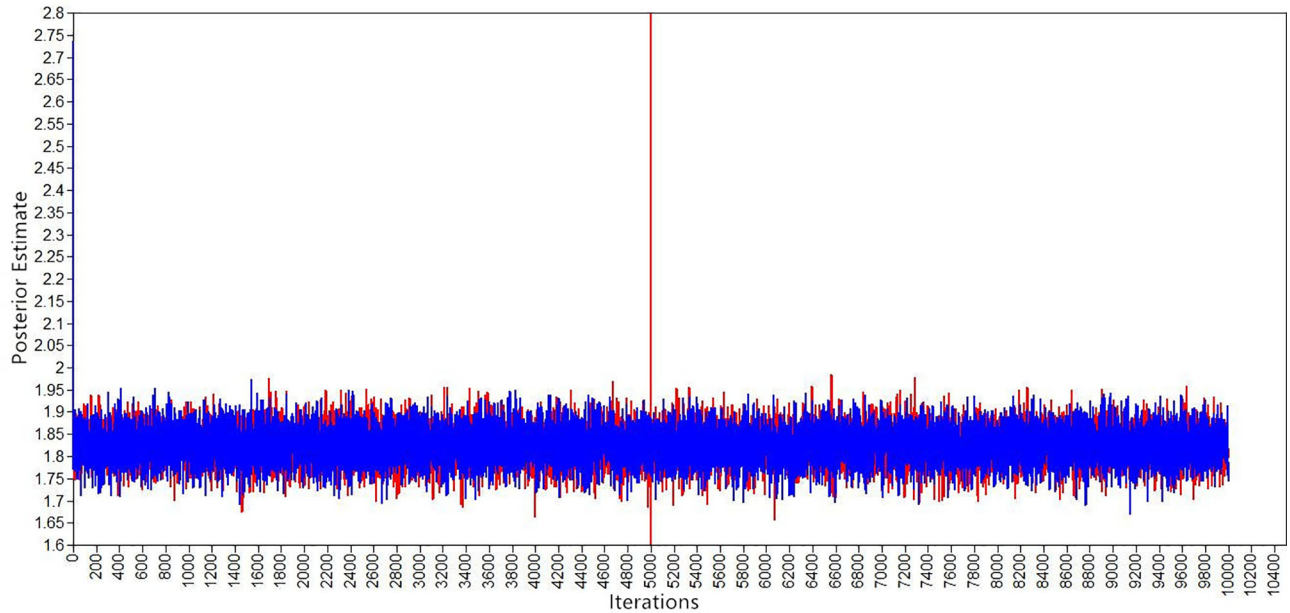

FIGURE 2 | Bayesian posterior parameter trace plots.

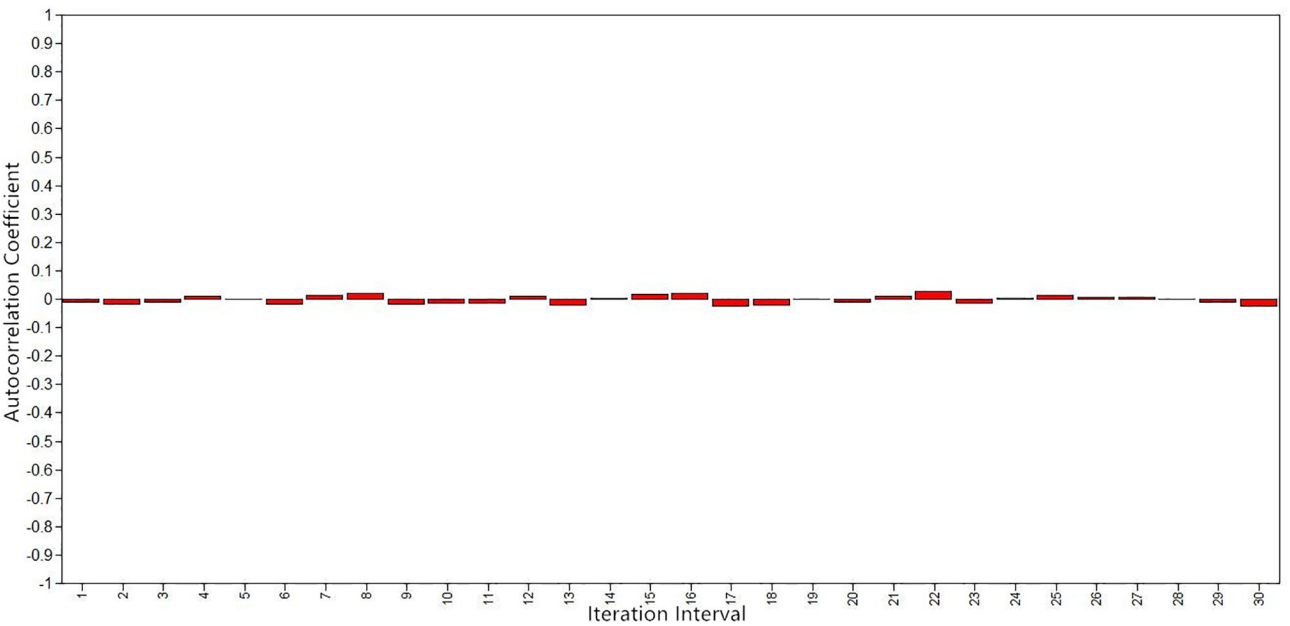

FIGURE 3 | Bayesian autocorrelation plots.

distributions plots. **Figure 2** shows the Bayesian posterior parameter trace plots. The two Markov chains reached a steady state after 10,000 iterations in trace plots. **Figure 3** shows the Bayesian autocorrelation plots. The autocorrelation coefficient is less than 0.1 in Bayesian autocorrelation plots. Bayesian posterior parameter distributions plots, trace plots and Bayesian autocorrelation plots are used to evaluate the convergence of a model. Overall, Bayesian mediation model parameter convergence is reasonable.

Figures 4 and **5** show the evaluation of model fitting. A 95% confidence interval for the difference between the observed and the replicated chi-square values was (−13.820, 13.383), and

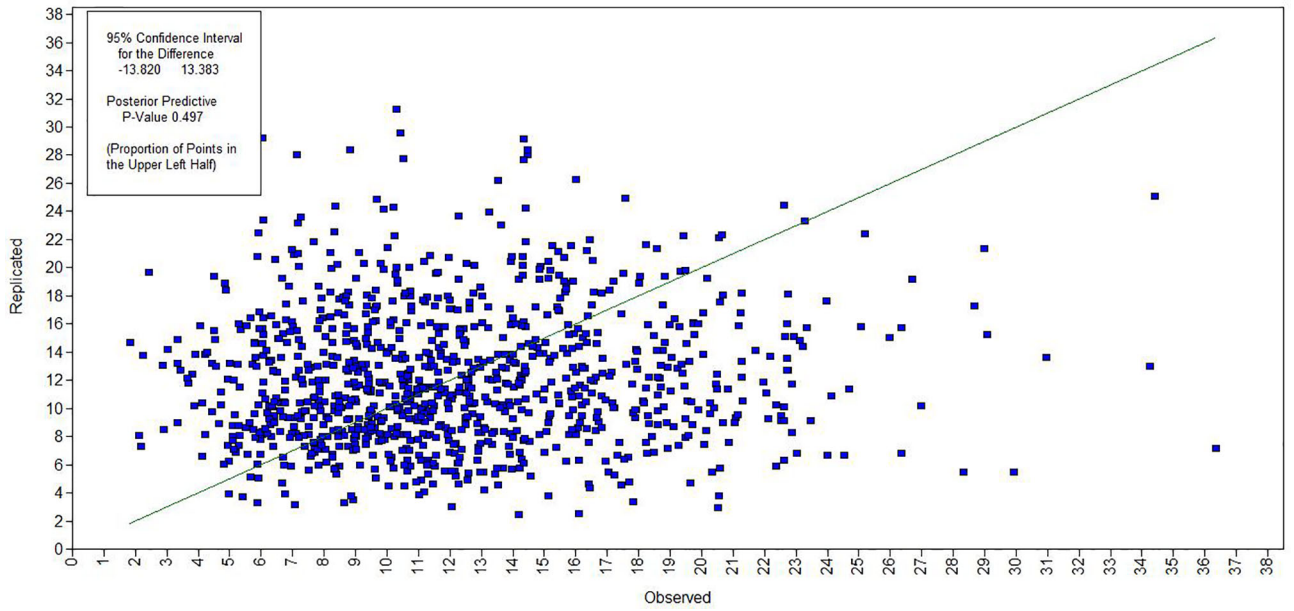

FIGURE 4 | Bayesian posterior predictive checking scatter plots.

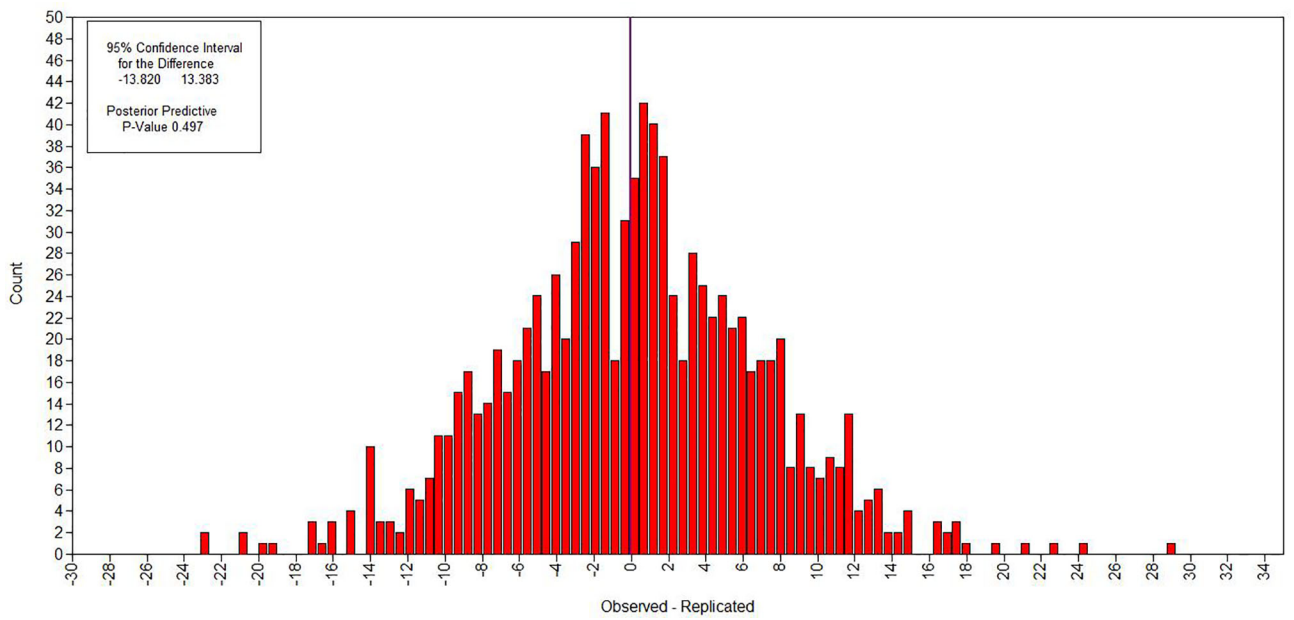

FIGURE 5 | Bayesian posterior predictive checking distribution plots.

posterior predictive p-value was 0.497, which is greater than 0.05. Additionally, Bayesian information criterion (BIC) was 228,842.421, and deviance information criterion (DIC) was 228,751.817. **Figure 4** shows the Bayesian posterior predictive checking scatter plots. Most of the scatters were observed fall on the 45° line in the scatter plot. **Figure 5** shows the Bayesian posterior predictive checking distribution plots. The histogram is continuous and the observed data results are in the middle of the distribution in the histogram. The scatter plots and posterior predictive checking distribution plots are often used to evaluate the goodness of model fit. Thus, the results show that the model had a good fitting.

DISCUSSION

The positive rate of depressive symptoms in adolescents in our study was higher than that in developed countries such as Japan (22.0%) and France (12.6%) (7, 8), and higher than the results of research in developing countries such as Jamaica (14.2%) and Bangladesh (25%) (43, 44). It is notable that our results are lower than the findings (44.3%) of another study using CDI in Chinese adolescents (6). Additionally, our finding that there was no gender difference of positive rate of depressive symptoms, which was somewhat inconsistent with the previous study (44). In general, our results are compatible with previous findings indicating that the positive rate of depressive symptoms in Chinese adolescents is high, and adolescent depressive symptom needs paying close attention.

The results of logistic regression showed that observed stronger associations between the positive rate of depressive symptoms, ST, FFs and SSBs in the logistic regression model. These findings are consistent with previous studies (45, 46). Previous studies suggest that TV time is more than 2 h per day on weekdays related to the increased risk of depression in boys (*OR* = 1.33, 95% CI: 1.02–1.73) and girls (*OR* = 1.62, 95% CI: 1.19–2.21) (13). Other studies revealed that consumption of FFs and SSBs is associated with depressive symptoms in adolescents (44, 47).

There is an argument that frequent consumption of FFs and SSBs lead to a higher intake of energy, saturated fat and sugar, and lower intake of vitamins A and C, milk, fruits, and vegetables (48). However, the latter is inversely associated with adolescent depression (49). On the contrary, the former is positively associated with adolescent depression (50). Moreover, these findings are consistent with previous studies on FFs related to SSBs (48, 51), and ST related to FFs and SSBs (45).

Our observations imply that FFs and SSBs play a role of an intermediary factor in the association between ST and depressive symptoms, and 21.4% of the effects are mediated by FFs and SSBs. The mediating effect through FFs is about three times as large as that through SSBs. Likewise, from the results of sensitivity analysis, the path coefficient from ST to SSBs is not statistically significant in the structural equation model. Therefore, it is clear that FFs is the most important mediator in this mediation model compared to SSBs.

Mediating effect analysis can explore the internal mechanism of variable associations (52). On the basis of this theory, our study explored partial mediating mechanisms between ST and depressive symptoms in adolescents. 78.6% of direct effect indicates that ST is a pivotal predictor of adolescent depression. Namely, adolescents addicted to smartphones, internet, and television may have a higher probability of developing depressive symptoms. Also, the mediating effect of the path only by FFs accounts for the highest proportion of the total mediating effect (70.6%) among the three mediation paths observed in the mediation model. Nevertheless, the proportion of path only by SSBs was lower (5.9%). It should be noted that the chain mediation effect of FFs and SSBs accounted for 23.5% of the total mediating effect. Previous researches reported that FFs and SSBs consumption could promote each other (48), co-consumption was more significantly associated with depressive symptoms in adolescents (51, 53). Generally, the path (ST → FFs → Depressive symptoms) is the main mediation path associated with depression time in adolescents, and chain mediation path (ST → FFs → SSBs → Depressive symptoms) strengthened the association. Possible explanations for our findings are from the following three perspectives.

In terms of social behavior, first of all, adolescents eat FFs instead of irregularities in the diet because of being addicted to use smartphones, computers and TV for online games, surfing the internet, or TV programs for a long time. This is a common phenomenon in China. Second, FFs restaurants (e.g., KFC, Pizza Hut, etc.) can be seen everywhere in China with the progress of internationalization. Some Chinese adolescents are fond of eating Western-style FFs, often consume FFs and use smartphone take a long time to leave the fast food restaurant and even stay for a whole day. What's more, there is an argument that long ST affects interpersonal and social functions, reduces communication with family and friends, even social isolation, which may lead to depressive symptoms (54). It is interesting to note that, there may be reverse associations, that is, depressed adolescents reduce interpersonal communication and long ST, and consume more FFs and SSBs.

In terms of neuropsychological and neuroimaging, the long ST and the frequent consumption of FFs and SSBs are closely related to the abnormal function of the brain's reward circuits. The function of the prefrontal cortex, especially the execution control function, is associated with internet addiction (55). However, dysfunction of execution control network is highly correlated with uncontrolled eating behavior (56). Recent studies have indicated that people are willing to pay more for fat and carbohydrate and that this reward is associated with response in areas critical including the dorsal striatum and mediodorsal thalamus, which is related to greater recruitment of central reward circuits (57). Similarly, dependence behaviors, such as smartphone dependence and internet addiction, are associated with dysfunction of reward circuits, which can result in mental and behavior problems, including but not limited to maladjustment of pressure, reduced social response, and depression (58). In terms of molecular biology, firstly, FFs and SSBs account for a growing proportion of the diet in adolescents (48), and plastic packaging materials are used extensively could create exposure to bisphenol A (BPA) and phthalic acid ester (PAEs) (59, 60), and exposure to BPA and PAEs is associated with adolescent depressive symptoms (61, 62). Secondly, adolescents are the main consumers of SSBs that caused caffeine exposure (63); next, caffeine exposure is associated with depression (64–66). Thirdly, FFs contain high total fat, saturated fat and energy density, low micronutrient density, and a large amount of pro-inflammatory cytokines (67).

Several studies have suggested that pro-inflammatory diet such as FFs and SSBs are significantly associated with increased risk of depressive symptoms compared with anti-inflammatory diet (68, 69). Dietary inflammatory index is positively correlated with the risk of mental health problems (70). Adolescents who

frequently consume FFs and SSBs may consume fewer fruits and vegetables. Vitamins, antioxidants, β-carotene and minerals in vegetables and fruits are associated with lower levels of inflammation and oxidative stress markers (71). A study of Australia adolescent aged 17 years suggests that Western dietary patterns were associated with body mass index (BMI) and inflammation biomarkers; and the association of Western dietary patterns and depression through biologically plausible pathways of adiposity and inflammation (72). Previous studies have shown that excessively long ST time of adolescents is associated with obesity and emotional symptoms such as depression and anxiety (11). Frequent consumption of SSBs and FFs were associated with adolescent obesity (73). Obesity is an important risk factor for mental problems such as inferiority, anxiety and depression (74). Furthermore, adolescents with long ST have relatively insufficient physical activity (75). Therefore, ST, FFs, SSBs, obesity and mental problems affect each other. Long-term unhealthy eating habits (e.g. watching TV, using computers and smart phone while consuming fast food and drinks) may cause obesity and affect the physical and mental development of adolescents (76).

Taken together, our data support the hypotheses that consumption of FFs and/or SSBs during ST may enhance the association with depressive symptoms in adolescents. Currently, the treatments could address one-third of the disease burden of depression (77). Therefore, prevention may be key to adolescent depression. Interventions could prove to be beneficial for preventing adolescent depressive symptoms. For instance, consumption of processed foods, FFs and SSBs should be limited, and the intake of anti-inflammatory diets (e.g., fruits, vegetables and nuts, etc.) should be increased in adolescents (77). Moreover, increasing physical activity time could be effective in reducing ST (78, 79). All that matters are avoiding consumption of FFs and SSBs, especially co-consumption, while using smartphones, computers, and watching TV.

Our study has several strengths. Above all, it's a survey of the Chinese adolescent population, and our results can be transposed to other populations for public health and clinical practice due to the population-based setting. Moreover, this is the first study, to our knowledge, to find the mediation effect of FFs and SSBs in the association between ST and depressive symptoms in adolescents. Additionally, 14,500 adolescents were sampled and surveyed from 32 middle schools in four provinces in China, with a wide sampling range and a large sample size. Our study has several limitations that deserve discussion. Firstly, the causal association inference isn't very strong because the data we used in our study were derived from cross-sectional surveys. There is a possible inverse association between screen time and depressive symptoms. Secondly, although our analysis shows that the mediation effect of ST in the association between FFs and SSBs consumption and depressive symptoms is not obvious, we still cannot explain clearly why FFs and SSBs lie on the pathway between ST and depressive symptoms. While there are some studies showing associations between ST, FFs, SSBs and depressive symptoms, there is no strong evidence presented why ST should lead to an increase in FFs and SSBs consumption. Further longitudinal studies are needed to clarify the associated direction and above questions. Thirdly, due to the general concern about adolescent mental health and discrimination against mental illness, adolescents are more sensitive to mental survey and may cover up their true mental conditions during the investigations. Therefore, there may be some social desirability bias in the research. However, we have taken some measures to reduce bias as much as possible. For instance, anonymous surveys establishing the good cooperative relations with schools, mobilizing adolescents to actively participate in the survey. Fourthly, this study used CDI to assess participants' depressive symptoms and did not conduct clinical interviews. It is difficult to conduct clinical interviews to assess psychological symptoms in a large sample survey. CDI is widely used in the assessment of adolescents' depressive symptoms with high reliability and validity, and the assessment results can reflect the mental health of adolescents. Fifthly, the consumption of FFs and SSBs in adolescents and ST are difficult to evaluate quantitatively. Consequently, we use consumption frequency to assess FFs and SSBs, and use subjective indicators to assess ST. For large sample association studies, the results should be meaningful. Sixthly, although the sample size of this study was large and the participants were distributed in four provinces of China, it may not be able to fully represent the Chinese adolescent population. From the geographical area of China, the sample of this study does not include North China, Northwest China and Northeast China. The eating habits of northern China may be different from other regions. However, this study focuses on the adolescent FFs and SSBs consumption behavior, not eating habits or dietary structure. The consumption of FFs and SSBs is a widespread phenomenon in Chinese adolescents, and there is little regional difference. In addition, obesity may be a factor that affects adolescents' mental problems. However, this study did not measure adolescent body weight. We will further study the association of ST, FFs, SSBs, obesity and depressive symptoms in adolescents.

CONCLUSION

Overall, we found that ST, FFs and SSBs consumption are associated with depressive symptoms in Chinese adolescents. FFs and SSBs consumption may play a role of mediating variable in the association between ST and depressive symptoms. There are chain-mediating effects. Thus, reducing ST and avoiding consuming FFs and SSBs during ST may be one of the effective measures to prevent adolescent depression.

DATA AVAILABILITY STATEMENT

The dataset supporting the conclusions of this article is available in the Mendeley Data repository, in http://dx.doi.org/10.17632/vy3wm76zzz.1. Further inquiries can be directed to the corresponding author.

ETHICS STATEMENT

The principles of anonymity, confidentiality and voluntariness were strictly followed in our study. Participants and their guardians provided written informed consent, and students can withdraw from the study at any time. This study was approved by the Ethics Committee of Anhui Medical University (batch number: 20140087).

AUTHOR CONTRIBUTIONS

FT designed the study. HoX took primary responsibility for writing the manuscript, managed the literature searches and analyses, and undertook the statistical analysis. All other authors undertook the acquisition of the data, contributed to and have approved the final manuscript.

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METHODS
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Assessment of Sensory Processing and Executive Functions at the School: Development, Reliability, and Validity of EPYFEI-Escolar

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The aim of this study was to determine the psychometric properties of the Assessment of Sensory Processing and Executive Functions at the School (EPYFEI-Escolar), a questionnaire designed to assess the sensory processing and executive functions as underlying processes for school participation. The total sample consisted of 536 children aged between 3 and 11 years old who lived in Spain. A total of 103 teachers completed the questionnaire. An exploratory factor analysis was conducted, which showed five main factors: (1) initiation, organization, execution, and supervision of the action; (2) inhibitory control; (3) sensory processing; (4) emotional self-regulation and play; and (5) self-competence. Some of these factors were similar to those found in the EPYFEI for parents in the home context. The reliability of the analysis was high, both for the whole questionnaire and for the factors it is composed of. The results provide evidence of the potential usefulness of the EPYFEI-Escolar in school contexts for determining academic needs and difficulties of children; moreover, this tool can also be used to plan intervention programs in the school environment according to the needs of each child and school.

Keywords: executive function, sensory processes, children, assessment, school

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INTRODUCTION

The participation of people in the different stages of life is fundamental for their development. In the case of childhood, the participation of a child in the school context is especially important (1). Several elements that can contribute to it have been pointed out, among which it is worth highlighting sensory processing (2) and executive functions (3). Disability in childhood is another risk factor that can reduce participation at the school (1).

Sensory processing refers to how the central and peripheral nervous systems organize the incoming sensory information from the sensory organs: visual, auditory, tactile, gustatory, olfactory, proprioceptive, and vestibular information (4). Three different stages can be distinguished within sensory processing: (1) detection of stimuli; (2) modulation or regulation of the intensity level of the stimuli; and (3) sensory discrimination (5, 6). Thus, it is considered that sensory processing allows registering and interpreting what happens in the environment to generate

an adaptive response, integrating and processing the obtained information, and developing specific skills depending on the vital moment and on the required activity (7). From the perspective of sensory integration, sensory stimuli are considered essential for the optimal functioning of the brain, as the experiments have shown the effect of sensory deprivation on human behavior, having an even more important effect in relation to the development of specific abilities and their critical periods, for example for vision, hearing, language, etc., and to maintain optimal health status, too (8–13).

According to Dunn's model of sensory processing, four sensory profiles have been proposed for the general population as a function of the neurological threshold and the self-regulation strategies of each individual. From this perspective, the neurological threshold refers to the threshold for response to a sensory stimulus, which can be described as showing a continuous range from low to high. A person is considered to show a low sensory threshold when they notice and respond quickly to sensory stimuli. This threshold can be different for each sensory modality. Instead, it is understood that a person with a high neurological threshold requires a more intense and/or frequent sensory stimulation to notice it. Neural regulation or modulation is produced by the balance of excitation and inhibition. In Dunn's model, Thus, four types of sensory profiles have been distinguished: (1) individuals with a high neurological threshold and active self-regulation strategies, with a seeking sensory; (2) individuals with a high neurological threshold and passive self-regulation strategies, which show a bystander sensory profile; (3) individuals with a low neurological threshold and active self-regulation strategies, showing an avoider sensory profile; and (4) individuals with a low neurological threshold and passive self-regulation strategies, with a sensory sensitivity profile (14, 15). In children, difficulties in sensory processing affect their participation at all levels, with a significant impact on school activities (16). This can generate problems in social relations, since these situations require interpreting facial expression, verbal communication, and body language in order to give an appropriate behavioral response to the situation (17, 18), both in the classroom and in the schoolyard or playground. In this sense, the teaching staff could collaborate in the detection of deficiencies in executive functions and sensory processing, with the aim of understanding how these children perceive the context, in order to teach them learning strategies according to their sensory characteristics (2).

Sensory processing can be affected in multiple neurodevelopmental disorders in childhood, such as attention deficit and hyperactivity disorder (ADHD) and autism spectrum disorder (ASD), among others (19, 20). Alterations in sensory processing are present in 15% of the general population (21) and in 95% of cases in populations with neurodevelopmental disorders (22). Alterations in any of the stages of sensory processing can generate a learning dysfunction or difficulty (4). In this sense, it has been reported that there is a strong relationship between learning problems, language difficulties, sensory integration, motor problems and adaptive behavior in the classroom (23, 24). Regarding autism, several authors have found a correlation between sensory processing and repetitive behaviors (25), showing a relationship between an atypical sensory functioning in the classroom and atypical sensory responses, emotional perception and rigid thoughts, accompanied by restrictive thoughts and anxiety symptoms (26, 27). Children with autism mainly show sensory modulation problems, with different responses grouped into three patterns (28, 29): (a) sensory hyporesponsiveness (i.e., low or absent reactions to stimuli); (b) sensory hyperreactivity (high sensitivity or aversive reactions to stimuli); and (c) restricted sensory interests, repetitions, and search for behaviors (intense fascination with specific stimuli, longing for repetitive stimuli, or sensory actions based on body parts or objects). With respect to children with ADHD, sensory search patterns have been observed, which, along with the sustained attention deficit, could contribute to the emergence of difficulties in the school environment, with fluctuations in the academic performance and problems in social activities (30). It has also been reported that these children may have difficulties to identify the fingers, which has been associated with reading problems and dyscalculia (30), whereas clumsiness and the lack of motor skills, detected with graphesthesia, hinder the learning of abstract verbal concepts and calculation operations (30).

Recent studies suggest that it is fundamental for occupational therapists to expand their predominant traditional perspective, which is almost exclusively focused on understanding the difficulties in the daily functions on sensory processing/integration, in order to include executive functions (1) and reflect on the relationship between sensory deficiencies and executive functions in the performance and participation in the different activities (30). Furthermore, it has been highlighted that the traditional paradigm, which considers disorders as excluding categories, must be replaced with a different paradigm that contemplates the underlying neurobiological mechanisms, beyond a group of symptoms, to allow understanding disorders by the concurrence of phenotypes, where one symptom can be common to different disorders, such as difficulties in sensory processing (17). Thus, a strong and positive relationship has been observed between difficulties in sensory processing and deficiencies in executive functions in children with neurodevelopmental disorders (31, 32). The results of these studies show that difficulties in sensory processing and in executive functions usually come together. In this sense, it has been suggested that inhibitory control and executive attention play a crucial role in the regulation of sensory processing (33), and that tactile sensitivity can be considered as an indicator of behavioral self-regulation (34).

In the school environment, high academic performance has been associated with an optimal development of executive functions (EF), (30), especially relevant in subjects such as mathematics (35) and language (reading) (36, 37). EF are a complex set of processes that lead and monitor our actions (38). Several authors have described two types of EF: basic and advanced (39–41). Within the basic EF, three processes have been distinguished: working memory, inhibitory control, and cognitive flexibility. Regarding complex EF, planning, problem-solving, and reasoning have been included (39, 42). EF allows us to regulate our thoughts and actions in order to achieve a

certain goal, in purposeful activities. For this, it is essential to keep the information active, and monitoring and updating it in our working memory in order to carry out the intended action. Inhibition let us suppress in a controlled way those distractors that can prevent us from achieving the objective of a certain task (39, 42). Likewise, EF allows a flexible behavior according to the demands of the context or activity. In daily life, in addition to basic EF, complex EF are needed, such as reasoning about the actions that will be carried out, planning and sequencing each one, and once the plan has been implemented, solving the problems that may occur in the course of time and activity (43, 44).

In summary, EF allows goal-directed behaviors, which are essential in all activities of daily living (ADL), school activities, or playing, among other human occupations. EF depend on the development and maturation of the frontal areas of the brain (45) and play a fundamental role in learning (46). In fact, one of the essential pillars of the success of classroom intervention programs is that they contemplate the development of executive functions with the aim of normalizing such behavior in the educational context, reducing the problems related to disruptive emotional, and social behaviors that could affect academic performance, such as the lack of inhibitory control, the presence of defiant conduct, and their emotional or behavioral regulation or self-control (1, 47, 48). Therefore, cognitive functions are understood as relevant skills that help children to value their performance, to be aware of their own actions and competence, and to identify and overcome possible obstacles with the aim of improving. Most children apply these skills automatically, whereas children with ADHD, for instance, require specific intervention to develop them (49). Executive functions consist of both cognitive and emotional components, and they are fundamental for the regulation of goal-targeted behavior (45, 50). Thus, they can be understood as underlying processes required for the effective performance of ADLs (51, 52), including self-directed, complex and non-routine activities in varied situations and environments (44). Therefore, further research is necessary in the field of executive functions and their influence on daily activities, highlighting the need for occupational therapists to design assessment tools for executive functions and intervention protocols, carrying out interventions based on specific evaluations that analyze the real daily performance (44). It is important to have useful tools that allow obtaining this information in an integrated way, in line with the usual childhood activities and contextualized in the school environment, since this is one of the most relevant contexts in childhood, along with play.

The study of EF in Occupational Therapy (OT) is an emerging topic in general, and specifically in children (44), as reflected the small number of instruments available to assess them (53, 54). Regarding to OT, the objective of assessment of EF is functional cognition (55). That is, the interest is to know how the different mental processes are carried out in a given context and with demands that are usually multitasking (53), rather than isolated processes, which can be better assessed with experimental laboratory tasks (54, 55). In OT, the focus is to know the impact of cognition on daily life (56), with the greater ecological validity and predictive value about functioning in the real world (57, 58).

Although there are instruments available for evaluating EF through questionnaires such as BRIEF (59), CHEXI (60), etc., these questionnaires have mainly considered cognitive processes and from OT perspective, children assessment is often focused on models of sensory processing (61, 62). However, the brain works as a whole in terms of sensory and cognitive processing, as recent studies of the human connectome show (63–65). Despite on this, and for the knowledge of the authors, there is only an instrument, developed for children aged between 3 and 11 years that assesses their participation in the different ADLs from the parents' perspective, called EPYFEI (51). This questionnaire is composed by five processes underlying the performance of ADLs: (1) attention control, working memory, and initiation of actions; (2) sensory processing; (3) emotional and behavioral self-regulation; (4) supervision, action corrections, and problem-solving; (5) inhibitory control.

All the above mentioned contributes to raising awareness about the importance of having assessment tools that allow obtaining this information and the relevance of helping the teachers to detect whether any of their students have a problem at the executive and/or sensory level, and, consequently, derive the child to the specific professional for early intervention. The aim of this study was to develop an instrument for the joint assessment of sensory processing and executive functions in children of school age, i.e., the EPYFEI-Escolar, that could be useful to teachers and occupational therapists and which would allow determining if a child had any difficulties that could affect his/her participation at the school, regardless of whether there was a clinical diagnosis.

METHODS

The methods used for the design and evaluation of the metric properties of the EPYFEI-Escolar questionnaire were based on the quality criteria for the measurement properties of health status questionnaires (66).

Content Validity

The development of the EPYFEI-Escolar began with a literature review, followed by a meeting with three occupational therapists, three early childhood and primary education teachers and a neuropsychologist. Initially, 74 items were listed, which were based on the different theoretical dimensions of sensory processing and executive functions. Then, two rounds of consultation were conducted with three occupational therapists experts in sensory integration and four teachers (one from early childhood education, two from primary education and one from special education, all of whom worked in the public education system). In the first round, the number of items was raised from 74 to 85, the writing of some of them was modified and some autism-specific items were discarded, since the instrument to be developed was intended to be useful for the different neurodevelopmental disorders (ADHD, ASD, SLI, dyspraxia, etc...). In the second round, the questionnaire was reduced to the 80 self-administered items with which the initial form was

created and with which the evaluation process was initiated. The completion of this form required between 25 and 30 min. All the consultations with the occupational therapists were conducted online and/or via phone call to verify the information provided when this was necessary. With respect to the teachers, all the consultations were carried out face-to-face. The teachers did not receive any type of compensation for participating in the study.

Study Population

The sample was constituted by 536 children, of whom 366 were "typical" healthy children and 170 were diagnosed with some neurodevelopmental disorder (ADHD, ASD, generalized developmental syndrome, developmental delay, or other difficulties). The sample of teachers was selected from an intentional sampling of different public educational centers of the province of Toledo, which belong to the Community Government of Castilla-La Mancha (Spain), and of the provinces of Jaén, Málaga, and Granada, which belong to the Government of Andalusia (Spain). The project was initially presented to the management team of each educational center; once the interest of the study to the educational community was considered, we requested the approval of the school board of each of the participating centers. Each main classroom teacher was asked to fill in at least five questionnaires. In the case of special education teachers, they were requested to complete the questionnaires of children diagnosed with ADHD and/or ASD with known special educational needs. The main classroom teachers were required to have been in contact with each of the evaluated children for at least 3 months. This was especially important in those who went to school for the first time, since the adaptation period must be taken into account. Among the several disorders related to disruptive behaviors in school-age children, ADHD, and ASD are the most prevalent (67, 68). On the other hand, ADHD and ASD are frequently comorbid, between 50 and 80% of cases, showing an increased risk of behavioral and emotional problems (67). Furthermore, adverse consequences are especially relevant in children with ASD who do not receive support from teachers (68). Therefore, the inclusion of a clinical group and a group with neurotypical development will allow us to study the discriminant validity of the questionnaire. The field work was carried out between April 2017 and June 2019.

To analyze the repeatability and validity of the construct, 65 children from several educational centers of Andalusia were selected, whose teachers were given the EPYFEI-Escolar questionnaire between March and April 2019. Of these 65 children, the re-test was obtained in 59 cases, between 20 and 25 days after the initial administration. Furthermore, the Spanish version of the Children's Executive Functions questionnaire (CHEXI) for parents and teachers (60, 69) and the Spanish version of the Sensory Profile-2 (SP-2) for teachers, known as School Companion (14), were completed.

Data Gathering

The participating teachers were gathered face-to-face in a first meeting, in which the purpose of the study and the questionnaire were explained and where the doubts derived from these were solved. Those who agreed to participate gave their consent and were given the questionnaire, which was required to be completed in 25–30 min. In addition to the items of the EPYFEI-Escolar questionnaire, information about the age, clinical diagnosis, school level, province, locality, and country of origin of the child was also gathered. The study was approved by the Human Research Ethics Committee of the University of Granada (code 449/CEIH/2017).

Development of the Final Questionnaire and Internal Consistency

An initial factor analysis was conducted with the aim of identifying the important domains or concept areas, reduce the number of items if possible and determine which of them should be kept. To decide on the relevance of the factor analysis, we estimated the sample adequacy statistic of Kaiser-Meyer-Olkin (acceptable for values >0.5) and the Barlett's sphericity test. The structure was evaluated by means of an exploratory factor analysis using oblimin rotation, with maximum likelihood extraction, and applying the rule of eigenvalues >1.8 to determine the number of factors. The items were removed if they had factor loadings <0.40 with their own factor, or if they were not discriminatory for presenting similar factor loadings in several factors. The process for removing the items was to remove them one by one by performing a factor analysis repeatedly at each step. The answer options to each item (question) were based on an ordinal five-point scale (0 = never; 1 = almost never; 2 = sometimes; 3 = almost always; 4 = always), with the higher answer codes being the most favorable ones. Some items presented a very low "missing" percentage (below 0.5%), so a missing value imputation was conducted by means of a single imputation procedure. To determine the internal consistency (that is, the homogeneity of the items that measure the same attribute), Cronbach's alpha was calculated for the questionnaire and for each of the factors found in the factor analysis. A Cronbach's alpha of 0.70–0.95 was generally considered to correspond to a good internal consistency.

Construct Validity

The validity of the construct refers to the relationship of the scores of the questionnaire with measurements of other questionnaires, in agreement with the theoretical hypotheses derived from the concepts that are being measured. To this end, the EPYFEI-Escolar questionnaire was correlated to CHEXI (60) and Sensory Profile-2 School Companion (14). CHEXI is a questionnaire aimed to evaluate executive functions in childhood, and it can be used by both teachers and parents. It consists of 24 items grouped into four factors: working memory, planning, inhibition, and regulation. This instrument has good psychometric properties, with a good internal consistency for both teachers and parents, a clear factor structure and a good predictive value on academic performance (60). On the other hand, SP-2 is a questionnaire designed to identify the characteristics of sensory processing in daily life. The Spanish version of this questionnaire can be used for the evaluation of children aged between 3 and 14 years. It consists of two models for parents (a long version and a short version, known

as Short-SP-2), and one model for teachers (Sensory Profile-2 School Companion). The model for teachers consists of 44 items, distributed into five dimensions (auditory processing, visual processing, tactile processing, movement processing and behavioral response), with a reliability coefficient of 0.90 for the Spanish population, and it showed a good test-retest reliability for each profile: sensory avoiding (0.93), sensory sensitivity (0.73), sensory seeking (0.76), and low registration (0.84); school factor 1 (0.83), school factor 2 (0.67), school factor 3 (0.86), and school factor 4 (0.91) (14).

The hypothesis was that the EPYFEI-Escolar questionnaire would strongly correlate to the Sensory Profile-2 School Companion (especially to school factors 1, 2, 3, and 4, which refer to the need for support in the classroom, attention in the classroom, tolerance to the school environment and willingness to learn) and that it would show a lower correlation with the profiles of sensory seeking, sensory avoiding, sensory sensitivity, and low registration. Likewise, it was hypothesized that EPYFEI-Escolar would have a strong correlation with CHEXI. Lastly, it was established that EPYFEI-Escolar would allow discriminating between children with and without difficulties in the school context associated with their executive functions and sensory processing. To this end, Spearman's correlation tests were carried out, considering Rho >0.7 as a good value.

Test-Retest Reliability

To determine the reliability of the questionnaire, the intraclass correlation coefficient (ICC) was used, with a 95% confidence interval, between the scores of the test and those of the re-test, in order to evaluate their temporal stability, considering ICC >0.7 as a good value.

Floor and Ceiling Effects

In this study, floor and ceiling effects refer to the percentage of children who had the highest or lowest possible scores. The percentages of children with the highest and lowest possible scores in the total of the EPYFEI-Escolar and in each of the four dimensions were calculated. These effects were considered to be present when 15% of the participants presented minimum or maximum scores, which reduces the reliability of the instrument, since the participants with extreme scores cannot be distinguished from one another.

Interpretability

The difference in the total score of the EPYFEI-Escolar and in the score of each of its five factors between typical (healthy) children and those with pathologies was analyzed using the Mann-Whitney's *U*-test. In addition, the ROC curve of the total score was also calculated, in order to determine the capacity of the instrument to predict whether a child is healthy or not. An additional analysis was conducted to determine the best cut-off scores. To determine the cut-off points, the coordinates of the ROC curve (sensitivity and 1-specificity) were calculated for successive scores of the total EPYFEI-Escolar score with respect to the correct classification of the child's clinical status (Healthy = neurotypical or with neurodevelopmental disorder = TEA and/or ADHD). The range of scores was between 7 and 176 points. From these data, the specificity and the Youden Index = sensitivity + specificity – 1, were calculated. The value of the EPYFEI-Escolar score corresponding to the maximum Youden index, that is, to the sensitivity and specificity, was considered as the optimal cut-off point higher.

Statistical Analysis

Statistical analyses were performed using IBM SPSS Statistics for Windows (version 23.0, IBM Corp., Armonk, NY). Statistical significance was set at $p < 0.05$ (bilateral). The characteristics of the participants were analyzed using simple descriptive statistics.

RESULTS

Sample Description

Table 1 includes descriptive data of the 536 children selected by the teachers who participated in the development of the EPYFEI-Escolar questionnaire. Of the total sample, 68.3 % ($n = 366$) were healthy children, with a majority of male children (68.3 %; $n = 366$). The average age was 7.5 ± 2.5 years (minimum 3 years, maximum 11 years), with a larger proportion of children aged between 8 and 10 years (40.7%; $n = 218$). Regarding the country of origin, 93.7% ($n = 502$) of the children were born in Spain.

Factor Analysis and Internal Consistency

Table 2 shows the results of the factor analysis of the five factors identified, the factor loading of each of the items, the "missing" percentage and the eigenvalues and Cronbach's alphas of the factors, as well as the explained variance after rotation. The "missing" percentage was very low in all the items (below 0.5% in all cases). A solution of five factors was reached, which were named as: (1) Initiation, organization, execution,

TABLE 1 | Sample description.

		n°	%
Group	Typical	366	68.3%
	ADHD	30	5.6%
	ASD or generalized developmental disorder	26	4.8%
	Developmental delay	11	2.1%
	Other learning difficulties	82	15.3%
	SLI	21	3.9%
Sex	Male	366	68.3%
	Female	170	31.7%
Age	≤4	84	15.7%
	5–7	157	29.3%
	8–10	218	40.7%
	≥11	77	14.3%
Country of origin	Spain	502	93.7%
	Other countries	34	6.3%

SD, Standard Deviation; ADHD, Attention Deficit/Hyperactivity Disorder; ASD, Autism Spectrum Disorder; SLI, Specific Language Impairment.

TABLE 2 | Results of the factor analysis.

	Factor loading	Statistic
FACTOR 1: INITIATION, EXECUTION, AND SUPERVISION OF THE ACTION: EXECUTIVE FUNCTIONS		
1. Has difficulties to conduct tasks that require concentration.	0.885	Eigenvalue: 19.3
2. Requires constant efforts to conduct and finish the activities	0.823	Cronbach's alpha: 0.966
3. Has difficulties to remember necessary information when some other activity is being carried out, for instance, the mental calculation in mathematics	0.822	IC 95% (0.961–0.97)
4. Takes a long time to complete the activities. Requires more time than other children in the same age	0.816	Explained variance
5. Has difficulties to understand the necessary instructions to carry out a task when explained verbally with no visual support (blackboard)	0.809	after rotation. %: 16.2
6. Finds it hard to pay attention when performing an activity and needs to take breaks in the course of it	0.802	
7. Has difficulties to initiate and plan actions required to write or initiate an exercise	0.801	
8. Finds it hard to select essential information or materials required to perform a task or problem	0.791	
9. Has difficulties to understand the tasks regardless of how they are explained	0.789	
10. Has difficulties with the directionality and organization of space, for instance, when writing	0.761	
11. Has difficulties to follow the thread of a conversation, activity or instructions	0.730	
12. Makes mistakes due to lack of focus	0.719	
13. Has difficulties to perceive letters and words, to distinguish shapes, etc. (in paper, blackboard, etc.)	0.711	
14. Has difficulties to tell something that occurred in a way that others can easily understand it	0.709	
15. Has difficulties to coordinate eyes and hands to form letters and words, or to copy from the blackboard or book	0.699	
16. Solves the problems that emerge in the activities	−0.695	
17. Stays thoughtful, looking at nothing in particular	0.691	
18. Has difficulties to defend his/her point of view	0.688	
19. Changes activity without finishing the one that he/she was carrying out	0.688	
20. Does not realize when something changes or finds it hard to acknowledge modifications in the activity	0.619	
21. Revises and corrects the activities or tasks once they are finished	−0.615	
22. Has many ideas, is very creative	−0.594	
23. Finds it hard to go from one activity to another, regardless of whether the first one is finished, even when the teacher demands so	0.593	
FACTOR 2: INHIBITORY CONTROL		Eigenvalue: 3.7
24. Finds it hard to stay still	0.787	Cronbach's alpha: 0.89
25. Find it very difficult to stop carrying out activities when he/she is asked to	0.745	IC 95% (0.88–0.90)
26. Reacts emotionally in an exaggerated manner when participates in activities that involve movement	0.716	Explained variance
27. Usually hums or makes noises while conducting activities that should be done in silence	0.689	after rotation. %: 9.6
28. Tends to touch or use everything he/she sees, for instance, on the teacher's table, the classmates, etc	0.662	
29. Rocks or rocks when sitting, standing or lying	0.651	
30. Gets very excited when something special is about to happen (for instance, a school trip)	0.634	
31. Shouts or talks louder than usual regarding the context	0.620	
32. Shows difficulty avoiding laughing in situations where it is inappropriate	0.609	
33. Tries to carry out the activities that involve jumping, squeezing, pushing, or pulling, etc	0.538	
34. Shows excessive physical contact with others	0.507	
35. Conducts physical activities that involve risks, for instance, climbing, jumping from a certain height, etc	0.422	
FACTOR 3: BEHAVIORAL – EMOTIONAL SELF-REGULATION AND PLAY		Eigenvalue: 2.9
36. Plays adequately for his/her age in the schoolyard	0.841	Cronbach's alpha: 0.85
37. Plays with other children of the same age in playtime	0.816	IC 95% (0.83–0.87)
38. Seems to enjoy playing	0.707	Explained variance
39. Has adequate tolerance to frustration when playing	0.618	after rotation. %: 8.8
40. Recognizes the feelings and needs of others	0.584	
41. Expresses his/her feelings and needs without help	0.533	
42. Cooperates in the performance of classroom activities	0.507	
Factor 4: SENSORY PROCESSING		Eigenvalue: 2.2
43. Finds it hard to make eye contact with others, including the teacher, sometimes avoiding eye contact	0.599	Cronbach's alpha: 0.81
44. Is very sensitive to light	0.589	IC 95% (0.77–0.83)

(Continued)

TABLE 2 | Continued

	Factor loading	Statistic
45. Finds it hard to recognize objects visually	0.565	Explained variance
46. Has difficulties to recognize where the sound or voice comes from	0.559	after rotation. %: 6.1
47. Avoids activities or materials that could get his/her hands or other body parts dirty, for instance, clay, etc	0.499	
48. Seems to have little strength	0.476	
49. Is very sensitive to loud noises, showing irritation or losing track	0.469	
50. Finds it hard to keep balance	0.450	
51. Usually leans on him/herself or some object or wall to hold his/her head, body, etc	0.427	
FACTOR 5: SENSE OF COMPETENCE		Eigenvalue: 1.8
52. Is afraid of failure, always wanting everything to be perfect, sometimes even eliminating the will to try, due to his/her high level of rigorousness	0.703	Cronbach's alpha: 0.68
53. Is afraid of being judged, limiting his/her desire to express thoughts on the paper or verbally	0.689	IC 95% (0.62–0.72)
54. Reacts inadequately to criticism	0.499	Explained variance after rotation %: 3.1

CI95%, confidence interval at 95% for Cronbach's alpha. Total Explained variance after rotation. %: 62.1. All items had <0.5% of missing values.

and supervision of the action; (2) Inhibitory control; (3) Self-Regulation and play; (4) Sensory processing; and (5) Sense of competence. All the items in each factor showed a rotated factor loading over 0.4. All the factors obtained an eigenvalue above 1.8 and a Cronbach's alpha of 0.68 or higher. The total percentage of the explained variance after rotation was 62.6%. The final questionnaire derived from the factor analysis included 54 items. Given that several items of factor 1 (items 16, item 21, and items 22) had negative loadings, the data were analyzed with the inverse score for those items. The correlation between the different factors of the instrument was calculated using the Spearman's Rho test. Factor 3 (Self-regulation and play), correlated negatively with the rest of the factors (Factor 1: -0.681, $p < 0.001$; Factor 2: -0.453; $p < 0.001$; Factor 4: -0.537; $p < 0.001$; Factor 5: -0.348; $p < 0.001$), so the scale was reversed for the items in factor 3 to calculate the total scale score.

Discriminant Validity

Table 3 compares the Spearman's correlations between the total score of EPYFEI-Escolar and the score of each of its factors with the scores of the CHEXI and SP2 questionnaires. The results show that the total score obtained by EPYFEI-Escolar was strongly and positively correlated to each of the subscales of SP-2: sensory seeking (0.71; $p < 0.001$), sensory avoiding (0.69; $p < 0.001$), sensory sensitive (0.71, $p < 0.001$), low registration (0.72 $p < 0.001$), and behavioral response (0.79; <0.001). Likewise, the total score of EPYFEI-Escolar showed a strong and positive correlation with the four factors of CHEXI: planning (0.76; $p < 0.001$), working memory (0.79; $p < 0.001$), regulation (0.72; $p < 0.001$), and inhibition (0.85; $p < 0.001$).

Test-Retest Reliability

Table 4 shows the test-retest differences in the total score and in the five factors of the EPYFEI-Escolar questionnaire, along with the ICC. All the differences were very small and statistically non-significant. The intraclass correlation coefficients were higher 0.9 in all the factors and in the total score.

Floor and Ceiling Effects

Table 5 shows the maximum and minimum scores of the EPYFEI-Escolar questionnaire and of its five factors, along with the percentage of individuals with maximum and minimum scores. All percentages were below 23%.

Interpretability

Table 6 shows the average scores obtained by healthy children and by those with pathologies in EPYFEI-Escolar and in each of its five factors. As can be observed, there were significant differences between healthy children and children with pathologies, with higher scores among the latter and Cohen's D values considered as great differences in all the factors and in the total score of the questionnaire. Likewise, **Figure 1** shows the ROC curve for the predictive level of EPYFEI-Escolar in the diagnosis of children with pathologies. The area under the curve was 0.869 (CI 95%, 0.838–0.9).

Table 7 shows the cut points of the total score of EPYFEI-Escolar as a function of the different levels of sensitivity and specificity to correctly classify healthy children and those with pathologies based on sensory processing and executive functions. The optimal cut-off score, which produced the maximum Youden's index (maximum sensitivity and specificity) was 68.5 points.

DISCUSSION

In this study we explored the psychometric properties of the EPYFEI-Escolar, a new instrument to assess sensory processing and executive functions at the school. After analyzing its items, 54 of the original 80 items were retained in the final version. The results indicate that the questionnaire has good psychometric properties in terms of validity, reliability, and discriminant value for children with typical development and children with neurodevelopmental disorders. Furthermore, the design allowed the development of cut-off scores for the EPYFEI-Escolar.

TABLE 3 | Correlation between the scores of EPYFEI-Escolar, CHEXI, and SP2 ($n = 59$).

		Total	Factor 1	Factor 2	Factor 3	Factor 4	Factor 5	
Planning CHEXI	Rho	0.786	0.821	0.456	0.569	0.614	0.597
	p	<0.001	<0.001	0.003	<0.001	<0.001	<0.001
	n	41	41	41	41	41	41
Working memory CHEXI	Rho	0.807	0.816	0.511	0.588	0.613	0.583
	p	<0.001	<0.001	0.001	<0.001	<0.001	<0.001
	n	41	41	41	41	41	41
Regulation CHEXI	Rho	0.727	0.728	0.637	0.410	0.483	0.615
	p	<0.001	<0.001	<0.001	0.001	<0.001	<0.001
	n	59	59	59	59	59	59
Inhibition CHEXI	Rho	0.836	0.724	0.740	0.601	0.795	0.697
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	58	58	58	58	58	58
Sensory seeking profile (SP2)	Rho	0.714	0.628	0.768	0.445	0.558	0.598
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	59	59	59	59	59	59
Sensory avoiding profile (SP2)	Rho	0.691	0.674	0.633	0.454	0.503	0.615
	p	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
	n	59	59	59	59	59	59
Sensory sensitive profile (SP2)	Rho	0.708	0.665	0.731	0.388	0.561	0.573
	p	<0.001	<0.001	<0.001	0.002	<0.001	<0.001
	n	59	59	59	59	59	59
Low registration profile (SP2)	Rho	0.721	0.757	0.678	0.371	0.424	0.593
	P	<0.001	<0.001	<0.001	0.004	0.001	<0.001
	n	59	59	59	59	59	59
Behavioral dimension (SP2)	Rho	0.791	0.840	0.765	–.131	0.723	0.600
	P	<0.001	<0.001	<0.001	0.604	0.001	0.008
	n	18	18	18	18	18	18

TABLE 4 | Mean scores in the test and re-test, difference and intraclass correlation coefficient.

		Pretest		Retest		Diference		IC 95% DIF				IC 95% ICC	
	n	Mean	SD	Mean	SD	Mean	SD	Li	Ls	*p*	ICC	Li	Ls
Total score	59	64.49	44.81	61.32	43.66	3.17	13.08	−0.20	6.54	0.068	0.98	0.96	0.99
Factor 1	59	31.15	23.23	29.32	22.23	0.98	7.89	−1.05	3.01	0.081	0.97	0.95	0.98
Factor 2	59	12.29	10.41	11.83	10.72	0.46	3.45	−0.43	1.35	0.313	0.97	0.95	0.98
Factor 3	59	18.92	7.17	8.25	5.97	0.83	4.04	−0.21	1.87	0.12	0.9	0.83	0.94
Factor 4	59	8.61	8.62	8.46	8.08	0.15	2.98	−0.61	0.92	0.695	0.97	0.94	0.98
Factor 5	59	3.36	3.55	3.46	3.48	−0.10	1.74	−0.55	0.35	0.655	0.94	0.89	0.96

SD, standard deviation; CI 95% DIF=confidence interval at 95% of the difference; LI, lower limit; Lu, upper limit; ICC, intraclass correlation coefficient; CI 95% ICC: confidence interval at 95% of the ICC.

The number of items in the final version of the EPYFEI-Escolar questionnaire, which was 54, was similar to that of other questionnaires for teachers about sensory processing, such as the Sensory Processing Measure (SPM) for Main Classroom Form (constituted by 62 items in the case of children in primary education and 75 items for preschool children), differing from other questionnaires, such as Sp-2 School Companion, which consists of 44 items. Regarding the SPM for Main Classroom Form, in both versions, i.e., the one for preschool children and the one for those in primary education, the items are grouped into seven theoretical dimensions: social participation, vision, hearing, touch, body awareness, balance and movement, and idea planning. The factor analysis of the SPM in the classroom for children between 6 and 11 years of age showed proprioception and the vestibular system as the principal factor for parents; a second factor comprised visual and auditory processing; another factor grouped the items of tactile processing (especially tactile hyperreaction); and two other

TABLE 5 | Floor and ceiling effects: percentage of values in the minimum and maximum.

	n	Mean	SD	Min	Max	*N* in min	*N* in máx	% in min	% in máx
Score factor 1	536	33.46	24.22	0.00	91.00	8	1	1.49	0.19
Score factor 2	536	14.30	10.89	0.00	44.00	29	1	5.41	0.19
Score factor 3	536	8.22	6.68	0.00	28.00	1	61	0.19	11.38
Score factor 4	536	5.82	5.94	0.00	29.00	94	1	17.54	0.19
Score factor 5	536	3.11	2.88	0.00	12.00	122	5	22.76	0.93
Total Score	536	64.91	41.27	2.00	178.00	1	1	0.19	0.19

SD, standard deviation.

TABLE 6 | Mean scores in typical children and in those with disorders.

	Typical			Disorders			Dif		
	n	Mean	SD	*n*	Mean	SD	Mean	D Cohen	*p*
Score total	366	47.78	32.99	170	101.77	32.22	53.99	1.65	<0.001
Score factor 1	366	23.42	19.87	170	55.08	17.78	31.66	1.65	<0.001
Score factor 2	366	11.29	9.30	170	20.77	11.27	9.48	0.95	<0.001
Score factor 3	366	6.27	5.87	170	12.42	6.39	6.14	1.02	<0.001
Score factor 4	366	4.25	4.66	170	9.21	6.90	4.97	0.92	<0.001
Score factor 5	366	2.56	2.53	170	4.29	3.22	1.74	0.63	<0.001

SD, standard deviation.

factors included the items of praxis and social participation, with the latter being the one with the highest explanatory power in the classroom and which clearly differed from the sensory systems as a different construct (70). The SPM for preschool children showed that the factor with the highest explanatory power in the classroom was social participation, along with the factors of proprioception and praxis. Furthermore, a new factor emerged which combined items of hearing and vision, as well as one last factor about body awareness (71). The 44 items of the SP-2 for teachers, known as School Companion, are grouped into auditory processing, visual processing, tactile processing, movement, and behavioral response (14). At present, the SP2-School Companion is the only standardized instrument validated and adapted to the Spanish population that can be used to assess the sensory processing of children aged between 3 and 14 years (14). However, to the best of the authors' knowledge, there are no factor studies in the literature for the Spanish version. The dimensions that are assessed through this questionnaire emerge from the theoretical proposal of the model of sensory processing, thus the initial dimensions of the questionnaire are retained. In any case, it is worth indicating that School Companion allows determining whether or not the child requires adaptations to pay attention at school, as well as the awareness and attention of the student toward the learning environment, his/her tolerance to the conditions of the learning environment and his/her willingness to learn in such environment (14).

The results of this study suggest that EPYFEI-Escolar is an optimal instrument for detecting those students, aged between 3 and 11 years, who have difficulties in their school participation based on their sensory processing, executive functions, self –regulation and self –competence, showing a specific functioning profile, with the strengths and weaknesses of each case, thus facilitating the decision-making about educational intervention or support requirements. Numerous tests based on performance for the evaluation of executive functions have been criticized due to their lack of ecological validity (58). In this sense, EPYFEI-Escolar aims to determine the repercussion of executive functions in the school context. The items were aimed to contextualize the executive functions with the demands of the classroom and schoolyard activities, as perceived by the teachers. Thus, the factor analysis of EPYFEI-Escolar produced the cognitive dimensions of CHEXI, considered as relevant for executive functions in childhood and which are included in EPYFEI-Escolar factor 1 (69): inhibition, regulation and, jointly, working memory, and planning. There was a positive and strong correlation between the factors of both questionnaires. In addition to the dimensions recognized by other questionnaires for the evaluation of executive functions, or sensory processing, which are also contemplated in EPYFEI-Escolar, two factor emerged in this questionnaire: self-regulation and play (factor 4), which explain 8.8% of the variance and the child's sense of competence in the classroom (factor 5), which explains 3.1% of the variance.

Reliability and Validity

The five factors of EPYFEI-Escolar demonstrated showed good internal consistency and reliability. They obtained good psychometric values for the individual's factors (attention, initiation, organization, and supervision of actions; inhibitory

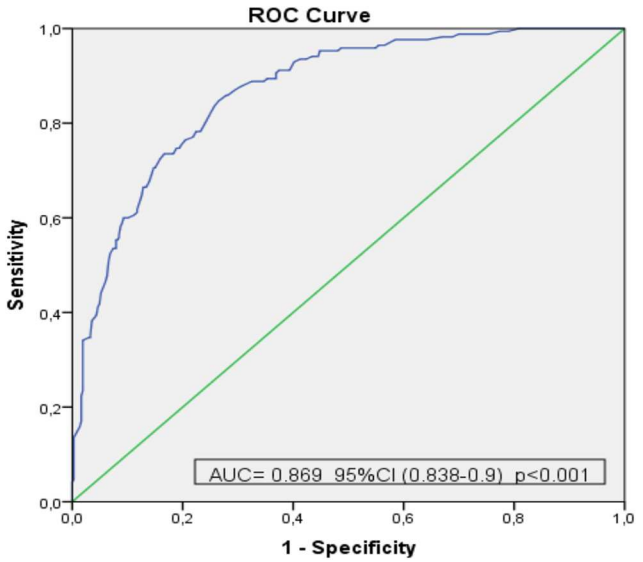

FIGURE 1 | ROC curve used to determine the predictive value of the assessment instrument for sensory processing and executive functions in childhood in the diagnosis of children with a disorder.

control; sensory processing; play and self-regulation; and self-competence) and for the total score of the questionnaire. The lowest α-scores were obtained for self-competence (0.60–0.72).

Discriminant Validity

The EPYFEI-Escolar questionnaire and each of its factors showed good construct validity. Similarly, in a previous work with EPYFEI (51), the factor analysis confirmed two basic executive functions: "cold" executive functions, as shown by factors 1 and 2, and "hot" executive functions, related to factors 3 and 5. In addition, the interest of sensory processing (factor 4) was established.

Interpretability

This study provides preliminary evidence of the discriminant validity of EPYFEI-Escolar. Validity was demonstrated by the fact that the scores of children with neurodevelopmental disorders significantly differed from those of children with typical development. The total score obtained for EPYFEI-Escolar makes it possible to consistently differentiate children with typical development from those with neurodevelopmental disorders and learning disabilities, with the cut-off point established at 68.5.

Description of the EPYFEI-Escolar Questionnaire

The final scale was composed of 54 items, which were grouped into five factors: (1) attention, initiation, organization, and supervision of actions, which includes 23 items; (2) inhibitory control, with 12 items; (3) self-regulation and play, which includes 7 items; (4) sensory processing with 9 items; and (5) self-competence, with 3 items.

As in previous works, the results of this study show that executive functions represent the principal factor that contributes to the child's participation in school activities (1), obtaining two factors of executive functions (46, 72): Factor 1 (initiation, organization, execution, and supervision of the action); Factor 2 (inhibitory control); and other third factor related with self-regulation and cooperation: Factor 3 (self-regulation and play). Our results are in line with those of studies that report the higher relevance of executive functions with respect to sensory processing at explaining the participation of children in different activities, especially the activities related to school learning (1). Other authors have reported a strong correlation between executive attention and self-regulation skills (23). These results are in agreement with recent suggestions, which encourage the expansion of evaluations and treatments in pediatric OT beyond sensory processing and integration, incorporating cognitive processes, and especially executive functions (44). The fact that no different factors were found between children aged 3–5 years and those aged 6–11 years could be due to the fact that the ability to solve conflicts develops throughout the period between 2 and 5 years of age, until it reaches a level similar to that of an adult at the age of 7 years (23). Likewise, it has been suggested that there is a sequential development of the executive functions, beginning with the control of motor impulses and inhibitory control (EPYFEI-Escolar factor 2), since these are present around the age of 3 years (45, 73). Children usually achieve a good interference control at the age of 6 years, along with the development of attention, which takes place fundamentally between the age of 4 and 6 years (74), although the maturation of functions of selective and sustained attention continues. Finally, cognitive fluidity and flexibility improve progressively (75). Regarding executive functions, it has been reported that, along with planning skills (4), self-regulation abilities, such as emotional inhibition, flexibility, and regulation, are more relevant for explaining the participation of children with ASD in school activities (1). This supports the factor resolution of the EPYFEI –Escolar questionnaire for teachers, where the first two factors that explain the difficulties to participate in the classroom are basic executive functions and the third factor refers to self-regulation and play. Furthermore, executive functions predict the level of reading comprehension (76). In this sense, it has been observed that children with ADHD and executive deficiencies are as twice as likely to repeat course, compared to children with a neurotypical development (77).

With regard to factor 4 (sensory processing), visual and auditory processing have been associated with the learning of reading (78). In the case of children with ASD, auditory processing, especially auditory filtering and modulation, has been related to activities such as participation in the classroom, the use of transportation, changes between two activities, etc. (78, 79). Other sensory systems which seem to be important in school participation are the tactile system (4), specifically tactile sensitivity (78), and vestibular processing (1) or movement sensitivity (78), which has been associated with defiant behaviors. Moreover, other studies have found that, according to teachers, children with ASD show greater dysfunction in social participation and praxis (4). Likewise, recent studies have stated that praxis and social participation, along with difficulties

TABLE 7 | Cut-off points of the assessment of sensory processing and executive functions for school questionnaire (EPYFEI-Escolar).

Pathological if >=	Sens	1 - Spe	Spe	I YOUDEN	TP	FP	TN	FN	PPV	NVP
30.5	0.976	0.593	0.407	0.384	238.3	5.7	513.0	747.0	97.6	40.7
40.5	0.953	0.481	0.519	0.472	232.5	11.5	654.1	605.9	95.3	51.9
50.5	0.912	0.393	0.607	0.518	222.5	21.5	764.3	495.7	91.2	60.7
68.5	**0.847**	**0.265**	**0.735**	**0.582**	**206.7**	**37.3**	**926.1**	**333.9**	**84.7**	**73.5**
80.5	0.741	0.186	0.814	0.555	180.8	63.2	1025.9	234.1	74.1	81.4
90.5	0.665	0.128	0.872	0.536	162.2	81.8	1098.2	161.8	66.5	87.2
100.5	0.565	0.085	0.915	0.480	137.8	106.2	1153.3	106.7	56.5	91.5
110.0	0.465	0.060	0.940	0.405	113.4	130.6	1184.3	75.7	46.5	94.0

N of pathological children = 170; N of typical children = 366; Total N = 536; Sens, sensitivity; Spe, specificity; Youden I, Youden's index; TP, true positive; FP, false positive; TN, true negative; FN, false negative; PPV, positive predictive value; NPV, negative predictive value; all the data corresponding to the maximum Youden's index are in bold.

in proprioception, seem to be more characteristic of ADHD, whereas social difficulties seem to be typical of ASD, which could be related to contextual hyperselectivity, as an inherent characteristic of ASD (80).

Our results show that factors 1, 2, 3, and 5 were positively related to CHEXI and SP2. However, there was a negative correlation between EPYFEI-Escolar factor 3, which refers to emotional and behavioral self-regulation, and the behavioral dimension of sensory profiles of SP2. This could be related to the findings of other authors, who observed that internalizing disorders, high-stress levels, anxiety, depression, shyness, and negative affection (81) are related to children with sensory processing disorders usually have learning difficulties (82). Furthermore, a strong relationship was observed between hyperactivity and the search for sensations, between inattention and the low registration profile, and between behavioral disorders and the sensory sensitive profile, although, surprisingly, the correlations were negative. That is, when the score increased in a variable it decreased in the other (21). All this indicates that specific intervention programs must be developed in order to help children with functional diversity to overcome the sensory challenges that they are facing (4, 79). Lastly, with respect to sensory processing, it has been reported that the sensory sensitive and sensory avoiding profiles are associated with lower competence in activities (83).

Regarding the self-regulation and play factor of EPYFEI-Escolar, it has been observed that the development of social skills, such as participating in cooperative plays, making eye contact with other people, keeping eye contact, recognizing and showing adequate non-verbal communication, initiating and keeping conversations, and developing long-lasting friendships, are especially sensitive aspects in children with ASD (84) and those with ADHD (72, 85). Moreover, other authors have reported that, in children with neurodevelopmental disorders (for instance, ASD, ADHD), deficiencies in executive functions, such as planning, organization, and working memory, are associated with a greater degree of isolation in the schoolyard and with difficulties at managing friendships. Children with better planning and organization skills spend more time with other children in the schoolyard (4, 86). Difficulties in social interaction are frequent in neuropsychiatric disorders. Although many processes, such as motivation and learning, contribute to establishing social behavior, the processing of external stimuli with the social context may be another important factor to consider, since all the information provided by the environment (including people and objects), is combined to compose a broad range of entities of sensory information that must be processed (17). Additionally, playing has been related to sensory processing, according to preferences for certain toys or games based on their sensory characteristics (colors, movement, sound, etc.), thus associating the sensory profile with the type of game, depending on its level of demand for activities: games with a low activity level, sedentary games, or games with a great demand for movement or physical activity (78). Moreover, children with ASD seem to require more support in social interactions (78), especially with peers, such as those which take place when playing games. Children with a low score in this factor could show difficulties at socializing with other children and participating adequately in the game with other participants, including both verbal and non-verbal communication. This type of results have been related to difficulties in sensory modulation (87). It is worth highlighting the emergence of a factor relating self-regulation and play (EPYFEI –Escolar factor 4), recognizing and expressing feelings and emotions and regulating one's behavior at school, which can be especially relevant during playtime, where the clear guideline of the teacher is usually absent and the children need to organize their own activity and behavior (4). The fact that these factors emerge in the different evaluation instruments, as it also occurs in SPM, suggests the importance of playing in the school environment (88).

These dimensions related to self-regulation are more complex from the cognitive perspective (23). In this sense, self-regulation may be understood as the ability to modulate one's behavior with the aim of achieving goals in the long term, requiring cognitive, emotional, and motivational skills (89), and that it depends on the most basic executive functions (90, 91). It is also necessary to recognize that the development of self-regulation is influenced by parenting guidelines and environmental characteristics, such as poverty, chronic stress, malnutrition, the quality of the school, groups of peers, etc. (74). The fact that emotional self-regulation emerges with playing, supports the multidimensional learning theory, which considers

that children involve in more complex interactions progressively, requiring social, and emotional skills that would allow them to socialize more adequately with their teachers and classmates. This creates a positive learning environment, where they receive and give emotional support (90), while also improving other academic competences, such as the acquisition of vocabulary and mathematical skills (88, 92), thus facilitating the development of healthy habits (91).

With respect to the last factor of EPYFEI-Escolar (factor 5: sense of competence), recent studies have reported that an increase in positive self-concept in childhood is related to better executive functions (80). Self-concept is a multidimensional construct which, in the case of childhood, may be understood as the personal valuation of strengths and weaknesses, related to the child's ideal, and real performance. Positive self-concept has been related to a good academic performance. In this sense, it is understandable that the teachers included this factor in the questionnaire, due to its relevance in school participation and in the psychological development of children. Children with a low self-concept show greater internalizing disorders, such as reduced affection and feelings of despair, or externalizing disorders, such as antisocial, aggressive, and/or criminal behavior (80). In addition to emotional self-regulation, executive functions include other complex skills, such as the self-perception of competence to achieve goals and obtain a good academic performance (80), which are relevant to learning to read, decode, and understand a text, along with writing and mathematical skills, where working memory, cognitive flexibility, and inhibitory control play a fundamental role.

To the best of the authors' knowledge, there is only one questionnaire that aims to determine executive functions and sensory processing jointly, although it is limited to the scope of activities of daily living (ADL) and it can only be filled in by parents: the EPYFEI (51). This questionnaire also has five factors: (1) executive attention, working memory and initiation of actions; (2) general sensory processing; (3) emotional and behavioral self-regulation; (4) supervision, correction of actions, and problem solving; and (5) inhibitory control. The factor solution obtained for the EPYFEI-Escolar questionnaire also consisted of 5 factors, in which the factors found in the EPYFEI for parents can be included, along with two additional dimensions. The first dimension is the sense of competence, which seems to be more closely related to childhood than academic performance. The second dimension is constituted by the skills for playing and social interaction, probably due to the fact that the school is a context in which socialization takes place, along with the development of social skills required for interacting with a group of peers. This may be relevant to educational inclusion practices and the participation of children with functional diversity at the school (93). Lastly, in both questionnaires, i.e., EPYFEI and EPYFEI-Escolar, the executive functions factor is more relevant to explaining difficulties in the school context than the sensory processing factor. The factorial solution of the EPYFEI for parents is shorter, it only consists of 36 items, unlike the EPYFEI-Escolar, which has 54 items. This may be due to the greater complexity involved in participating in school activities. In the school version, the first factor of the EPYFEI-Escolar, which includes the initiation, execution, and supervision of the action, contains 23 items, while the EPYFEI for parents has only 11 items. On one hand, the development of inhibitory control seems to be more relevant in school than in ADL. At school, it constitutes the second factor (with 10 items), while at home it is the fifth factor (with 5 items) This may be because, in the classroom, children have to be in a certain posture, sitting, attentive, without moving and following the teacher's instructions, inhibiting the possible interferences of auditory or visual stimuli that are not relevant to carry out the school tasks. On the other hand, sensory processing is the fourth factor in relevance to participation in the school, unlike in ADL from EPYFEI for parents, which is the second factor in interest. In both questionnaires, emotional, and behavioral self-regulation arises in participation in the two contexts. Finally, a difference between the two questionnaires is due to the importance of participation in the school field in the development of a sense of competence. This can be explained according to developmental theories, from which it is understood that from the age of 6, the achievement of academic activities are relevant for the psychological and emotional development (94).

One of the relevant characteristics of EPYFEI-Escolar vs. other instruments that assess EF (60), is that this new tool understands that participation in the activity depends not only on the demands of the activity itself, because of the context, too. In the case of CHEXI, four factors are considered regardless of the context: working memory, planning, inhibitory control, and regulation. Instead, the BRIEF considers more factors, although always the same for parents and teachers: inhibition, self-supervision, flexibility, emotional control, initiative, working memory, planning and organization, homework supervision, and organization of materials (59).

Implications in the Practice

One of the advantages of EPYFEI-Escolar is that it could help teachers to be more aware of the importance of the different processes that can influence the performance and participation of children in the classroom, allowing them to guide the learning strategies for each child.

Another advantage is that this tool is easy to complete, which allows conducting a relatively easy screening. Similarly, in the field of OT, the development of the EPYFEI-Escolar questionnaire proposes an advance, since, according to the best knowledge of the authors, it would be the first instrument to approach sensory processing and executive functions jointly in the school context. The creation of this tool may help occupational therapists who work in the school environment to guide teachers and parents about the best intervention strategies, in order to plan specific programs according to the needs of each child and each educational center, such as programs to improve self-regulation.

Limitations and Future Work

The present study has some limitations. First, the socioeducational level of the parents was not obtained, which could influence in the development of executive functions and

the differentiation of the results according to this variable. Second, the study did not include children over 11 years of age who were still in primary education after repeating a course at some point. Although this is a generally infrequent circumstance, it could represent a group of children with greater difficulties. However, considering that the development of EF reaches a level similar to that found in adults at about 11 years of age, we believe that including these children would not have produced significant differences in the obtained results. Third, the sample was obtained using non-probability convenience sampling. Therefore, the study must be replicated in a representative sample of healthy children and in another representative sample of children with a neurodevelopmental disorders. With respect to future research lines, it would be interesting to carry out studies in which a confirmatory factor analysis of the EPYFEI-Escolar was conducted. Another possible future line of research is to compare the results of the EPYFEI for parents and the EPYFEI-Escolar in different clinical populations. Likewise, it would be convenient to carry out studies including children with other educational needs, to determine possible profiles and provide guidelines for educational intervention, in order to improve executive functions and sensory processing. It would be interesting to analyse whether executive deficiencies would contribute to explaining the presence of sensory problems in autism or other neurodevelopmental disorders (25).

CONCLUSIONS

The EPYFEI-Escolar questioonnaire makes a unique contribution to understanding neurodevelopmental disorders, since it considers sensory processing and executive functions simultaneously in activities carried out in the school environment.

EPYFEI-Escolar is a tool that complements other tools used by professionals who are in charge of making a more specific diagnosis and it can be a very useful instrument for teachers, since it facilitates the screening of children, allowing for the early detection of children with learning difficulties. This could help to provide a quick response to their educational needs, guiding the teacher about the strengths and weaknesses of the children regarding their executive functions and sensory processing, with the aim of optimizing the learning of the children and influencing their sense of competence, which is associated with academic success in this age range.

The psychometric results confirm the internal consistency of the instrument, as well as its construct validity and discriminant validity, according to the information provided by the participating teachers.

The factor result of EPYFEI-Escolar shows the role of multiple factors in the successful school participation, beyond academic performance, cognitive capacity, or sensory processing. EPYFEI-Escolar supports a wide perspective, and includes socioemotional competences, such as recognizing the emotions of other children and/or teachers, and responding adequately to the demands of the environment, regulating their own behavior, and emotions. All that allows developing an optimal sense of competence that could lead to the successful transition of the child to other educational stages and contexts.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Comité de Ética e Investigación (CEI) de la Universidad de Granada. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

DR-A contributed to the design and implementation of the research. AT-G and MR-M contributed to implementation of the research. AS-F analyzed the data, and all authors contributed to the writing of the manuscript.

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BRIEF RESEARCH REPORT
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Psychiatric Diagnoses and Treatment Preceding Schizophrenia in Adolescents Aged 9–17 Years

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Objective: Our study aimed to examine psychiatric diagnoses and treatment preceding a schizophrenia diagnosis in adolescents, stratified by sex and race/ethnicity.

Methods: Using Medicaid physical and behavioral health and pharmacy claims data, we identified 1,459 adolescents who were aged 9–17 years and diagnosed with schizophrenia between January 2006 through June 2009. Psychiatric diagnosis, mental health service use including psychiatric hospitalization, residential treatment and outpatient therapy and psychotropic medication use preceding schizophrenia were identified.

Results: Forty-five percent of the adolescents were diagnosed with one or more psychiatric conditions. More than 40% of the adolescents were hospitalized or placed in a residential treatment facility for other psychiatric conditions preceding schizophrenia. Overall, 72% of the adolescents were prescribed with one or more psychotropic medications and 22% were prescribed with three or more psychotropic medications in the year prior to their first schizophrenia diagnosis. We found that sex and race/ethnicity influence preceding psychiatric conditions and psychiatric treatment use.

Conclusions: Careful screening and evaluation to validate diagnoses is important as the presence of certain psychiatric morbidity is common among adolescents with schizophrenia during the prodromal period. Developing acceptable and accessible interventions that will reduce psychiatric hospitalization and residential treatment care and improve care connection for schizophrenia treatment is important to mitigate complexity in treatment for adolescents and reduce cost burden for families and the society. Integrating health claims data in the development of schizophrenia risk conversion models can be useful in effectively predicting ideal timing of tailored interventions for adolescents with preceding psychiatric conditions.

Keywords: schizophrenia, preceding psychiatric diagnoses, preceding psychiatric treatment, adolescents aged 9–17 years, health claims data

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INTRODUCTION

Many individuals who develop schizophrenia exhibit a gradual increasing rate of psychiatric symptoms preceding psychosis onset. This prodromal stage can span months to years prior to a schizophrenia diagnosis (1). During the prodromal period, genetic and environmental risk factors, such as substance abuse, often are linked with increased risk of psychosis later on (2, 3). The prodromal symptoms are often characterized by symptoms consistent with other psychiatric disorders, thereby leading to early contact with mental health services (4). Previous evidence from birth cohort studies identifies increased risk for schizophrenia among those who have been diagnosed in childhood with conduct disorder, oppositional defiant disorder (ODD), depression, anxiety disorder, or attention-deficit/hyper activity disorder (ADHD) (5).

Examining whether psychiatric conditions have been diagnosed prior to a diagnosis of schizophrenia has two important implications. First, psychiatric symptoms that are common among adolescents (6) may complicate early detection and treatment. About half of individuals with schizophrenia have comorbid psychiatric disorders (7), most commonly depression (8). Schizophrenia symptoms may be misinterpreted in the presence of other symptoms and result in inappropriate labeling and treatment. For example, one study found that patients identified as high risk based on prodromal symptoms were enrolled in treatments like psychotherapy and pharmacotherapy and given medications including antidepressants, antipsychotics, stimulants, and mood stabilizers (9). If these treatments are provided under inappropriate labeling, this delays treatment for psychosis, namely schizophrenia, when diagnosis is determined later on.

Second, early diagnosis and treatment initiation can result in much better outcomes than when diagnosis is delayed (10). The first five years after schizophrenia diagnosis is the stage of maximum risk for treatment disengagement, relapse, and suicide. At the same time, adolescents go through major developmental challenges such as forming a stable identity, peer networks, and intimate relationships, and obtaining vocational training (11). If the presence of certain psychiatric morbidity is common among adolescents with schizophrenia during the prodromal period, it can act as a red flag that leads to more careful screening and evaluation. Early onset schizophrenia in adolescents has substantial loading of externalizing behavior disorders, such as mood/emotional dysregulation disorders, attention deficit disorders, and oppositional defiant/conduct disorder (12). Given that the age of first diagnosis and patterns of other behavioral comorbidities are important factors that differentiate early onset schizophrenia populations (13), identifying comprehensive patterns of comorbid psychiatric disorders and treatments in adolescents can produce more effective outcomes by enabling clinicians to better stratify treatment interventions.

Preceding psychiatric conditions may differ by sex and race/ethnicity. Recent epidemiological studies have indicated that there is a higher incidence of schizophrenia in males compared to females (14). A higher proportion of African Americans than whites are diagnosed with conduct disorder and ODD (15). A higher proportion of whites than other race/ethnic groups are diagnosed with ADHD, bipolar disorder, and autism (15–17). Post-traumatic stress disorder (PTSD) is a more common diagnosis among females than males (18).

Empirical studies on first episode of psychosis and schizophrenia have focused on predictors of symptom remission and functional recovery (19–21). Coordinated specialty care interventions such as the Recovery After an Initial Schizophrenia Episode (RAISE) and the Early Detection and Intervention for Prevention of Psychosis Program (EDIPP) have proven the positive effect of early detection, outreach for treatment engagement and early treatment (21–24), suggesting that early identification of adolescents with schizophrenia is critical. These studies have found that baseline symptom severity, time in treatment and decrease or remission of substance use are key predictors of symptomatic and functional outcome of psychosis and schizophrenia treatment (19–21).

Despite the well-established line of research on first episode of and early intervention for psychosis and schizophrenia, there is significant lack of insights into psychiatric diagnoses and treatment that adolescents go through preceding a schizophrenia diagnosis. Research findings on psychiatric diagnosis and treatment prior to schizophrenia in adolescents can inform effective schizophrenia care delivery. Our study examined psychiatric diagnoses and treatment including both mental health service and psychotropic medication use preceding a schizophrenia diagnosis in adolescents. We stratified the analysis by sex and race/ethnicity based on the previous research finding that psychiatric diagnoses and treatment can differ based on sex and race/ethnicity.

METHODS

Data came from the Pennsylvania behavioral and physical health and pharmacy claims. Adolescents aged 9–17 years with at least two claims with a primary diagnosis of schizophrenia or psychotic disorder (19) between January 1, 2006 through June 30, 2009 were included in the study sample. The Pennsylvania Medicaid data we could use were available only for this duration. International Classification of Disease (9^{th} ed., ICD-9) codes including 295xx, 297.1, 297.3, 298.1, 298.3, 298.4, 298.8, 298.9, and 301.22 were identified as having schizophrenia. The first dates identified for the ICD-9 codes for psychotic disorders or schizophrenia were indexed as the initial schizophrenia diagnosis date. Considering that individuals who receive the first diagnosis of any psychotic disorder subsequently receive a schizophrenia diagnosis, the ICD-9 codes for psychotic disorder were included in identifying the index date for schizophrenia diagnosis. A total of 1,459 adolescents aged 9–17 years with a schizophrenia diagnosis and continuous Medicaid enrollment for one-year prior to the first schizophrenia diagnosis were included in the study sample. The University of Pennsylvania's Institutional Review Board approved this study and the Pennsylvania State Office of

Mental Health and Substance Abuse Services approved the use of Medicaid claims data for this study.

Adolescents' ages were measured at the index date of first schizophrenia diagnosis. Race/ethnicity categories included African American, Hispanic, white, and other. Sex abstracted from the claims data as well was measured as male or female. More than one-half of the sample (57%) was male and aged 15–17 years at their first schizophrenia diagnosis (58.5%). The largest racial/ethnic group was African American (44.7%), followed by white (38.2%), Hispanic (14.8%) and other racial/ethnic group (2.4%). The distribution of sex and age did not significantly differ by race/ethnicity.

Psychiatric diagnoses from ICD-9 codes associated with claims during one year prior to the first schizophrenia diagnosis were identified as preceding diagnoses. Diagnoses included bipolar disorder, depression, substance use disorder, post-traumatic stress disorder (PTSD), other mood disorder, adjustment disorder, attention deficit hyperactivity disorder (ADHD), conduct disorder/oppositional defiant disorder (conduct/ODD), autism, and anxiety disorder.

Mental health service use including outpatient therapy, inpatient hospitalization, and residential treatment care was identified through the current procedural technology (CPT) codes and the specialty codes available through the Medicaid claims data. Wraparound services for children were categorized as one of outpatient therapies. Other mental health service use including partial treatment, drug and alcohol treatment and mental health crisis service were excluded from the analysis as these treatment types were associated with only 7.2% of total claims matched for the study sample. The percentage of these mental health service use was minimal at the person-level, and was not meaningful to compare by subgroups. Psychotropic medication classes included: antidepressants, antipsychotics, benzodiazepine, central nervous system (CNS) stimulants, epileptic mood stabilizers, and other sedation. We created a separate variable named as "epileptic mood stabilizers" which included valproic acid, carbamazepine and lithium to distinguish the possible prodromal stage of schizophrenia from other sedation use. These active ingredients are known to be prescribed prior to schizophrenia in adolescents (25, 26).

Statistical analyses were conducted using SAS 9.4 (27). Percentages of psychiatric diagnoses, mental health service use and psychotropic medication use, and mean number of days prescribed for psychotropic medication were calculated for each intersectional sex and race/ethnic group (African American male, African American female, Hispanic male, Hispanic female, White male, White female, males in other race/ethnicity, and females in other race/ethnicity). The other race/ethnicity recoded in Medicaid claims included Asian, American Indian/Alaskan Native and other race/ethnicity, and Asians were the majority of this group included in the study.

Generalized linear models (GLMs) were used to test whether the following dependent variables differ by sex and race/ethnicity: presence of preceding psychiatric diagnoses including ADHD, adjustment disorder, anxiety disorder, autism, bipolar disorder, conduct/ODD, depression, other mood disorder, PTSD, and substance use disorder measured as binary variables (Yes vs. No); total number of preceding psychiatric diagnoses measured as a categorical variable (none, 1, 2, and 3 or more diagnoses); use of psychiatric outpatient therapy, psychiatric hospitalization and psychiatric residential treatment measured as binary variables (Yes vs. No); use of antidepressant, antipsychotic, benzodiazepine, CNS stimulants, epileptic mood stabilizers, and other sedation measured as binary variables (Yes vs. No) and as mean number of days prescribed with each medication; and total number of psychotropic medications used (a categorical variable of none, 1, 2, and 3 or more medication classes). Sidak correction (28) to adjust inequality for all main-effect means for the multiple comparisons was used in the GLMs.

RESULTS

Preceding Psychiatric Diagnoses

Forty-five percent of the adolescents were diagnosed with one or more psychiatric conditions (see **Table 1**). Significantly higher percentage of white females was diagnosed with bipolar disorder than were African American and Hispanic males. Hispanic males had the lowest percentage of those diagnosed with bipolar disorder (3.1%, $p < .0001$). Significantly higher percentages of African American males (32.5%) and African American females (28.3%) were diagnosed with conduct/ODD than were all other groups except other racial/ethnic males and females ($p < .0001$). Hispanic males had the lowest percentage of those diagnosed with depression (0.8%) and this was significantly lower than that for Hispanic females and white females (11.4% and 9.1%, respectively, $p < .01$). The percentages of Hispanic females (5.7%) and African American females (4.6%) diagnosed with PTSD were more than double the percentages of all other adolescent groups diagnosed with PTSD. The difference was not statistically significant, but it was approaching the significance level with $p = 0.051$. Other racial/ethnic male group had the highest percentage of those diagnosed with autism (10% vs. 0%–3.8% for all other groups at $p < .0001$) and those diagnosed with anxiety disorder (5% vs. 0%–0.3% for all other groups at $p < .0001$).

Mental Health Service Use

More than 40% of the adolescents were hospitalized or placed in a residential treatment facility for psychiatric conditions (see **Table 1**). Higher percentages (about 30%) of African American females, Hispanic females, and both males and females in other racial/ethnic group compared to all other groups were hospitalized for psychiatric conditions in the year prior to their first schizophrenia diagnosis. Of the groups, the percentage of African American females with psychiatric hospitalization was significantly higher than that for Hispanic males (29.7% vs. 12.5%, $p < .01$). Forty percent of males in other racial/ethnic group and more than one third of African American females and males were placed in residential treatment facilities, while 21% of white females and males and 14%–16% of Hispanic females and

TABLE 1 | Psychiatric diagnosis and mental health service use preceding schizophrenia diagnosis.

	African American female (N = 283)	African American male (N = 369)	Hispanic female (N = 88)	Hispanic male (N = 128)	White female (N = 243)	White male (N = 314)	Other ethnic female (N = 14)	Other ethnic male (N = 20)
Psychiatric diagnosis	%	%	%	%	%	%	%	%
Bipolar disorder ($p < .0001$)	12.0	6.5[a]	10.2	3.1[b]	20.2[a,b,c]	11.8[c]	14.3	20.0
Depression ($p < .01$)	7.8	3.8	11.4[a]	0.8[a,b]	9.1[b]	6.1	21.4	5.0
Substance use disorder	0.7	0.8	0	0	2.5	1.3	0	0
PTSD	4.6	0.5	5.7	0	2.1	1.3	0	0
Other mood disorder ($p < .05$)	15.2	10.3	13.6	5.5[a]	17.7[a]	14.0	7.1	10.0
Adjustment disorder ($p < .01$)	2.1[a]	1.6[a]	0.0[a]	0.0[a]	1.2[a]	1.6[a]	14.3[a,b]	0 [b]
ADHD	4.6	10.8	5.7	10.2	4.5	11.5	7.1	15.0
Conduct/ODD ($p < .0001$)	28.3[a]	32.5[b]	12.5[a,b]	14.8[b]	12.6[a,b]	17.5[a,b]	7.1	35.0
Autism ($p < .0001$)	0.4[a]	0.5[b]	0[c]	0[d]	1.2[e]	3.8[a,b,d]	0	10.0[a,b,c,d,e]
Anxiety disorder ($p < .0001$)	0[a]	0.3[a]	0[a]	0[a]	0[a]	0[a]	0[a]	5.0[a]
Number of psychiatric diagnoses ($p < .001$)								
None	47.4	52.9	64.8	72.7	54.3	54.5	57.1	35.0
1	35.3	29.5	19.3	21.1	26.8	28.0	28.6	45.0
2	12.7	14.6	9.1	5.5	14.8	13.1	7.1	10.0
3 or more diagnoses	4.6	3.0	6.8	0.8	4.1	4.5	7.1	10.0
Mental health service use								
Outpatient therapy ($p < .0001$)	2.1[a]	1.6[a,b]	1.1[a]	0.8[a]	7.0[b]	9.6[a]	0	15.0
Inpatient hospitalization ($p < .01$)	29.7[a]	22.8	29.6	12.5[a]	25.1	19.8	28.6	30.0
Residential treatment care ($p < .0001$)	33.6[a]	34.7[b]	14.8[a,b]	16.4[a,b]	21.4[a,b]	21.3[a,b]	21.4	40.0

Generalized Linear Models (GLMs) were used to identify significant differences in preceding psychiatric diagnoses and mental health service use. All variables were measured as binary variables (yes vs. no) except the number of psychiatric diagnoses. Sidak correction to adjust for the multiple comparisons was used in the GLMs. Significant differences by intersectional sex and race/ethnicity are presented in the parentheses if $p < .05$. Pairwise significance between intersectional sex and race/ethnicity are noted with small letters. The same letter indicates significant difference between the intersectional groups at $p < .05$.

males were placed in residential treatment facilities. The residential treatment use significantly differed between whites and other groups except other race/ethnic females and males ($p < .0001$). Seven percent of white females and 9.6% of white males and 15% of males in other racial/ethnic group received outpatient therapy for one year prior to their first schizophrenia diagnosis, while only 0.8%–2.1% of all other adolescent groups received outpatient therapy. The outpatient therapy use significantly differed between whites and other groups except other racial/ethnic males and females ($p < .0001$).

Psychotropic Medication Use

Overall, 71.9% of the adolescents used one or more classes of psychotropic medications and 21.6% were prescribed medications from three or more classes in the year prior to their first schizophrenia diagnosis. As shown in **Table 2**, more than 30% of white females and males and about 25% of Hispanic females and males were prescribed with three or more psychotropic medication classes. The difference in the three or more psychotropic medication use was more prevalent by race/ethnicity than by sex. African American females and males had the lowest percentages (12.4% and 12.7%, respectively), and 32% of white adolescents, 24%–25% of Hispanic females and males, and 14.3% of females and 20% of males in other racial/ethnic group were prescribed with three or more psychotropic medication classes ($p < .0001$).

The most prescribed psychotropic medication was antipsychotics, followed by antidepressants and CNS stimulants. More than two thirds of white females and males and nearly two thirds of females and males in other racial/ethnic group were prescribed with antipsychotics. Mean number of days prescribed for antipsychotics were significantly higher for white females and males (191.3 days and 210.5 days, respectively) than those for African American females and males and Hispanic males (mean days ranging from 90.4 days to 121.1 days, $p < .0001$).

One half of white females, 46.8% of white males and 48.9% of Hispanic females were prescribed with antidepressants. The mean number of days prescribed for antidepressants was significantly higher for white females and males (122.5 and 106 days, respectively) than those for African American and Hispanic females and males (ranging from 29.6 to 86.6 days, $p < .0001$).

Benzodiazepines were the most prescribed among white females (16.1%) followed by white males (8.3%). The mean number of days prescribed for benzodiazepines was significantly higher for white females compared to those for African females and males (13.7 days vs. 1.9 - 2.3 days, $p < .001$).

Sixty-five percent of males in other racial/ethnic group, 47% of Hispanic males and white males, and 42.9% females in other race/ethnicity were prescribed with CNS stimulants. The mean number of days prescribed for CNS stimulants was the highest for white males (124.5 days vs. 30.3 days–114.1 days for other groups, $p < .0001$).

The percentages of adolescents prescribed for epileptic mood stabilizers significantly differed with white males prescribed the

TABLE 2 | Psychotropic medication use preceding schizophrenia diagnosis.

	African American female (N = 283)	African American male (N = 369)	Hispanic female (N = 88)	Hispanic male (N = 128)	White female (N = 243)	White male (N = 314)	Other ethnic female (N = 14)	Other ethnic male (N = 20)
Percentage of adolescents with psychotropic medication use				%				
Antidepressant ($p < .0001$)	27.9[a]	20.6[b]	48.9 [b]	29.7[c]	50.6 [a,b,c]	46.8 [a,b,c]	42.9	20.0
Antipsychotic ($p < .0001$)	46.3[a]	46.1[b]	51.1	59.4[c]	66.3 [a,b]	68.2 [a,b,c]	64.3	70.0
Benzodiazepine ($p < .001$)	2.1[a]	2.2[b]	4.6	3.9	16.1[a,b]	8.3	0	5.0
CNS stimulant ($p < .0001$)	18.0[a]	29.0[b]	34.1[c]	47.7[a,b]	28.8[d]	46.8[a,b,c,d]	42.9	65.0
Epileptic mood stabilizers ($p < .0001$)	7.4[a]	5.4	6	8.8[c]	16.7[b]	21.5[b]	1	1.4[a,b,c]
Other sedation	12.0	13.3	19.3	19.5	18.5	16.2	14.3	0
Number of psychotropic medications used ($p < .0001$)								
None	43.1	42.3	27.3	25.0	25.5	19.8	21.4	20.0
1	21.6	20.6	20.5	20.3	15.2	15.9	7.1	25.0
2	23.0	24.4	27.3	30.5	27.2	32.5	57.1	35.0
3 or more medications classes	12.4	12.7	25.0	24.2	32.1	31.9	14.3	20.0
Mean number of days on psychotropic medication				Mean				
Antidepressant ($p < .0001$)	51.7[a]	29.6[b]	86.6[b]	39.3[c]	122.5[a,b,c]	106.0[a,b,c]	62.0	43.0
Antipsychotic ($p < .0001$)	90.4[a]	106.4[b]	103.2	121.1[c]	191.3[a,b]	210.5[a,b,c]	141.6	221.9
Benzodiazepine ($p < .001$)	1.9[a]	2.3[b]	2.1	3.8	13.7[a,b]	7.4	0	1.4
CNS stimulant ($p < .0001$)	30.3[a]	60.9[b]	58.4[c]	114.1[a,b]	64.9[d]	124.5[a,b,c,d]	92.3	67.5
Epileptic mood stabilizers ($p < .0001$)	15.8[a]	14.1[b]	5.6[c]	5.1[d]	39.1[b]	36.8 [b,d]	52.6	80.3[a,b,c,d]

Generalized Linear Models (GLMs) were used to identify significant differences in psychotropic medication use. Sidak correction to adjust for the multiple comparisons was used in the GLMs. Significant differences by intersectional sex and race/ethnicity are presented in the parentheses if $p < .05$. Pairwise significance between intersectional sex and race/ethnicity are noted with small letters. The same letter indicates significant difference between the intersectional groups at $p < .05$. The mean numbers of other sedation (other than epileptic mood stabilizers) use is not presented here as the percentages adolescents using other sedation did not differ by the intersectional sex and race/ethnicity at $p < .05$.

most (21.5%), followed by white females (16.7%), Hispanic males (8.8%), African American females (7.4%), African American males (5.4%), and other racial/ethnic females and males (1% and 1.4%, respectively). The mean number of days prescribed for epileptic mood stabilizers were significantly higher for other racial/ethnic males (80.3 days) than that for other groups (ranging from 5.1 to 39.1 days, $p < .0001$), except other racial/ethnic females. Other sedation use did not significantly differ by sex and race/ethnicity.

DISCUSSION

We found that a wide spectrum of psychiatric conditions that are commonly diagnosed in adolescents in the year prior to when they are first diagnosed with schizophrenia as previously reported in the literature (7, 8, 29). Over forty-five percent of the adolescents had one or more psychiatric diagnoses preceding schizophrenia. Previous research reports that the risk of developing schizophrenia is up to 4.4 times higher among adolescents who have been diagnosed with conduct disorder/ODD for five years or longer (30). Our study finds that at least one in every four African American males and females and males in other racial/ethnic group are diagnosed with conduct disorder/ODD before getting diagnosed with schizophrenia.

The prior psychiatric diagnoses may reflect the psychiatric comorbidities, but it may also be that psychosis or schizophrenia symptoms are misinterpreted in the presence of other symptoms and result in inappropriate labeling and treatment. For example, mood or psychotic symptoms are frequently associated with initial onset of bipolar disorder or schizophrenia in adolescence (25); thus, the chance of inappropriate labeling and treatment increases for these symptoms. The instability of first psychotic diagnoses given in children and adolescents should also be noted. Psychiatric diagnosis in adolescents are frequently revised during the subsequent course of treatment from affective psychosis or schizoaffective disorder to schizophrenia and vice versa as the adolescents and their illness mature. Careful screening and evaluation to validate diagnoses is important as the presence of certain psychiatric morbidity is common among people with schizophrenia during the prodromal period (31–35).

As found in previous studies, there were significant differences in psychiatric diagnoses by sex and race/ethnicity among adolescents. Significantly higher percentages of white males and females are diagnosed with bipolar disorder; significantly higher percentages of African American males and females are diagnosed with conduct/ODD; a significantly higher percentage of Hispanic females are diagnosed with depression; and higher percentages of African American and Hispanic females are diagnosed with PTSD.

Previous findings on differences in psychiatric diagnoses by sex and race/ethnicity have been limited to additive effects of sex and race/ethnicity. For example, although females are known to have higher prevalence of depression compared to males, little empirical evidence on the interplay of sex and race/ethnicity on

depression exists. Different application of diagnostic criteria by clinicians, clinician bias against different sex and race/ethnicity, families' distrust in mental health professionals, and stigma associated with mental illness can result in misinterpretation of psychiatric symptoms and lead to inappropriate treatment of preceding psychiatric conditions and schizophrenia. Our study findings indicate the importance of further research on interplay of sex and race/ethnicity to gain in-depth insights into this disparity.

According to the data from the 2014 National Survey on Drug Use and Health, 21.3% of young adults aged 18–25 years with mental illness receive outpatient mental health services (36). Based on this report, we expected a similar level of outpatient therapy use for our study sample. The low use of outpatient therapy among the adolescents to treat their preceding psychiatric conditions is alarming. As the lack of outpatient therapy use can negatively affect symptom remission and recovery after getting diagnosed with schizophrenia (20–22), developing innovative ways to engage adolescents in outpatient therapy is important.

The high utilization of hospitalization and residential treatment care particularly, among African Americans and other race/ethnicity to treat their preceding psychiatric conditions confirms the documented disparity in mental health service use among adolescents. Individualized care to meet unique treatment need of adolescents by sex and race/ethnicity is important. Interventions such as the Recovery After an Initial Schizophrenia Episode (RAISE) and the Early Detection and Intervention for Prevention of Psychosis Program (EDIPPP) (21–24) that provide individualized specialty care coordination for psychosis or schizophrenia are currently available only by help-seeking or referral by health care professionals for individuals with first episode. To maximize the benefit of these interventions, there needs to be public policy to offer these individualized care coordination interventions at the population level. Additionally, developing innovative bridge or care connection programs that will smoothly connect the care between treatment for preceding psychiatric conditions and schizophrenia and a smooth transition from psychiatric hospitalization or residential treatment care to community-based care for adolescents is important.

Over 70% of the adolescents included in our study used one or more classes of psychotropic medications during one year prior to the first schizophrenia diagnosis. Considering that 45% of adolescents were diagnosed with preceding psychiatric disorders, it is likely that they also were prescribed with psychotropic medications from primary care physicians. Use of prescription medication for psychiatric disorders has increased among adolescents as evidenced in previous research (37). Using a nationally representative data, Anderson et al. (38) found that almost one-third of adolescents with outpatient visits for mental health conditions see primary care physicians and only a little over a quarter see psychiatrists. The study also reports that primary care physicians prescribe medications to a higher percentage of children with ADHD than did psychiatrists (73.7% vs. 61.4%) (38).

Our study reveals that more than one third of Hispanic adolescents, white males and adolescents in other racial/ethnic group are prescribed with CNS stimulants one year prior to their first schizophrenia diagnosis. Previous research reports that one in 660 adolescents and young adults with ADHD who receive prescription stimulants develop onset of psychosis (39). Our finding that CNS stimulants are commonly prescribed for the adolescents in the year prior to their being diagnosed with schizophrenia raises the question as to whether the prescription of stimulants may have increased the risk of schizophrenia as they are known to exacerbate psychotic symptoms (40).

For the early detection of psychosis, personalized psychosis risk prediction models have been developed and tested. For example, the North American Prodrome Longitudinal Study (NAPLS2) identifies clinical high-risk based on unusual thoughts, suspiciousness, verbal learning, symbol coding, social functioning decline, age, and family history (41). Integrating health claims data in the psychosis risk prediction models can lead to gaining in-depth insights into ideal timing of tailored interventions for adolescents with preceding psychiatric conditions.

Future research that analyzes temporal relationship between diagnoses given and different psychotropic medications prescribed can provide insights into practitioner understanding and behavior at the time of the diagnoses. The analysis also can provide more in-depth insights into the practical effects of the delay in making schizophrenia diagnosis or identifying a psychotic disorder at the time the preceding psychotic diagnoses were made. For example, our finding on the significantly higher percentage of adolescents with epileptic mood stabilizer prescriptions and the significantly higher percentage of adolescents with anxiety disorder diagnosis for other race/ethnic group compared to all other groups may indicate prescribers' behavior of reluctance to put a psychotic diagnosis into record of adolescents with certain race/ethnicity rather than failing to recognize that the adolescents were experiencing some psychosis.

Several study limitations should be mentioned. Our study included adolescents enrolled in Medicaid in Pennsylvania and thus, the interpretation of the study findings is limited to geographic areas with similar sociodemographic conditions. The preceding conditions were identified for one year prior and post the adolescents' first schizophrenia diagnosis. Due to the limited observation period, there is a chance that we have failed to identify certain conditions that tend to develop for longer term during adolescence. Medicaid populations can differ from non-Medicaid populations in their access to treatment. Thus, the study results cannot be generalized to the overall adolescent population. Finally, the Medicaid data we used is old and there may have been some changes in clinicians' diagnosis, prescription and treatment behaviors. Despite the

limitations, our study findings provide much needed information on comprehensive psychiatric diagnoses and mental health treatment use preceding schizophrenia in adolescents and address important future directions for research, policy and practice.

CONCLUSION

Careful screening and evaluation to validate diagnoses is important as the presence of certain psychiatric morbidity is common among people with schizophrenia during the prodromal period. Developing acceptable and accessible interventions that will prevent psychiatric hospitalization and residential treatment care and improve care coordination to smoothly connect to the care for schizophrenia is important to mitigate complexity in the treatment for adolescents and reduce cost burden for families and the society. Integrating health claims data in the development of schizophrenia risk conversion models can be useful in effectively predicting ideal timing of tailored interventions for adolescents with preceding psychiatric conditions.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available. The data license agreement restricts the access only to the University of Pennsylvania Center for Mental Health.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the University of Pennsylvania Institutional Review Board. Written informed consent from the participants' legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

AUTHOR CONTRIBUTIONS

CK-Y led conceptual design of the study, literature review, data analysis, interpretation of the study results, and manuscript writing. BC and ST contributed to literature review and manuscript writing. JL contributed to interpretation of the study results and manuscript writing. DM contributed to conceptual design of the study, interpretation of the study results and manuscript writing. Y-LW contributed to conceptual design of the study and manuscript writing. CE provided clinical expertise and contributed to conceptual design of the study and manuscript writing.

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Children of Patients Undergoing Psychiatric Treatment: An Investigation of Statutory Support Services After Referrals to Child Protection Services

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Aims: Preventive interventions for children of parents with mental illness are widely recommended. Mental health services entrust concern for patients' children by referrals to child protection services. We investigated service coverage for children following referrals.

Methods: Data from referrals regarding 376 children of adult psychiatry patients over 2008–2012 was linked to information from municipal records and Danish national registers. We conducted Cox regression and used Kaplan–Meier curves to show time to intervention and cumulative incidence of any child and family support services with one-year follow-up from referral date.

Results: At follow-up, 32% of children were provided with a child and family support service on average 73.4 days after referral. The most common services were family treatment (18%) and family counseling (11%). A statutory child assessment was conducted for 21% of children. Contents of the referrals suggested that 60% of children experienced adverse home environments and/or acute situations due to parents' psychiatric illness. Predictors of initiation of support services included a child living alone with the patient, hazard ratio 2.09 (1.41–3.08), the patient being the mother, hazard ratio 1.72 (1.11–2.65), and an adverse home environment presenting an acute situation specified in referral, hazard ratio 1.89 (1.01–3.51).

Conclusion: Our finding that only one third of children receive support after referrals from psychiatry within an average of three months suggests an underserved population of at-risk children. These findings warrant reconsideration of resource allocation and creation of more efficient intervention strategies to protect at-risk children and prevent development of mental illness and adversity.

Keywords: parental psychiatric disorders, early intervention, child protection, psychiatry, statutory intervention

INTRODUCTION

Psychiatric illness in a parent affects the whole family, particularly when it concerns children dependent on the care of their parents for well-being and healthy development. These children are at increased risk of developing a mental illness due to genetic influences, shared adverse environmental factors with their parents and gene–environment interactions (1–3). Studies have shown that psychiatric symptoms interfere with parenting capacities, while population-based studies from France, Belgium and Denmark demonstrate that 10–40% of children are removed from home and placed in care when parents have psychiatric disorders (4–6).

Randomized, controlled trial results focusing on child-resilience, parenting skills and family functioning have shown family-based interventions to be effective in promoting well-being and preventing mental disorders in children and preventing their unnecessary separations from their parents (7–10). For these reasons, preventive and supportive interventions are widely recommended (7, 11, 12). A recent review in Lancet Psychiatry has presented a mental health prevention strategy and identifies the children of parents with mental illness (COPMI) as a subpopulation, who, owing to their increased risk for mental illness alone, acquire selective primary preventive intervention to shift expected trajectories towards mental illness (13). A high proportion of 7-year-old COPMI already displays sub-clinical manifestations of mental illness or meet the diagnostic criteria thereof, indicating that primary preventive interventions or secondary preventive interventions are warranted (14).

According to the United Nations' Convention of the Rights of the Child, all the relevant agencies are responsible for children's welfare (15). These include staff working in adult psychiatry, responsible for notifying local child protection services upon concern for the children of patients. Referrals are sent for a minority of patients, the children of whom staff is concerned due to their knowledge about the patients' condition and the child's general circumstances. Thus, the threshold for referrals is high. The referral procedure exists in most countries outside Denmark, including many parts of Europe, the UK, Australasia and the USA. In this intersection of statutory child protection and adult mental health, effective inter-agency communication is vital to determine necessary intervention by responsible authorities.

Scientific documentation of service coverage is lacking internationally where the requirement should be that decision-makers act on adequately-informed grounds when making structural adjustments and securing necessary resource-allocation for service provision. The long-term perspective is to promote children's well-being while they are growing up, so increasing their resilience and reducing social deprivation and future mental illness cases as children grow into adults (10).

Aims of the Study

We aim to document the service coverage for children of psychiatric patients following referrals from Mental Health Services to Child Protection Services by investigating the proportion of children receiving a statutory child and family support service, the time between referral and intervention, as well as types of support services within Child Protection Services.

METHODS

Data Sources

Data on the written referrals concerned the children of patients treated at three mental health hospitals in the Capital Region of Denmark. Approximately 500,000 individuals live in the catchment areas of the three hospitals, which treat patients of all ages, and with all psychiatric diagnoses. All psychiatric hospitals in Denmark are public. All the referrals had been collected in sequence by the Head Social Workers over 2008–2012. This procedure was initiated to keep track of referrals and follow-up on action taken by local child protection services. Referrals contained personal identification numbers of parents and qualitative descriptions on circumstances which caused concern for the children.

The data drawn from the referrals was linked to information obtained from municipal records and Danish population-based registers. Here, data linkage was facilitated by using the unique personal identification number assigned to all live-born children and new residents in Denmark; established in 1968, it is now used across all the relevant registration systems.

The Danish Civil Registration System (CRS) contains dates of birth and data on gender, address and family members living in the same household from January 1st each year (16). Information on statutory child and family support services (SCFS service), and out-of-home placements of children, was then retrieved from Statistics Denmark, with information dating back to 1980. As Statistics Denmark does not provide information on family-based services, this data had to be obtained directly from municipal records. The authors contacted child protection services in the eight municipalities containing the districts within which the three mental health centers belonged. Child protection services were then contacted through a formal letter, formal email and then follow-up emails or telephone calls. Three municipalities accepted participation, three refused and two failed to respond to any request for assistance.

Information on patients' diagnosis and treatment was obtained from the Psychiatric Central Research Register (PCRR) (17) listing all psychiatric inpatient contact since 1968, in addition to every outpatient and emergency room contact since 1995 (17). The study was approved by the Danish Data Protection Agency, the Danish Health Data Protection Agency, with informed consent waived by the National Scientific Ethical Committee as stipulated in the Data Protection Act (18).

Study Population

Altogether, 376 children aged 0–17 years were included as the offspring of 218 patients whom, having been admitted as their parents to the respective mental health hospitals, were the object of a referral sent to child protection services in the three

participating municipalities. The parents had been inpatients (n = 211) or exclusively outpatients (n = 3) between 2008 and 2012, although information on four parents was missing in the Psychiatric Central Register.

Referrals are only sent concerning the minority of patients in cases where personnel were concerned about the child's wellbeing, because the patients' conditions were assumed to interfere with parenting capacities. Crucially, most parents in the study (86%) had previous psychiatric admission.

Referrals

In cases where a child is or assumed to be in need of special social support, public employees must report their case to the social services department at the local municipality by means of a referral. The way such referrals are handled is shown in **Figure 1**. This form of mandatory reporting is stipulated in section 153 of the Danish Social Services Act (19).

Here, parental consent is unnecessary, although it is preferable where available. It is generally acknowledged that these duty-based referrals override the secrecy duties of health personnel, cf. the Consolidated Health Act (20). Hence, if the child in question is assumed to need special support, a more thorough assessment, a statutory child assessment, must be carried out within 4 months. In cases of acute protection concern for children the assessment can be conducted at the same time of a support service or out-of-home placement.

There are no formal requirements regarding the content of the referrals. For the purpose of this study the researchers classified the referrals according to their contents. The rating was conducted by a child psychiatrist (AT), clinical psychologist (AR) or a research anthropologist (KBJ). Interrater reliability based on 30 cases showed an interclass correlation of 0.87. A referral was classified as a *Vague Concern* when concern was expressed for the child's wellbeing based on vague not specific grounds. A referral was classified as a *Specific Concern* in presence of specific examples of neglect, abuse and other adverse conditions of upbringing. A referral was classified as an *Acute Concern* when acute situations caused by patients' psychiatric illness and involving children were mentioned in the referral. Vague and Specific Concern were mutually exclusive, while referrals mentioning a critical situation, but not prolonged adverse conditions of upbringing were classified as both a vague and acute concern (see **Appendix 1** for classification criteria). The length and degree of details varied greatly between referrals, some counting several detailed pages and others short providing only the most basic information about the parent's diagnosis, time of hospitalisation and child's age.

Diagnostic Categories of Parents

Information on the parents' psychiatric diagnoses was drawn from the Danish Psychiatric Central Register. Based on the hierarchy of ICD-10 the following diagnostic hierarchy was used if the parents had more than one diagnosis: The highest up the scale was schizophrenia (F20), then other psychosis (F21–F29), bipolar disorder (F30–31), unipolar depression (F32–34), while the lowest in the hierarchy were other disorders. Substance abuse (F10–F19) and suicide attempt (X60–X84) were considered co-morbid diagnoses.

Outcome Measures

After the referral date, the primary outcome was initiation and time to initiation of any statutory child and family support

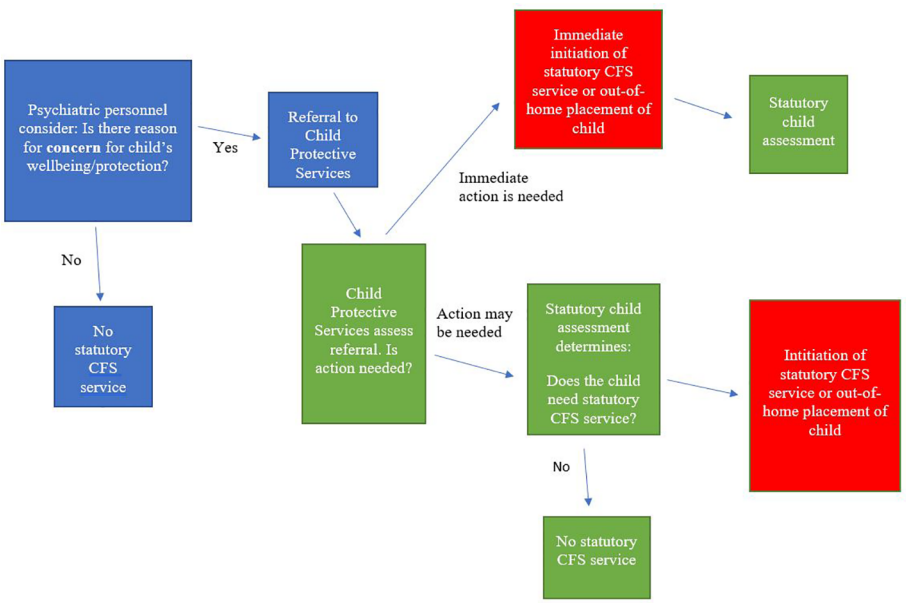

FIGURE 1 | Flow-chart showing the process of referral of children of patients from mental health services to Child Protective Services and subsequent statutory child and family support services (Statutory CFS service).

service or out-of-home placement by child protection services subdivided into the following categories: 1) Family treatment, 2) Short family counseling/short assessment, 3) Support persons, including family support workers. 4) Financial support including free daycare, 5) Institutional or family-based relief care and 6) Out-of-home placement of child. As a secondary outcome we investigated whether the child had undergone a statutory child assessment i.e. an investigation of the circumstances regarding the child's family, school and general health etc., to determine the need for statutory intervention.

Statistical Analysis

Cox regression was conducted to calculate hazard ratios when initializing any statutory child and family support (CFS) service in the first year after referral.

Hazard ratios were calculated as a function of the child's gender and age group, parent's gender, parent's psychiatric diagnosis, classification of referral, child's living situation, his or her municipality, and whether he or she had previously received a statutory CFS service.

Kaplan–Meier curves were used to determine the initiation of statutory CFS service with the days since referral as the underlying time variable. This analysis was performed in Stata/MP version 16.1. With log-rank test it was analyzed whether there were significant differences in the time lag and the proportion receiving services after referral for children referred for the first time versus children for whom support services were already established at the referral date, as their probability of receiving a new service may differ from children with no previous support service.

RESULTS

Table 1 summarizes the characteristics of the 376 children studied. In 31 cases (14.2%), the referral was made upon the parents' first psychiatric contact while 187 (86%) had previous psychiatric admissions. The median number of previous psychiatric contacts was six. A total of 42 children (11.2%) had already received support from child protection services before each referral date. Referrals concerning 60% of children were classified as either specific or acute concern, or a combination hereof.

The Kaplan–Meier curves in **Figure 2** depict the cumulative incidence of any statutory CFS service or outplacement. Here, 32% of children without service at the date of referral obtained a statutory CFS service during follow-up within an average of 73.4 days. For the children receiving an ongoing service at the referral date, 38% obtained a new service during follow-up within an average of 86.8 days. Log-rank test showed no statistical difference between the two groups (**Figure 2**).

The curves in **Figure 3** illustrate specific types of services initiated within a year after referral. When examining the group of children without service at referral, family treatment (18%), short family counseling/short assessment (11%) and financial support (8%) were found to be initialized most frequently. Six percent of children were

TABLE 1 | Descriptive characteristics of the cohort of the 376 children of psychiatric patients referred to Child Protection Services by Adult Psychiatric Services.

Characteristics	n/%	Offered service* 1 year following notification in %
Female child	180 (48.6%)	35.0%
Male child	190 (51.4%)	31.8%
Age average	7.9 (SD 5.3)	N/A
Mother is a patient	257 (68.4%)	37.4%
Father is a patient	111 (29.5%)	23.6%
Municipality A	79 (21.0%)	43.0%
Municipality B	266 (70.7%)	31.6%
Municipality C	31 (8.2%)	24.2%
Parent's diagnosis		
Schizophrenia	60 (16.0%)	40.0%
Other psychosis	42 (11.2%)	31.0%
Bipolar disorder	37 (9.8%)	37.8%
Unipolar depression	102 (27.1%)	28.4%
Other mental illness	135 (35.9%)	33.5%
Suicide attempt	8 (2.1%)	50.0%
Substance abuse	67 (17.8%)	33.5%
Child's living situation		
With both parents	137 (36.6%)	27.0%
With the patient	141 (37.7%)	45.5%
With the other parent	75 (20.1%)	25.5%
With neither parent	5 (1.3%)	20.0%
Missing information	16 (4.3)	19.6%
Children with service at date of referral (Previous support service)	42 (11.2%)	38.2%
Classification of referral		
Vague concern	132 (40.5%)	26.5%
Specific concern	129 (39.6%)	37.6%
Acute concern	26 (8.0%)	30.8%
Vague concern and acute concern	6 (1.8%)	0%
Specific concern and acute concern	33 (10.1%)	42.6%

Statutory child and family support service and out-of-home placements.

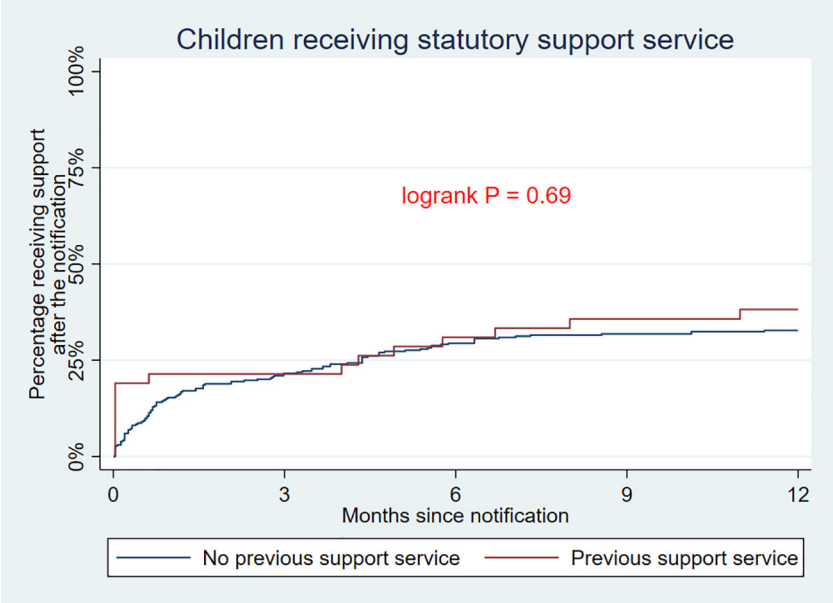

FIGURE 2 | Kaplan–Meier curves depicting the cumulative incidence of any statutory child and family support service or outplacement from referral date.

placed in out-of-home care while 21% of children had been subject to a statutory child assessment at the end of follow-up. Parental orders occurred in only one case, i.e. initiation of child protection services without parental consent. Log-rank test showed statistical difference between the two groups with higher incidence of support persons being appointed to children with prior services compared to those without, and higher incidence of statutory child assessments being initiated for children with no prior services (**Figure 3**).

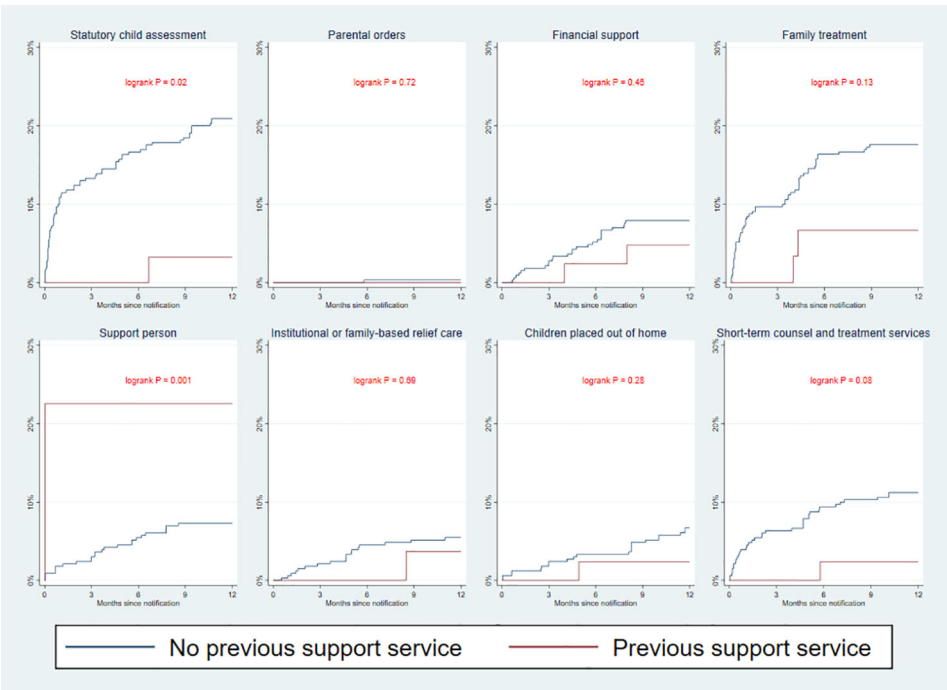

FIGURE 3 | Kaplan–Meier curves depicting the cumulative incidence of specific statutory child and family support service or outplacement from referral date.

In recognition that statutory child assessment is a part of the process of service initiation, we performed an explorative analysis of the beginning of child assessment in the support services. For the children with no previous statutory CFS service we found services were provided to 36% of children during follow-up within an average of 79.1 days.

Table 2 shows the results of the Cox-regression analysis of different predictors of service provision: Compared to children living with both parents, children living alone with a parent in treatment had a significantly higher probability of a service being initialized with a hazard ratio (HR) of 2.09 (1.41–3.08) p value = 0.0002. Classification of both specific concern and acute concern in the same referral was associated with a higher HR of service provision at 1.89 (1.01–3.51), with a p value = 0.05 when a vague concern was the reference. When the mother was the patient, the HR was higher (1.72 (1.11–2.65), p = 0.01) than for fathers. Other factors such as the municipality's status, parent's psychiatric diagnosis and child's gender and age group were not found to be predictive of the initiation of service.

DISCUSSION

The study of 376 children mostly involved parents who were repeatedly admitted in-patients, undergoing treatment for psychiatric disorders. The findings were that only one-third of children were provided with a statutory child and family support service following referrals from psychiatric services due to protection concerns for children. For 60% of these children, the referrals specified the existence either of adverse home environments, including child abuse and neglect, and/or critical situations arising due to a parent's psychiatric disorder. For the children who have received a support service, the mean number of days from referral to intervention was 74. Meanwhile, the children of maternal patients and children who lived alone with the patient had the greatest likelihood of receiving a support service. The children whose referrals included specific examples of poor conditions and acute situations related to their parent's psychiatric disorder had a better chance of receiving child protection services.

Possible Mechanisms and Explanations for the Findings

Social Services Considered the Referrals to be Unfounded

One possible explanation to the low service coverage after referrals may be that Child Protection Services (CPS) determined the children's environment not be detrimental and their well-being as unproblematic, thus finding the reasons for concern raised by psychiatric services invalid. However, we find this explanation to be unlikely for most children for several reasons; one being that staff in psychiatric services send referrals only for a selected group of children for whom they are especially concerned, hence a such referral is an indicator of severity in terms of adverse environmental

TABLE 2 | Hazard ratio of being provided with a statutory child and family support service by the first year as a function of child- and parent-related characteristics.

Characteristics	Hazard ratio (95%CI)	P-value
Female child	1.14 (0.80–1.63)	0.46
Mother is a patient	1.72 (1.11–2.65)	0.01
Father is a patient	1 (ref.)	
Age group 0–5 years	1.11 (0.72–1.72)	0.34
Age group 5–12 years	0.82 (0.51–1.30)	
Age group 13–17 years	1 (ref.)	
Municipality A	1 (ref.)	0.06
Municipality B	0.67 (0.45–1.00)	
Municipality C	0.45 (0.20–1.02)	
Parents' diagnosis		
Schizophrenia	1.57 (0.92–2.70)	0.56
Other psychosis	1.08 (0.56–2.08)	
Bipolar disorder	1.33 (0.70–2.52)	
Unipolar depression	1 (ref.)	
Other psychiatric disorder	1.26 (0.79–2.02)	
Substance abuse	0.98 (0.62–1.56)	0.94
Suicide attempt	1.73 (0.64–4.69)	0.28
Child's living situation		
With both parents	1 (ref.)	0.003
With the patient	1.95 (1.30–2.92)	
With the other parent	0.96 (0.55–1.67)	
With neither parent	0.79 (0.11–5.79)	
Children with service at date of referral	1.23 (0.73–2.08)	0.44
Classification of referral		
Vague concern	1 (ref.)	0.05
Specific concern	1.44 (0.93–2.23)	
Acute concern	1.14 (0.53–2.46)	
Vague concern and acute concern	No cases of support service	
Specific concern and acute concern	1.89 (1.01–3.51)	

Statutory child and family support service and out-of-home placements.

conditions. As recommended by Arango and colleges all children of parents with mental illness (COPMI) should receive selected preventive interventions owing to their high-risk status, and especially those children experiencing multiple environmental risk-factors (13). As 60% of referrals specified that children experienced neglect, abuse or other types of damaging domestic conditions the low level of service coverage is unsatisfactory. Furthermore, a high proportion of COPMI show sub-clinical manifestations of mental illness or meet the diagnostic criteria thereof, indicating that primary- or secondary preventive interventions are warranted (14). As CPS had only conducted a thorough child assessment in 20% of cases, their understanding of children's environmental conditions are limited, and children with early clinical manifestations or an already-developed mental illness are easily overlooked.

Poor Information and Limited Resources

A higher degree of service provision was found associated with referrals for both specific and acute concerns compared to vaguely worded referrals. The existence of imprecise information has indeed been shown to makes it difficult to gauge the degree of urgency and may be associated with longer time delays from referral to accommodation (21). The limited resources available for processing and evaluating the referrals by CPS are a possible explanation of the subsequent low service coverage and long time lag to intervention from referral date. Inadequate resources impede every aspect of social, welfare and health care, while heavy caseloads prevent social workers providing services for these children (22). A likely consequence of both imprecise information in referrals and limited resources is that CPS reacts only to the most serious or acute cases. An average of 73 days was found from referral date until intervention starts. This is a considerable amount of waiting time, yet, it is presupposed in the statutory demands for thorough, holistic assessment of up to 4 months duration. However, our exploratory analyses, did not suggest the process of statutory child assessment to account for the time to service initiation, nor for the proportion of children being accommodated with a service.

Legal and Psychological Barriers

A legal barrier for intervention may be that the Consolidation Act of Social Services is based on voluntary participation of the families; hence, parents may reject interventions causing child protection services to close the case. In cases where consent from parents is missing, municipalities can use parental orders, although this approach had only been used in one case in this study. Stigma of mental illness may be a barrier for service provision when a parent has mental illness: Both for parents who experience a clear need for support, but fear disclosing their parenting difficulties out of concern for losing custody of their children (23) and for children who keep silent about home problems because they feel ashamed and fear being placed out-of-home (24).

Perspectives on Supportive and Preventive Interventions

We found higher incidence for service provision for children of maternal versus paternal patients, as well as for children living with the parent with a psychiatric disorder. This is in accordance with previous register-based studies showing a substantial proportion of COPMI living with a single mother (25) and higher incidence of intervention by Child Protective Services in terms of child-placements in presence of maternal versus paternal psychiatric disorders (5). One potentially fruitful strategy may be to build up services for COPMI within the mental health sector. Even though adult psychiatric services do not traditionally offer support to patients' children, the existing formal structure does not exclude such services. On the contrary, the responsibilities of the Convention on the Rights of the Child refer to all public authorities. By combining family intervention with the parents' psychiatric treatment, patients and clinicians with mental health expertise can focus on patients' recovery while taking care of children's well-being, with less risk of delay or missing out on possible intervention because of sole reliance on referring the family to social services. This model has been implemented on a national level in Sweden and show improvements in parent–child relationships and child wellbeing (26, 27). The same approach has been applied in Finland and shows reduction in children's emotional symptoms and anxiety (28, 29). Interventions of these kinds are of low-to-moderate cost and progressive in focusing on stronger functioning families and fostering resilience in children. Improving the possibilities—and obligations—of mental health services to offer support to COPMI would hence be in line with policy trends in other areas, such as school and family law sectors, where counselling and treatment services for at-risk children have been implemented over recent years (30, 31). Another strategy would be more radical change to the infrastructure of the referral process such as the newly developed Finnish "Let's Talk about Children Service Model (LT-SM)" (32). Here, referrals concerning at-risk children are sent to a "one contact service" connecting relevant stakeholders such as mental health—and social services, kindergartens and schools who join together on a case-based collaboration around the family. Results of the study show that this interagency collaboration is indeed feasible.

Strengths and Limitations

To the best of our knowledge, the present study is the first to investigate statutory child and family support services for children following referrals of concern from adult mental health services. However, the study has some limitations, one being that we did not have information about referrals from other agencies, such as the child's school, family doctor, neighbours or others, being sent during the study period. Thus, the causal relation between referrals from mental health services and the delivery of subsequent services is unclear. Although we obtained information on outplacements and relief stays of children, shorter, informal relief stays of children within the social network may have been arranged but not registered in municipal records. In addition, parents may have obtained practical support in the home from the adult service department. Another limitation is that some children may have moved to a different municipality after the date of referral and services have not been initialised for this reason. Such limitations may cause underestimation of the proportion of children accommodated via a service. Another further

limitation is then possible selection bias in the municipalities who have either accepted or refused participation in the study. For instance, one municipality refused participation out of concern for public criticism if the proportion of children receiving support was found to be very low. After the 2008–2012 study period, the number of referrals concerning at-risk children increased considerably, with a 20% national increase over 2015–2017 (33). Thus, the proportion of children being accommodated with a support services following a referral has likely decreased in recent years, as the resources of social services have not increased according to demands. Furthermore, it is uncertain to what degree these research findings can be generalized to other countries, with their different organisation of sectors and distribution of target groups. Referrals may be 'false-negative' regarding child abuse or neglect, due to a lack of awareness from mental health personnel. The proportion of false-negatives is therefore unknown.

Concluding Remark

Our findings strongly suggest an under-served population of children of patients with severe psychiatric disorders with severe flaws in the inter-agency organization of entrustment and intervention for a population of vulnerable children and their families. The creation of more effective intervention strategies and better allocation of resources is thus required, with the aim of strengthening resilience and preventing trajectories towards mental illness and adversity for the children concerned.

DATA AVAILABILITY STATEMENT

The datasets generated for this study will not be made publicly available due to ethical, legal, and privacy restrictions. Requests to access the datasets should be directed to the corresponding author.

ETHICS STATEMENT

The study was approved by the Danish Data Protection Agency, the Danish Health Data Protection Agency, with written informed consent waived from participants waived by the National Scientific Ethical Committee as stipulated in the Data Protection Act (The Ministry of Justice 2018). Ethical approval was not required as per local legislation and national guidelines.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version. CH and AR have been responsible for data management and quantitative analyses. AR, AT, and KJ have conducted the evaluation of contents of the written referrals.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

APPENDIX 1 CRITERIA FOR CLASSIFICATION OF THE REFERRALS OF CHILDREN OF PSYCHIATRIC PATIENTS

Classification	Contents of the referral
Vague concern:	Expression of concern for the child's wellbeing based on vague not specific grounds.
Specific concern:	Includes specific examples of neglect, abuse and other detrimental conditions, usually characterized as childhood trauma or prolonged psychological strain affecting children in view of their parents' psychiatric illness. Neglect was defined as long-term lack of parental attention and nurturing, while child abuse includes psychological and physical abuse. Parental suicide attempts and long-term, daily substance abuse are also rated here.
Acute concern	Mentions acute situations, like those involving the police or when a parental suicide attempt is discovered by the child. The referrals call for authorities to conduct an immediate examination of the child's life circumstances; an example of an acute concern might be a patient with severe psychotic symptoms walking in the middle of the highway with his 2-year-old child.

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Alterations in Task-Related Brain Activation in Children, Adolescents and Young Adults at Familial High-Risk for Schizophrenia or Bipolar Disorder - A Systematic Review

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Children, adolescents, and young adults with at least one first-degree relative [familial high-risk (FHR)] with either schizophrenia (SZ) or bipolar disorder (BD) have a one-in-two risk of developing a psychiatric disorder. Here, we review functional magnetic resonance imaging (fMRI) studies which examined task-related brain activity in young individuals with FHR-SZ and FHR-BD. A systematic search identified all published task-related fMRI studies in children, adolescents, and young adults below an age of 27 years with a first-degree relative with SZ or BD, but without manifest psychotic or affective spectrum disorder themselves. The search identified 19 cross-sectional fMRI studies covering four main cognitive domains: 1) working memory (n = 3), 2) cognitive control (n = 4), 3) reward processing (n = 3), and 4) emotion processing (n = 9). Thirteen studies included FHR-BD, five studies included FHR-SZ, and one study included a pooled FHR group. In general, task performance did not differ between the respective FHR groups and healthy controls, but 18 out of the 19 fMRI studies revealed regional alterations in task-related activation. Brain regions showing group differences in peak activation were regions associated with the respective task domain and showed little overlap between FHR-SZ and FHR-BD. The low number of studies, together with the low number of subjects, and the substantial heterogeneity of employed methodological approaches within the domain of working memory, cognitive control, and reward processing impedes finite conclusions. Emotion processing was the most investigated task domain in FHR-BD. Four studies reported

differences in activation of the amygdala, and two studies reported differences in activation of inferior frontal/middle gyrus. Together, these studies provide evidence for altered brain processing of emotions in children, adolescents, and young adults at FHR-BD. More studies of higher homogeneity, larger sample sizes and with a longitudinal study design are warranted to prove a shared or specific FHR-related endophenotypic brain activation in young first-degree relatives of individuals with SZ or BD, as well as to pinpoint specific alterations in brain activation during cognitive-, emotional-, and reward-related tasks.

Keywords: fMRI—functional magnetic resonance imaging, neurocognitive function, familial high-risk, schizophrenia, bipolar disorder, children, adolescents

INTRODUCTION

Schizophrenia (SZ) and bipolar disorder (BD) are severe and highly heritable (1) mental illnesses with a substantial impact on the individuals concerned, their families, and the society. By early adulthood, the offspring of parents with severe mental illnesses, including SZ, BD, and major depressive disorder, have a one-in-three risk of developing a psychotic or major mood disorder and a one-in-two risk of developing any mental disorder (2). Heritability shows partial phenotypical specificity with largest risk ratios for SZ among offspring of parents with SZ and largest risk ratios for BD among offspring of parents with BD. Additionally, offspring of parents with SZ have a significantly increased risk of BD and offspring of parents with BD have a significantly increased risk of SZ (2). According to data extracted from Danish registries, child and adolescent offspring of parents with severe mental illness express increased incidence rates for all diagnoses of child and adolescent mental disorders compared to reference offspring of parents without severe mental illness (3).

SZ is characterized as a neurodevelopmental disorder and manifests in adolescence or early adulthood (4, 5), whereas the developmental nature of BD is less understood (6). However, genome-wide association studies of SZ and BD have shown overlapping genetic risk loci (7, 8). Approximately, two-thirds of the genetic expression profile are shared across SZ and BD (9, 10). Thus, the genetic risk profile for SZ and BD may also be shared across the offspring of parents with these severe mental illnesses. Whether these disorders also share phenotypic expression profiles, e.g., brain responses, during early stages of pathogenesis is unclear.

First-degree relatives of individuals with SZ or BD, referred to as individuals with familial high-risk (FHR), show impairments on a variety of neurocognitive and motor functions on a group level, even at young age (11–17). Moreover, deficits in neurocognitive functioning in individuals with the manifest disorder and in adult FHR individuals have been linked to altered brain functioning and have been suggested as endophenotypic of the disorders (18–22). This, in turn, may reflect an increasing dysfunction during brain maturation in critical brain regions. Various childhood mental disorders including ADHD, autism, and childhood onset schizophrenia (COS) are associated with abnormal developmental trajectories for cortical thickness (23). Interestingly, healthy siblings of patients with COS show significant reductions in regional gray and white matter volume, suggesting a trait marker (24, 25). In keeping with this, characteristics of cortical morphology in child and adolescent offspring of SZ patients show cross-sectional decrease in global and parieto-occipital surface area compared to a control group, and a decrease in occipital surface area compared to offspring of BD patients (26). In that study, global and parietal surface area scaled with the expression of positive and negative prodromal symptoms in offsprings of SZ patients (26).

Throughout post-natal development, the brain undergoes continuous maturation (27–29). This is also the case for the frontal cortex, (30), but the maturational trajectories of frontal cortical areas differ from the trajectories of other inter-connected brain regions, such as the basal ganglia (31, 32). This discrepancy may render the brain vulnerable and favor the emergence of mental disorders during adolescence and early adulthood (32, 33).

Studies on the brain development in young individuals at high risk of severe mental disorders may not only reveal underlying neurobiological mechanisms but also identify markers associated with risk and resilience. Multiple studies of FHR individuals have investigated cognitive, motor or social capabilities in vulnerable populations (2, 11, 13, 17) also in combination with neuroimaging methods (34, 35), which has resulted in several systematic reviews and meta-analyses (18, 19, 36, 37). No systematic review or meta-analysis to date, however, has exclusively focused on neuroimaging studies in children, adolescents, and young adults at FHR of severe mental disorders. This is surprising, because the inclusion of adult individuals with FHR substantially impacts the interpretation of the results, as these individuals may already have passed the peak onset period and alterations may, thus, rather represent factors of resilience or compensation than vulnerability and risk.

Here, we systematically reviewed the existing literature investigating children, adolescents, and young adults at FHR for SZ (FHR-SZ) or FHR for BD (FHR-BD) with task-related functional magnetic resonance imaging (fMRI). We only considered studies of FHR individuals who had not yet manifested signs of serious mental illness. Half of all lifetime mental disorders start by the mid-teenage years and three quarters by the mid-20s (38). Therefore, we narrowed our search to studies

including individuals with a group mean age under or equal to 21 years and did not include studies with participants above the age of 27 years. We aimed to answer the following questions; Firstly, do brain activation patterns associated with task-related activity in children, adolescents, and young adults at FHR-SZ or FHR-BD, differ from the patterns observed in healthy controls (HC)? Secondly, do the two FHR groups show shared or specific differences in brain activation patterns? Lastly, we relate the findings to earlier reports in patients with the manifest disorders, as well as adult FHR populations and clinical high-risk populations. Our approach aims at identifying early neurobiological alterations associated with FHR for severe mental disorders with fMRI, knowledge that may assist the optimization of diagnostic tools and improve the design of early interventions and preventive measures. Neurobiological approaches of child, adolescent and young adult offspring of patients with severe mental illnesses offer the opportunity to assess the early neural imprint of a genetic vulnerability to disease and make way for the study of preclinical features and the interaction between illness-related progressions and normal brain maturation.

METHODS

We combined the search terms "MRI", "fMRI", "children", "adolescents", "bipolar disorder", "schizophrenia", "risk", "first-degree relative", and "genetic predisposition" in PubMed, EMBASE, and PsychINFO followed by a screening of inclusion criteria to identify fMRI studies including children and adolescents at FHR-SZ or FHR-BD (**Table 1**). The time-period covered in our search included all publications published in this area until September 10th, 2019. The protocol for this systematic review was registered on Prospective Register for Systematic Reviews (PROSPERO; registration ID: CRD42018086995) and is available on their International website (https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42018086995). Identification, screening, eligibility, and inclusion procedures followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (Prisma) 2009 flow diagram (39) (**Figure 1**). We screened and included articles based on the following inclusion criteria: 1) peer-reviewed articles in English; 2) study population of children, adolescents and/or young adults at FHR (familial high-risk defined as having a first-degree relative diagnosed with SZ or BD) of developing SZ or BD; 3) absence of a diagnosis in the spectrum of psychotic or affective disorders as well as no reported symptoms in these areas; 4) mean age of study population below or equal to 21 years, with no individuals above 27 years of age; 5) direct comparison with a HC group; and 6) employment of task-related fMRI. Screening, eligibility and study selection procedures were completed according to the inclusion criteria by authors AV and LJ, independently. These procedures were completed by following EndNote specific review procedures (40). Any disagreement was followed up by KP. Data extraction was done by LJ under supervision from KL and HS. Summary measures include differences in mean values for behavioral variables as well as peak activation differences between the respective FHR group and HC.

RESULTS

A total of 1,137 articles were screened by title and abstract according to the inclusion criteria listed in the *Methods* section, resulting in exclusion of 562 articles. During the eligibility procedure, we assessed 575 articles by full-text reading of which 556 full-text articles were excluded (**Figure 1**). As a result of the exclusion process, 19 task-related fMRI articles were included of which five studies included individuals at FHR-SZ, 13 studies included individuals at FHR-BD, and one study pooled FHR-SZ and FHR-BD into one FHR sample (**Table 2**). All studies employed blood oxygen level–dependent (BOLD) fMRI and identified task-related changes in regional activity at the voxel level by specifying a general linear model (GLM). Three studies performed additional psycho-physiologic interaction (PPI) analysis (41, 42, 49) and a single study applied dynamic causal modeling (53). This review only concerns task-related brain activation as revealed by a GLM based approach. We divided the included articles into four main task domains: 1) Working memory (WM), 2) Cognitive control, 3) Reward processing, and 4) Emotion processing. Note that two articles have been included in two different task domains, i.e., Ladouceur, Diwadkar (55) in WM and emotion processing, and Hart, Bizzell (54) in cognitive control and emotion processing, as the applied tasks contrasts expand both domains. Division of studies into these four main task domains was based on the empirical evidence, when regarding the study specific contrasts applied in the respective GLM designs. We employed this pragmatic and bottom-up approach when reviewing the finally included papers. For details about the study specific contrast of interest see **Supplementary Tables S1–S4**. Due to the limited total number of articles identified at this point, we included all articles concerning task-related fMRI findings in children, adolescents, and young adults at FHR-SZ or FHR-BD independent of behavioral differences between groups. We have, however, explicitly reported the behavioral differences present in the respective studies.

In addition to the low number of existing articles within this specific field of research, we observed a high heterogeneity in terms of behavioral tasks, analytic methods, and reporting practices within the four main task domains. This heterogeneity precluded the use of quantitative meta-analytic methods, such as activation likelihood estimation (ALE) (60).

Task-Related fMRI Findings

Working Memory

Four studies were identified in young individuals at FHR-SZ or FHR-BD within the WM domain. An overview of the brain peak activity differences between individuals at FHR-SZ or FHR-BD relative to HC within the WM domain are shown in **Figure 2**. Two studies investigated individuals at FHR-SZ. In the first study, the authors found hypo-activation in the left parietal

TABLE 1 | Detailed overview of the three database-specific search strings applied in PubMed, EMBASE, and PsychINFO, respectively.

PubMed	**Methods**	**Age group**	**Clinical**	**Descriptive**
TX	MRI, fMRI, Neuroimaging	Children, Child, Adolescent*, Youth*	Bipolar, Schizophrenia*	Risk, "impaired parent", "impaired parents", "disabled parent", "disabled parents"
MeSH term	Neuroimaging, Magnetic Resonance Imaging	Child, Adolescent	Bipolar and related disorders, Schizophrenia Spectrum and Other Psychotic Disorders	Genetic predisposition to disease, Child of impaired parents, Risk
EMBASE	**Methods**	**Age group**	**Clinical**	**Descriptive**
Keyword	MRI, fMRI, Neuroimaging, "Nuclear Magnetic Resonance Imaging"	Children, Child, Adolescent*, Youth*	Bipolar, Schizophrenia*	Risk, first degree relative, genetic predisposition to disease
Subject heading	Neuroimaging, Nuclear Magnetic Resonance Imaging	Juvenile	Bipolar disorders, Schizophrenia spectrum disorder	Risk, first degree relative, genetic predisposition
PsycINFO	**Methods**	**Age group**	**Clinical**	**Descriptive**
TX	MRI, fMRI, Neuroimaging, Magnetic Resonance Imaging"	Child, children, adolescent*, teenage*, young adults, youth	Bipolar, Schizophrenia*, schizophrenia,	Risk, genetic predisposition, "impaired parent", "impaired parents", "disabled parent", "disabled parents", first degree relative
MeSH term	Neuroimaging, Magnetic Resonance Imaging	Children, adolescent*, teenagers, young adults, youth	Bipolar disorder, bipolar, Schizophrenia, Schizophrenia disorders	Risk, genetic predisposition to disease, child of impaired parents, first degree relative

*Methods, age group, clinical, and descriptive word categories was assembled by the AND function, while TX (free text)/Keyword and MeSH (Medical Subject Headings) term/Subject heading was assembled by the OR function. The asterisk (*) serves as the truncation (or wildcard) operator. Words match if they begin with the word preceding the * operator.*

cortex in 19 FHR-SZ offspring (mean age: 14.3) relative to 25 HC (mean age: 14.6) during high versus low WM demand (**Table 2** and **Figure 2**). Furthermore, FHR-SZ relative to HC displayed lower response latencies but did not differ from HC with respect to hit rate and the effect of WM load on performance (41). In a second study, during correct versus incorrect memory performance in a WM task, it was found that 19 FHR-SZ offspring (mean age: 14.3) showed hyper-activation in the right dorsal prefrontal cortex (PFC) and left head of caudate relative to 25 HC (mean age: 14.6) (42) (**Table 2** and **Figure 2**). Of the two studies in FHR-BD, one study reported hypo-activation during high versus low WM load in 10 individuals (mean age: 18.4) in the left cerebellum, bilateral insula, as well as in the right brainstem and right para-hippocampal gyrus/amygdala relative to 10 HC (mean age: 17.1). The same task contrast in this study also elicited hyper-activation in FHR-BD relative to HC in the left frontopolar cortex (43) (**Table 2** and **Figure 2**). Another study also reported hypo-activation during high versus low WM load, though in a different area, namely the left ventro-lateral prefrontal cortex (VLPFC) in 16 FHR-BD offspring (mean age: 14.2) compared with 15 HC (mean age: 13.8) (55). None of the studies in FHR-BD summarized above found behavioral differences relative to HC.

In summary, no behavioral differences were found between FHR-BD and HC, whereas one study in FHR-SZ reported differences between FHR-SZ and HC on response latency with FHR-SZ being faster (41). Brain activity during WM performance differed between both FHR groups and HC groups in brain regions normally associated with WM processing. Although three out of four studies applied a similar high WM load versus low WM load contrast (41, 43, 55), no common altered brain activity patterns between FHR and HC were apparent between these studies. Likewise, no commonalities between FHR-SZ and FHR-BD were seen. However, without taking directionality or magnitude of the observed brain activity differences into account, the three studies, two in FHR-BD individuals and one in FHR-SZ individuals, reported altered frontal activity compared to HC. More specifically, differences were present in the left VLPFC (55), the left frontopolar cortex (43) and the right dorsal PFC (42).

Cognitive Control

The five included studies of FHR within the cognitive control domain have focused on attention, response inhibition, and cognitive flexibility (**Table 2**). Differences in peak brain activation in FHR-SZ and FHR-BD relative to HC within the cognitive control domain are depicted in **Figure 3**. One study pooled FHR-SZ and FHR-BD offspring into one high-genetic-risk group (n = 22, mean age: 14.1). During both high and low attention load versus passive viewing, respectively, the FHR group showed hypo-activation in the dorsal PFC and hyper-activation in the parietal cortex relative to 24 HC (mean age: 15.4). Moreover, the FHR group showed a lack of additional activation during higher attentional demand as opposed to HC (44). A second study investigated selective attention in 21 individuals at FHR-SZ (mean age: 14.4) relative to 21 HC (mean age: 14.1) with FHR-SZ individuals showing lower accuracy on identification of non-targets. In terms of brain activation, FHR-SZ relative to HC displayed hypo-activation during target identification versus task-irrelevant stimuli in the right middle frontal gyrus, left frontal operculum cortex, right supplementary motor area, left insula, right precentral gyrus, right postcentral gyrus, right superior temporal gyrus, right precuneus, and left occipital cortex. Hyper-activation during the same contrast was found in the left inferior frontal cortex, bilateral caudate, left inferior temporal gyrus, and bilateral frontal

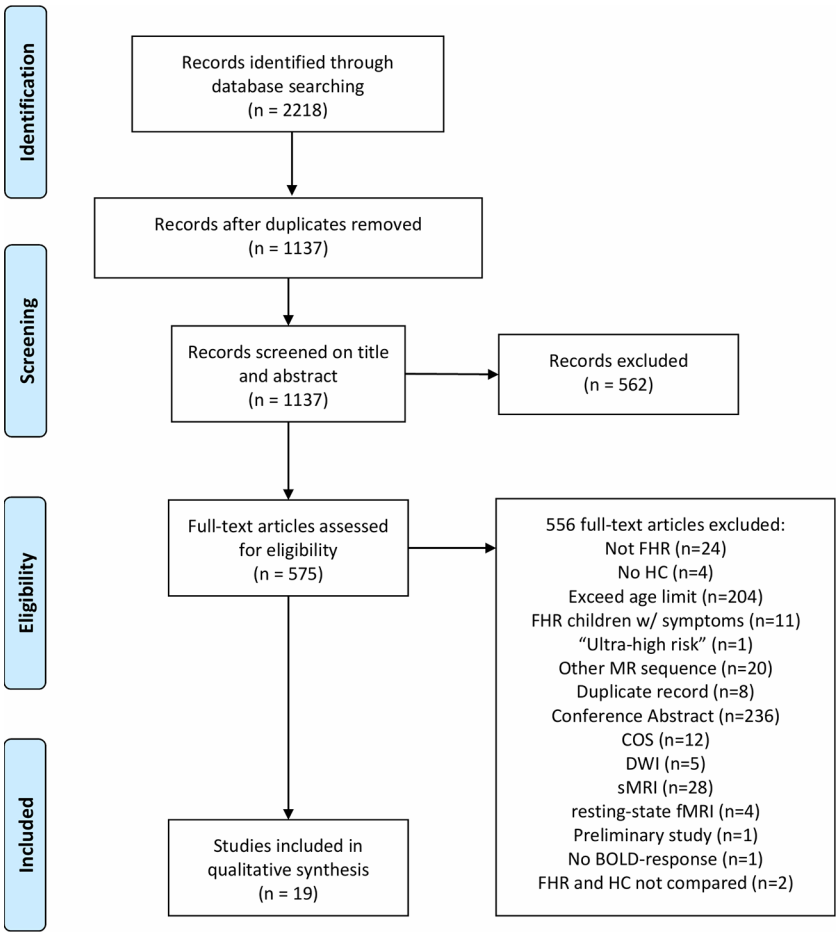

FIGURE 1 | The Preferred Reporting Items for Systematic Reviews and Meta-analyses (Prisma) flow-chart illustrating the systematic review procedure. FHR, familial high-risk; HC, healthy control; MR, magnetic resonance; COS, childhood-onset schizophrenia; DWI, Diffusion-weighted imaging; sMRI, Structural magnetic resonance imaging (MRI); fMRI, functional MRI; BOLD, Blood-oxygen-level-dependent.

pole in FHR-SZ relative to HC (54). In a third study, using a similar selective attention task, 29 individuals at FHR-BD (mean age: 14.9) showed larger reaction time variability and displayed hyper-activation in a group-by-reaction time interaction analysis in the left medial frontal gyrus and in the left superior frontal gyrus in comparison with 53 HC (mean age: 18.7) (47). Investigating response inhibition, one study of 13 individuals at FHR-BD (mean age: 13.5) relative to 21 HC (mean age: 13.8), showed hyper-activation during successful motor inhibition (stop incorrect versus stop correct) and unsuccessful inhibition (stop incorrect versus go) in the left and bilateral putamen, respectively (45). Lastly, in a study investigating cognitive flexibility, 13 individuals at FHR-BD (mean age: 13.9) relative to 21 HC (mean age: 13.7) showed hyper-activity in the right inferior parietal gyrus, the right inferior frontal gyrus (IFG) and in the left cerebellum in change versus go trials (i.e., successful cognitive flexibility). Unsuccessful change versus go trials, i.e., unsuccessful cognitive flexibility, evoked hyper-activation in the right caudate and left cerebellum in FHR-BD relative to HC. Successful cognitive flexibility relative to unsuccessful showed hyper-activation in FHR-BD relative to HC in the right IFG (46).

In summary, two studies found behavioral differences on selective attention, one between FHR-SZ and HC (54), the other between FHR-BD and HC (47). In both studies, the FHR group performed worse than HC. Interestingly, all studies on FHR-BD groups found hyper-activity relative to HC, independent of paradigm design and task contrast (44–47) (**Figure 3**). Finally, when comparing young individuals at FHR-SZ or FHR-BD with HC during diverse cognitive control tasks, observed differences in brain activity generally involved areas within frontal, temporal, parietal, midbrain areas, as well as cerebellar sub-areas. Of note, only one study with FHR-SZ individuals contributed to these finding (54), while in another study FHR-SZ individuals were pooled with FHR-BD individuals into one high-risk group (44).

TABLE 2 | Overview of study characteristic of included articles in the qualitative synthesis.

Study	High-risk disorder	Task	Performance	Age range	Healthy control			Familial high-risk				
					n (m/f)	Mean age (SD)	IQ	n (m/f)	Mean age (SD)	IQ	Existing diagnoses	Relation
Working memory												
1. Bakshi et al. (41)	SZ	N-back task	Response latency; FHR-SZ > HC	8–20	25 (17/8)	14.6 (2.80)	93.8	19 (12/7)	14.3 (3.10)	93.1	SAD, ADHD, SP	Offspring
2. Diwadkar et al. (42)	SZ	Emotional face valence n-back task	No difference	HC: 10–19 FHR: 8–19	25 (17/8)	14.6 (NR)	94.0	19 (12/7)	14.3 (NR)	93.0	SAD, ADHD	Offspring
3. Thermenos et al. (43)	BD	N-back task	No difference	13–24	10 (5/5)	17.1 (1.40)	100.9	10 (5/5)	18.4 (4.20)	106.8	NR	Mix
Total					60			48				
Cognitive control												
4. Diwadkar et al. (44)	SZ & BD	Continuous performance task	No difference	8–20	24 (NR)	15.4 (2.70)	93.1	22 (NR)	14.1 (3.1)	94.2	NR	Offspring
5. Deveney et al. (45)	BD	Stop signal task	No difference	NR	21 (13/8)	13.8 (2.00)	113.7	13 (6/7)	13.5 (1.80)	109.0	None	Mix
6. Kim et al. (46)	BD	The change task	No difference	8–17	21 (13/8)	13.7 (1.96)	113.7	13 (6/7)	13.9 (2.02)	107.9	None	Mix
7. Pagliaccio et al. (47)	BD	Global-local selective attention task	CV RT; FHR-BD > HC	8–25	53 (21/32)	18.7 (4.09)	115.1	29 (15/14)	14.9 (3.47)	110.7	ADHD, MDD	Mix
Total					119			77				
Reward processing												
8. Manelis et al. (48)	BD	Number guessing reward task	No difference	7–17	23 (12/11)	13.7 (1.80)	105.8	29 (15/14)	13.8 (2.45)	103.2	MDD, ADHD, AD, ODD, phobia, TD, ED	Offspring
9. Singh et al. (49)	BD	Monetary incentive delay task	No difference	8–15	25 (10/15)	11.8 (2.37)	115.1	20 (7/13)	12.7 (2.85)	111.3	None	Offspring
10. Soehner et al. (50)	BD	Card-number guessing game	NR	9–17	21 (10/11)	14.0 (2.24)	106.1	25 (14/11)	14.2 (2.25)	100.4	DD, AD, ADHD, disruptive behavior, ED	Offspring
Total					69			64				
Emotion processing												
11. Brotman et al. (51)	BD	Facial emotion processing paradigm	No difference	8–19	29 (16/13)	14.9 (1.90)	110.0	15 (9/6)	14.5 (2.20)	108.2	ADHD, AD	Mix
12. Barbour et al. (52)	SZ	Continuous affective task	No difference	HC: 10–19 FHR: 8–19	25 (17/8)	14.9 (2.80)	93.3	19 (12/7)	14.3 (3.19)	93.8	SAD, ADHD, SP	Offspring
13. Diwadkar et al. (53)	SZ	Continuous visual memory task of faces with affective valence	No difference	8–20	24 (16/8)	14.6 (2.60)	92	19 (12/7)	14.3 (3.10)	96.2	SAD, ADHD, SP	Offspring
14. Hart et al. (54)	SZ	Emotional odd ball task	No difference	9–18	21 (11/10)	14.1 (2.57)	NR	21 (10/11)	14.4 (2.56)	NR	ADHD, learning disorder, AD	Mix
15. Ladouceur et al. (55)	BD	N-back task with emotional distractors	No difference	8–17	15 (4/11)	13.8 (2.70)	NR	16 (9/7)	14.2 (2.30)	NR	None	Offspring
16. Manelis et al. (56)	BD	Facial emotion processing paradigm	No difference	7–17	23 (12/11)	13.7 (1.80)	105.8	29 (15/14)	13.8 (2.45)	103.2	MDD, ADHD, AD, ODD, phobias, TD, OCD, ED	Offspring
17. Olsavsky et al. (57)	BD	Face-emotion labelling task	No difference	8–18	56 (26/30)	14.0 (2.60)	112.0	13 (7/6)	14.0 (2.40)	113.0	AD, ADHD	Mix
18. Tseng et al. (58)	BD	Face-emotion memory task	No difference	9–19	37 (16/21)	14.7 (2.29)	108.9	13 (8/5)	13.7 (2.28)	112.9	AD, ADHD	Mix
19. Welge et al. (59)	BD	Emotional visual oddball task	No difference	10–20	32 (11/21)	14.6 (3.00)	101.0	32 (9/23)	15.3 (3.00)	104.1	ADHD	Offspring
Total					262			177				

Note that Hart et al. (54) is also included in Cognitive Control and Ladouceur et al. (55) in Working Memory in the main text. FHR, Familial high-risk; HC, Healthy control; CV, Coefficient of variation; RT, Reaction time; SZ, Schizophrenia; BD, Bipolar disorder; Mix, Group was offspring and siblings combined; SD, Standard deviation; NR, Not reported; TD, Tourette's disease; ODD, Oppositional defiant disorder; ADHD, Attention-deficit/hyper-activity disorder; SAD, Separation anxiety disorder; SP, Social phobia; AD, Anxiety disorder; MDD, Major depressive disorder; ED, Eating disorder; OCD, Obsessive compulsive disorder.

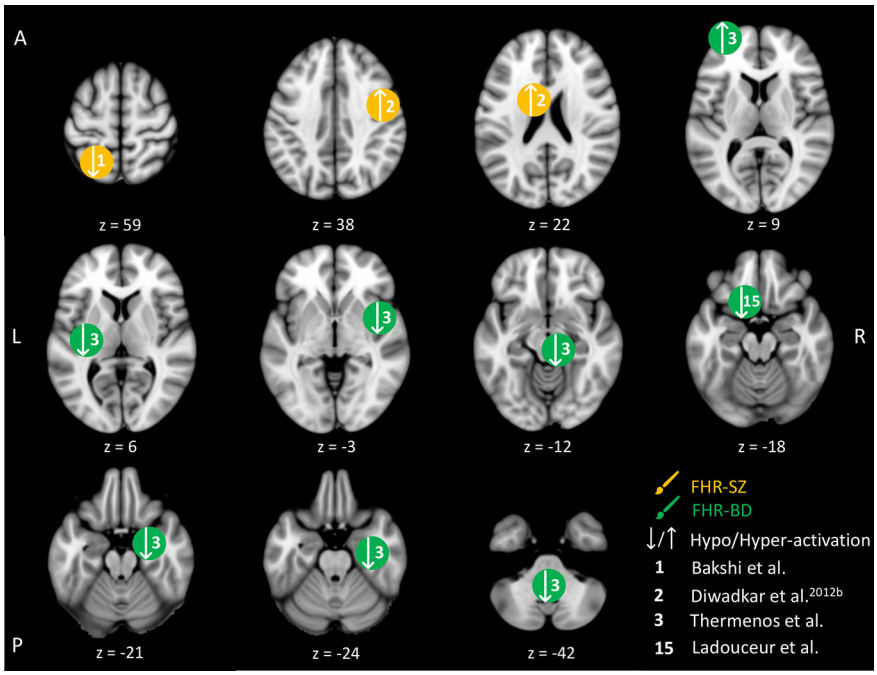

FIGURE 2 | Working memory-related brain activity differences between children and adolescents at familial high-risk (FHR) for schizophrenia (SZ) and healthy control (HC, yellow circles), and for bipolar disorder (BD) and healthy control (green circles). Circles mark the peak coordinate activation difference but do not reflect the extend of activation. The coordinates of peak activation reported in Talairach space were translated to Montreal Neurologic Institute (MNI) coordinates using the MNI<->Talairach with Brodmann Areas (1.09) website (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Using FSLview (version 4.0.1 ©2004-2009 Oxford University), the reported peak coordinates in each article were entered to localize brain area on a standard MNI152 brain. For visualization of areas of peak activation differences between FHR-SZ, FHR-BD, and HC, we created figures using FSLview and Mango (Version: 4.1, Jack L. Lancaster, Ph.D., Michael J. Martinez © 2019 Research Imaging Institute, UTHS CSA). Exact coordinates and details on contrasts and statistics can be found in **Supplementary Table 1**.

Reward Processing

Three studies investigated reward processing in children, adolescents, and young adults at FHR-BD and HC (**Table 2**). Independent of winning or losing versus control trials, 29 FHR-BD offspring (mean age: 13.8) showed hyper-activation in the right frontal pole relative to 23 HC (mean age: 13.7) (48) (**Figure 4**). In another study, hyper-activation was reported in the right posterior insula in 25 FHR-BD offspring (mean age: 14.2) relative to 21 HC (mean age: 14.0) when contrasting the winning versus the control condition (50) (**Figure 4**). On the other hand, anticipation of loss versus non-loss resulted in hypo-activation in 20 FHR-BD offspring (mean age: 12.7) in the right pregenual cingulate cortex relative to 25 HC (mean age: 11.8). Furthermore, FHR-BD offspring also showed hyper-activation during reward feedback versus non-reward feedback in the left lateral orbitofrontal cortex relative to HC (49) (**Figure 4**).

In summary, differences in brain activity during reward processing in young individuals at FHR-BD relative to HC were mainly found in frontal cortical areas (**Figure 4**). Depending on the contrast of interest, i.e., anticipation or feedback, and winning or losing trials, these activation differences consisted of both hypo- and hyper-activity relative to HC. Although two studies applied similar number guessing reward tasks in FHR-BD [i.e., Manelis, Ladouceur (48) and Soehner, Bertocci (50)], activity differences were present in distinct areas and of opposite direction leaving little overlap in findings. Of note, we did not identify any studies investigating reward processing in young individuals at FHR-SZ.

Emotion Processing

We identified nine studies in young individuals at FHR-SZ or FHR-BD, dealing with brain responses related to the processing of faces showing emotional expressions or pictures with affective valence. This makes the emotion processing domain the most investigated domain in the present reviewed literature (**Table 2**). An overview of the emotion-related peak brain activity differences between young individuals at FHR-SZ and HC, and young individuals at FHR-BD and HC are depicted in **Figure 5**. None of the included studies reported behavioral differences between any FHR group and HC. One study did not find activation-related differences between 19 FHR-SZ offspring (mean age: 14.3) compared with 24 HC (mean age: 14.6) when viewing faces with emotional expressions versus distorted images (53). On the contrary, other studies employing similar emotion processing paradigms found that young FHR-BD individuals relative to HC show amygdala hyper-activation during viewing of emotional faces versus shapes (56), when viewing faces and rating them as fearful versus passive viewing (57), as well as

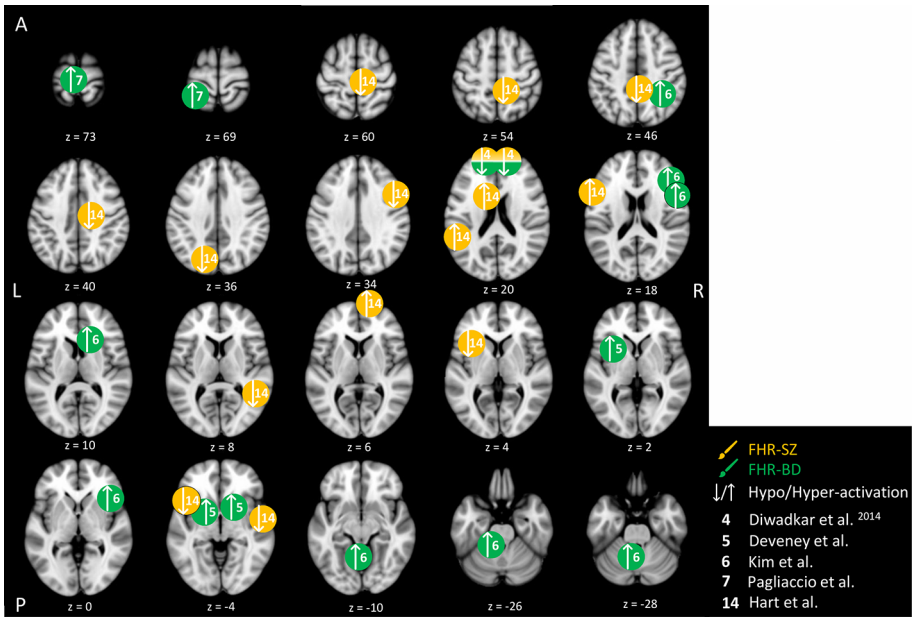

FIGURE 3 | Cognitive control-related brain activity differences between children and adolescents at familial high-risk (FHR) for schizophrenia (SZ) and healthy control (yellow circles), and for bipolar disorder (BD) and healthy control (HC, green circles). Circles mark the peak coordinate activation difference but do not reflect the extend of activation. The coordinates of peak activation reported in Talairach space were translated to Montreal Neurologic Institute (MNI) coordinates using the MNI<->Talairach with Brodmann Areas (1.09) website (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Using FSLview (version 4.0.1 ©2004-2009 Oxford University), the reported peak coordinates in each article were entered to localize brain area on a standard MNI152 brain. For visualization of areas of peak activation differences between FHR-SZ, FHR-BD, and HC, we created figures using FSLview and Mango (Version: 4.1, Jack L. Lancaster, Ph.D., Michael J. Martinez © 2019 Research Imaging Institute, UTHS CSA). Exact coordinates and details on contrasts and statistics can be found in **Supplementary Table 2**.

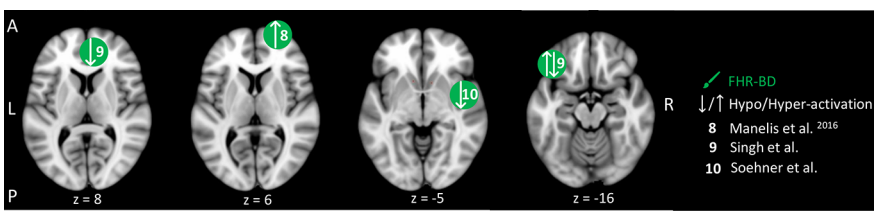

FIGURE 4 | Reward-related brain activity differences between children and adolescents at familial high-risk (FHR) for schizophrenia (SZ) and healthy control (yellow circles), and for bipolar disorder (BD) and healthy control (HC, green circles). Circles mark the peak coordinate activation difference but do not reflect the extend of activation. The coordinates of peak activation reported in Talairach space were translated to Montreal Neurologic Institute (MNI) coordinates using the MNI<->Talairach with Brodmann Areas (1.09) website (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Using FSLview (version 4.0.1 ©2004-2009 Oxford University), the reported peak coordinates in each article were entered to localize brain area on a standard MNI152 brain. For visualization of areas of peak activation differences between FHR-SZ and HC, and between FHR-BD and HC, we created figures using FSLview and Mango (Version: 4.1, Jack L. Lancaster, Ph.D., Michael J. Martinez © 2019 Research Imaging Institute, UTHS CSA). Exact coordinates and details on contrasts and statistics can be found in **Supplementary Table 3**.

during successful versus unsuccessful encoding of emotional faces (58). Further, distraction versus no distraction by happy faces during WM performance elicited hyper-activation in the right VLPFC in 16 FHR-BD (mean age: 14.2) relative to 15 HC (mean age: 13.8) (55). Moreover, 15 FHR-BD (mean age: 14.2) relative to 29 HC (mean age: 14.9) displayed hypo-activation in bilateral amygdala and in the left IFG with increasing anger intensity in face expressions, as well as in the left IFG during increasing happiness intensity in face expressions (51). In line with this, 19 FHR-SZ offspring (mean age: 14.3) relative to 25 HC (mean age: 14.9) showed hypo-activation in the left amygdala (centro-medial nuclei) in response to happy face expressions (52). Another study, reported hypo-activation in the left anterior cingulate cortex (ACC) and the left precuneus but hyper-activation in the central opercular cortex in 21 FHR-SZ (mean age: 14.4) relative to 21 HC (mean age: 14.1) in response to unpleasant images (53). Finally, 32 FHR-BD offspring (mean age: 15.3) relative to 32 HC (mean age: 14.6) showed hyper-activation in the left IFG during the viewing of unpleasant and pleasant images versus neutral images (59).

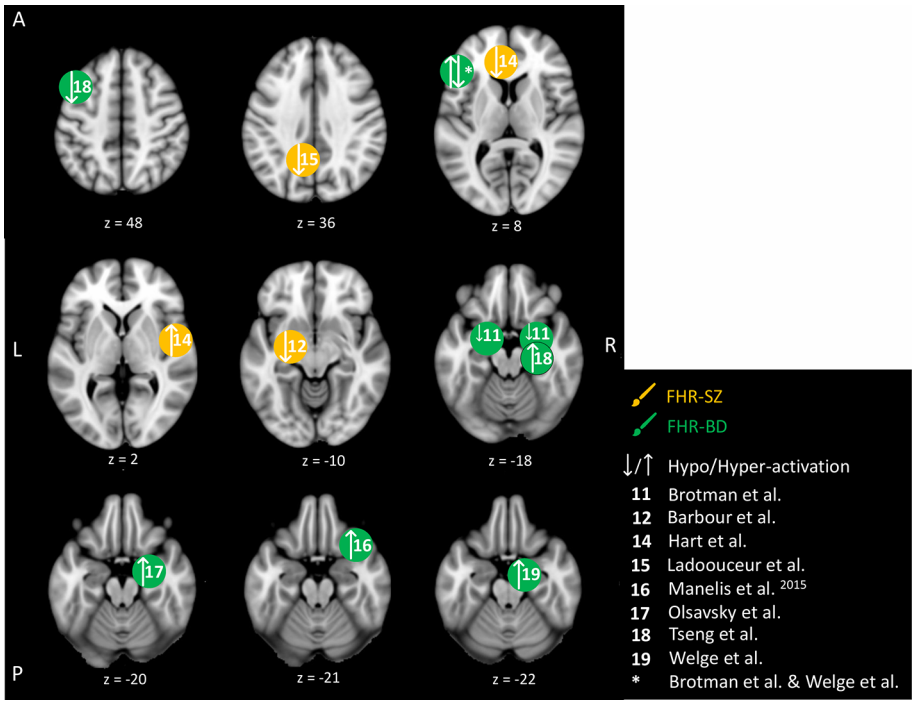

FIGURE 5 | Emotion-related brain activity differences between children and adolescents at familial high-risk (FHR) for schizophrenia (SZ) and healthy control (yellow circles), and between bipolar disorder (BD) and healthy control (HC, green circles). Circles mark the peak coordinate activation difference but do not reflect the extend of activation. The coordinates of peak activation reported in Talairach space were translated to Montreal Neurologic Institute (MNI) coordinates using the MNI<->Talairach with Brodmann Areas (1.09) website (http://sprout022.sprout.yale.edu/mni2tal/mni2tal.html). Using FSLview (version 4.0.1 ©2004-2009 Oxford University), the reported peak coordinates in each article were entered to localize brain area on a standard MNI152 brain. For visualization of areas of peak activation differences between FHR-SZ, FHR-BD, and HC, we created figures using FSLview and Mango (Version: 4.1, Jack L. Lancaster, Ph.D., Michael J. Martinez © 2019 Research Imaging Institute, UTHS CSA). Exact coordinates and details on contrasts and statistics can be found in **Supplementary Table 4**.

In summary, young individuals at FHR-BD and FHR-SZ did not show behavioral differences compared with HC in the studies investigating emotional processing included in the present review. Across emotion processing paradigms, four studies reported altered activation (i.e., hypo- or hyper-activation) of amygdala in FHR-BD individuals compared with HC (51, 56–58), although each study applied individual task contrasts. FHR-BD individuals also showed altered activation in inferior/middle FG across two different studies and task contrasts (51, 59). Findings in FHR-SZ were less clear; one study showed amygdala hyper-activation (52), while another study showed ACC hypo-activation and central opercular cortex hyper-activation (54), which may relate to differences in task setup as well as applied analytical methods.

DISCUSSION

We have reviewed the existing literature to clarify whether children, adolescents, and young adults at familial high risk for either schizophrenia (FHR-SZ) or bipolar disorder (FHR-BD) show altered brain activation during task performance when compared to HC, and to determine shared or distinct patterns of brain activation in FHR-SZ versus FHR-BD. In this review, we have focused on task-based functional brain alterations with a specific emphasis on the susceptibility to SZ and BD, given the significant heritability for SZ or BD. The genetic variations that have shown to confer increased life-time risk to develop SZ or BD show a large overlap (7–10). This explains why a child's vulnerability is not exclusively associated with a high-risk to develop the same illnesses as the parent, but vulnerability applies to a broader range of psychiatric and neurodevelopmental disorders (2, 3).

The main results of this review revealed that young individuals at FHR-SZ or FHR-BD did not show behavioral impairments in the experimental setting of a neuroimaging environment. Normal task performance in fMRI studies contrasts with several neuropsychological studies that assessed the behavioral performance only (11–17). Only two fMRI studies reported performance differences in FHR-SZ in a WM-related task and in an attention-related task, respectively, and only one study found impairments of performance in FHR-BD in an attention-related task. Across all task domains, FHR-SZ and FHR-BD showed altered brain activation when compared to HC. In the absence or the presence of a minimal overlap in altered brain activation between FHR-SZ and FHR-BD, the existing fMRI data suggest that FHR-SZ and FHR-BD are associated with distinct patterns of aberrant brain activation. This evidence,

however, is of circumstantial character as most studies did not directly contrast brain activation patterns between the two groups.

Within the WM domain, young individuals with FHR-SZ or FHR-BD show altered brain activation patterns in frontal cortex, including the left VLPFC and left frontopolar regions compared to HC. These findings are in line with the existing neuroimaging literature in adult individuals at FHR-SZ (61), as well as in individuals at clinical high-risk (e.g., first-episode patients) of SZ (62) and confirmed SZ and BD patients (63). WM encompasses the ability to maintain information in an easily accessible state over short periods of time to enable goal-directed behavior (64). Lesion studies, transcranial magnetic stimulation (TMS) studies, and neuroimaging studies in humans, as well as single-cell recordings in monkeys have pinpointed the DLPFC, areas in the parietal cortex (superior, ventral and inferior), the cerebellum, striatum, and the medial temporal lobe (MTL) as being the significant brain regions involved in WM processes (65). Impairment of WM is a well-known feature in individuals with SZ spectrum and has been shown to be associated with PFC and fronto-striatal dysfunction in adult individuals with SZ and their unaffected adult first-degree relatives (66). WM deficits in patients with BD are one of the most frequently observed cognitive impairments and have been linked to brain dysfunction (i.e., hyper-activation) in frontal areas (67). Similarly, WM impairments have been shown in healthy adult first-degree relatives of BD patients (15). We did not find evidence of an impaired WM performance in young individuals at FHR-SZ or FHR-BD, and the alterations in WM-related brain activation in frontal regions resembled the pattern present in adult FHR individuals (18, 36). Taken together, these findings may indicate a compensatory mechanism or reflect neural inefficiency.

In the cognitive control domain, FHR individuals showed widespread altered brain activation in areas supporting cognitive control compared to HC. However, this finding was almost exclusively obtained in FHR-BD, and the number of studies and participants producing these widespread differences in activation patterns was low. Of note, cognitive control unifies several top-down cognitive processes supporting attention, problem-solving abilities and making appropriate decisions (64). Due to the small number of studies, however, we pooled all studies related to cognitive control, although some studies were more focused on attentional demands while others tapped into inhibitory abilities. Therefore, it is not surprising that there was little to no overlap between reported results in terms of brain areas that showed peak activation differences. Decreased attention span and poor inhibitory control are well-characterized deficits associated with SZ (68), which has been linked to abnormal brain activation in the DLPFC, ACC, thalamus, and in inferior/posterior parietal areas (69). These brain areas are known to support cognitive control task performance in HC (70). Further, a study on adult FHR-SZ (mean age >21) also found abnormalities in prefrontal activation during cognitive control tasks (22). One study included in the present review investigated young individuals at FHR-SZ, showing that altered brain activation in frontal, medial and parietal brain regions associated to cognitive control performance is already expressed in young individuals at FHR-SZ (54). Similarly, symptomatic individuals with BD show impaired cognitive control, such as sustained attention and inhibitory control, which persists in remission (15, 71). During cognitive control-related task performance, altered brain activation in IFG and limbic areas have been observed in individuals with confirmed BD as well as in adult individuals at FHR-BD (mean age >21) (18, 72). In summary, the abnormal fMRI activation patterns in the cognitive domain in young individuals with FHR match the findings reported in studies of individuals with confirmed SZ or BD as well as adults at FHR-BD and adults at FHR-SZ.

Studies in the reward processing domain only investigated young individuals at FHR-BD and showed differences in brain activity in frontal and medial areas during reward processing relative to HC. Depending on the investigated contrast of interest in the different studies reflecting brain responses to, e.g., anticipation, feedback, winning or losing, these activation differences in individuals at FHR-BD consisted of hypo- and hyper-activation relative to HC. Reward is a central component for facilitating motivation-based learning and the learning of appropriate responses to stimuli, as well as the formation of habits (73). The foundation of the reward system consist of circuits connecting specific frontal- and basal ganglia regions, including the ACC, the orbitofrontal cortex, the ventral striatum, the ventral pallidum, and the midbrain regions (74, 75). Manic episodes, a core symptom in BD, have been associated with impulsive decision making and risk taking that may arise from hyper-sensitivity to reward or general reward dysregulation (76). In the absence of reward-related behavioral impairments in young individuals at FHR-BD, the altered activation patterns of reward-related brain regions observed in the present review may indicate hyper-sensitivity or dysregulation in response to reward-related cues or compensatory mechanisms. We did not identify any studies investigating reward-related brain activity in young individuals at FHR-SZ compared with HC although negative and positive symptoms in SZ may relate to dysfunction of the reward system in the brain (77).

Emotion processing was the most investigated cognitive domain in children, adolescents, and young adults at FHR-BD. Altered amygdala function in individuals at FHR-BD was reported across different emotion processing studies (51, 56–58). Also, IFG/middle FG showed altered activation in FHR-BD compared with HC across two different studies and task contrasts (51, 59). These alterations are consistent with literature investigating BD patient populations, underlining these deficiencies as possible endophenotypic markers of the disorder (78). The two studies focusing on FHR-SZ yielded less consistent results, showing hypo-activation in amygdala in response to positive faces (52), and in ACC in response to aversive images (54). Viewing of aversive images also elicited hyper-activation in the central opercular cortex in FHR-SZ compared to HC (54). The neurobiological alterations in FHR-SZ youth compared to HC is adding to a growing body of evidence for endophenotypic traits of SZ which is also present in

individuals at ultra-high risk (UHR) for psychosis, showing hyper-activation of frontal areas compared to controls when viewing negative pictures (79). The ability to regulate and process emotional responses depending on affective and social cues enables appropriate adaptiveness in various events throughout the lifespan (80). Subcortical structures, such as the amygdala and other limbic areas, play a key role in the processing of emotions. Emotion dysregulation is a core feature of almost every severe mental disorder, causing maladaptive decision making and social interactions (81). Patients with SZ and BD show an affective bias toward erroneous interpretation of emotional stimuli and general emotion dysregulation (82, 83). Individuals with SZ are impaired when making affective judgment and regulation, which may lead to misinterpretation of social cues and poor social skills (84). Individuals with BD show deficits in emotional processing even during euthymic periods (85). Of note, individual studies included in the emotion processing domain in the present review spanned several behavioral paradigm designs, but individual analytical approaches incorporated an emotion processing contrast (see **Supplementary Table S4**). Despite heterogenous task setups, reported results were fairly converging on differences between FHR-BD and HC on amygdala and IFG acivation.

A between-group comparison, including confirmed SZ or BD, FHR, and HC groups, may expand the current knowledge in three directions. First of all, brain-based measures found in FHR individuals and in individuals with confirmed SZ or BD, but not in HC, may reflect neurobiological markers of risk for severe mental illness, and thus may be classified as potential risk endophenotypes (86). Second, the comparison may also identify potential biomarkers for resilience to severe mental illness (87). This may be the case for brain regions where FHR individuals showed regional increases in brain activity, relative to confirmed SZ, BD, and HC, and where task-related brain activity scales positively with task performance. Finally, regions where individuals with confirmed SZ or BD showed dysfunction relative to FHR and HC may reflect potential illness-related adaptations. In these areas, regional brain activity should not reflect high quality of performance, but may rather scale with measures of task impairment. These neurobiological illness-related adaptations may be heavily influenced by important factors, such as duration of illness, medication, illness onset time, etc. As earlier stated, attenuated symptoms in psychosis may precede the manifest disorder.

An alternative way to investigate this hypothesis is by examining whether behavioral and neurobiological impairments are already present in individuals with an At-Risk-Mental-State (ARMS), also known as individuals at UHR for psychosis. This UHR category was introduced with the goal of developing preventive strategies of psychotic disorders and requires individuals to present with either (a) positive symptoms that are typical of psychotic disorders but of subthreshold severity or duration or (b) genetic high risk accompanied by functional decline (88). Individuals at UHR have an increased risk for developing psychosis with transition rates of 29% after 2 years (89, 90). As all UHR criteria rely on help-seeking individuals, the prevalence of the UHR state in the general population is not known to date. Widespread mild cognitive deficits are present in UHR individuals, falling at a level in between that of healthy individuals and those with confirmed SZ, and the magnitude of deficits is comparable with those at FHR (91). Further, abnormalities in brain activity and/or functional connectivity during a variety of cognitive tasks, including verbal memory and WM, verbal fluency, social cognition, as well as in the context of functions directly associated to the emergence of psychotic symptoms has also been shown [for a review, see Andreou and Borgwardt (92)]. Of note and as was the results of the present review, neuroimaging abnormalities in UHR is observed even in the absence of differences in behavioral performance (92), which may point to a compensatory mechanisms for the brain circuits to uphold sufficient behavior.

Behavioral differences between FHR individuals and HC were limited to the domains of WM and cognitive control. FHR-SZ showed lower response latency during an n-back task (41), and poorer performance in detecting non-targets compared to HC during an emotional odd ball task (54). Further, individuals with FHR-BD compared with HC displayed higher reaction time variability in a global attention task (47). The lack of behavioral differences in most studies summarized in the present review may be due to the chosen behavioral variables (e.g., accuracy and reaction time) that may lack sufficient sensitivity. Previous discussions have focused on the limitations of measuring high-level cognitive processes by simply inferring on accuracy and reaction time variables, and argue that some aspects of cognitive processes may be detectable with fMRI but not with these crude behavioral variables (93). Recent computational efforts and behavioral modeling approaches such as Bayesian modeling could help disentangle, explain, and even predict the different contributions from various behavioral sub-parameters within behavioral domains and task paradigms, which may then show a behavioral separation between children, adolescents, and young adults at FHR-SZ or FHR-BD, and HC. An important factor to consider may also be the effect of specific paradigm designs to fit them into an fMRI setting. During the recording of fMRI, a collection of images covering the whole brain is generally acquired every 1–3 s, and hundreds of brain volumes are gathered during completion of an entire fMRI scan, lasting around 2–15 min (94). In this setting, the time constraints for the cognitive tasks need adjustment to this temporality. The limited temporal resolution inherent in fMRI acquisition thus narrows the complexity and speed with which the cognitive paradigm may be carried out and is different from the cognitive paradigms completed outside a neuroimaging environment.

Sample sizes in the included studies were in general small to moderate of size with the smallest being 10 and the largest being 56. The mean sample size of all included studies was 26 for HC and 20 for FHR. Large effect sizes (Cohen's $d > 0.8$) have been found in individuals with manifest BD when tested on different cognitive domains, but in first-degree relatives effect sizes are generally small to medium (Cohen's $d < 0.5$) yet still significantly different from HC (15). In addition, individuals with SZ perform

on average about 0.92 standard deviations worse than controls across many cognitive tasks, whereas the average effect size in healthy relatives on the same metric compared with appropriate control groups is approximately 0.35 (19). Hence, patient studies generally require smaller sample sizes, whereas studies of relatives require larger sample sizes to observe statistically significant group differences. Therefore, valuable evidence may have been missed due to insufficient statistical power inherent in small sample sizes. Also, when investigating a heterogeneous group of individuals (i.e., age span, sex, FHR disorder, comorbidities, etc.) small sample sizes could further obscure significant findings. In addition to small sample sizes in included studies, overlapping of study populations may present a potential confounding factor. Several studies may have originated from the same overall study and/or shared recruitment details and methods, and may thus not stem from independent populations, however, we did not investigate this further.

To fully establish a link between task-related activity and risk or resilience factors of psychiatric disorders, longitudinal fMRI data needs to be acquired. Indeed, longitudinal studies following symptom-free at risk or vulnerable individuals through maturation and possible development of severe mental illnesses would allow for identification of relevant pre-clinical and clinical markers of vulnerability, disease onset and/or resilience. The cross-sectional design of the studies included in the present review is thus a major limitation. While cross-sectional studies allow mapping of neurobiological differences between young individuals at FHR and typically developing controls, observed group differences may reflect vulnerability, brain alterations leading to disorder, or compensational mechanisms as well as variability in developmental stage. As an example of variation, grey matter volume in the frontal cortex peaks between age 7 to 11, but total cortical volume can vary up to 50% between typically developing individuals which enhances the relevance of inter-individual variability (95). Likewise, the subcortical structures undergo developmental changes in volume and shape in a non-linear fashion (96). General for the studies included here is that they do not report other environmental factors than socio-economic status and parental educational level. Since FHR studies cannot disentangle the effects of shared genes from shared environmental influences, designing studies with focus on, e.g., epigenetic analysis as well as home-, school-, and work- environment, and adverse lifetime events might contribute to a better understanding of contributing factors in the complex development of both SZ and BD.

In line with the longitudinal perspective mentioned above, the age of the included participants, as well as the age-range in the groups are of importance when evaluating vulnerability factors. Investigating young individuals at FHR for severe mental illnesses is of importance given the brain's susceptibility to maladaptive changes within this period of the lifespan (33). The studies reviewed herein included individuals within an age range of at least seven years [age span 8–15 (49)] and at maximum 17 years [age span 8–25 (47)] This is a significant age span when considering neurodevelopment, since both grey and white matter undergoes substantial maturation throughout childhood and adolescence, with different structures reaching adult maturity level at different time points in different individuals (97). Including individuals within a broad age span during development may therefore include unwanted variability, which subsequently may impede clear conclusions. Future studies should thus strive to establish longitudinal cohorts with a limited age span.

Inclusion of FHR individuals with comorbid diagnoses, such as ADHD, anxiety disorder, phobia, major depressive disorder, etc. (see **Table 2** for details) varied considerably across the different included studies and consequently some of the investigated individuals at FHR were on medication. Specifically, 13 of the included studies in the present review investigated FHR individuals with existing diagnoses (41, 42, 47, 48, 50, 54, 56, 59). Of importance, the reported diagnoses could be associated with behavioral and neurological changes not related directly and exclusively to the FHR status, but to the specific diagnoses or medications. For example, it has been proposed that whole-brain immature functional connections may underlie ADHD (98) and medication-naïve children with ADHD display reduced error-signaling within cingulo-opercular regions (99). However, it is also important to consider that individuals at FHR-SZ with ADHD might constitute a subgroup with enhanced risk for psychosis compared to FHR-SZ without diagnoses (100). Hence, these participants constitute an important group when studying underlying neural vulnerability factors for psychosis. Most of the studies that included FHR individuals with existing diagnoses performed exploratory or *post hoc* analyses in which participants with existing diagnoses/non-medication naïve were excluded. The *post hoc* analyses ruled out effects of diagnoses on the main results (41, 42, 47, 48, 50, 51, 54–58). Three studies did not perform such *post hoc*/exploratory analyses (52, 53, 59) and the effect of existing diagnoses on these particular results is therefore speculative.

Here, we specifically focused on reviewing studies including young individuals with a mean age ranging from 12.7 to 18.4 years of age (11.8 to 18.7 years of age for controls). Even though this is an advantage, given that this age is before the usual onset of SZ or BD, it narrowed the number of included articles substantially. Lastly, the decision to include only publications in English further reduced the number of included articles in this systematic review.

CONCLUSION

Mapping functional brain alterations in offspring of parents with confirmed SZ or BD may provide important insights into the underlying neurobiological processes that convey vulnerability to these disorders. Given the heterogeneity of the measures, methods and findings, supplementary fMRI studies are needed. These studies should preferentially aim at a longitudinal design and include large groups of individuals with a narrow age range to facilitate the interpretation of altered activity patterns during a specific cognitive task. Our literature search yielded no study that directly compared task-related brain activation between young individuals at FHR-SZ and young individuals at FHR-BD and HC. Given the empirical evidence by Lichtenstein et al. (7) and Schulze et al. (8) mentioned in the introduction section of the present review, the comparison between studies investigating

FHR-SZ and studies investigating FHR-BD in larger groups and with more homogeneous methods will hopefully allow for a dissociation between the early stages of pathogenesis of these severe mental illnesses in the future. Ultimately, the understanding of the neurobiological mechanisms will guide and optimize future treatment and prevention practices toward higher precision.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

AUTHOR CONTRIBUTIONS

LJ, AV, BB, HS, and KP contributed to conception and design of the review. LJ and AV organized the database. LJ wrote the first draft of the manuscript. KL and KP wrote sections of the manuscript. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00632/full#supplementary-material

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Parents' Attitudes Toward and Experience of Non-Suicidal Self-Injury in Adolescents: A Qualitative Study

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Background: Non-suicidal self-injury (NSSI) is prevalent in adolescents and brings a series of serious consequences to their well-being. However, little is known about parents' attitude toward NSSI in Chinese adolescents. The study aims to investigate the parents' attitudes toward and perceptions of adolescents who have engaged in NSSI behaviors, and the impact of NSSI on their parents.

Methods: Purposive sampling was used in the study. The biological parents of adolescents with NSSI were recruited from the psychiatric ward of a tertiary hospital in China. Semi-structured interviews were conducted which contained three aspects, that is the history of NSSI, the process of seeking or maintaining help and the impacts on the family. Each interview typically lasted 40–50 min. All of the interviews were audio-recorded. Their responses were analyzed by the thematic analysis.

Results: Twenty participants completed the interview, consisting of 16 mothers and 4 fathers. Three themes and eight sub-themes were extracted: (1) the attitudes to children's NSSI behaviors (ignorance, shame, and stereotype); (2) coping strategies of parents (the initial response to adolescents' NSSI, and the way of help-seeking); (3) the impacts on family (altered parenting and communication styles, limited personal lives, and increased psychological pressure).

Conclusion: The results showed that parents lack the knowledge about NSSI and its treatment and are suffering great emotional stress. It is recommended to expand the popularization of knowledge of NSSI in adolescents and more interventions adapted to China's sociocultural climate are required for the well-being of parents and NSSI in adolescents.

Keywords: non-suicidal self-injury, adolescents, parents' attitude, parents' experience, qualitative

INTRODUCTION

Non-suicidal self-injury (NSSI), also called deliberate self-injury, refers to a self-injury behavior that is intentional, unsanctioned by society, and not intended for suicide (1). Common forms of NSSI include cutting, burning, scratching, pinching, biting, and poisoning, and such behavior is considered a way to relieve negative emotions, attract others' attention, or exact revenge on or threaten someone (2, 3). NSSI can occur in any group, including adolescents, college students, and patients with mental illness. However, it is most common among adolescents, and the onset of NSSI is most often between 12 and 15 years old (4) The global prevalence of NSSI among adolescents is approximately 17% in nonclinical samples (5), with most cases occurring among females (6). In China, the prevalence of NSSI is higher than this, reaching 17.0%–29.2% in different community samples (7).

NSSI is known to be associated with a combination of factors (8). The most common co-occurrences with NSSI are depressive disorders and borderline personality disorder (BPD) (9). Nearly 50% of patients with NSSI were diagnosed with severe depressive disorder (10) and it was reported that 49%–90% of BPD patients have NSSI. Similarly, patients with anxiety disorders and eating disorders also have a high risk of NSSI (11). In addition, substance use is one of the antecedents leading to adolescent NSSI, and nearly 50% of adolescents with NSSI have a history of substance use (12). Moreover, individuals with NSSI are more likely to have specific temperamental profiles. Mitsui et al. reported that the lower the scores of self-directedness and cooperativeness in the temperament and character inventory (TCI) are, the higher the incidence of NSSI is (13). In addition to the internal factors, it is generally known that family provides a critical background in the process of the growth of adolescents. Previous studies have shown that the relationship with parents is one of the risk factors for adolescent NSSI behaviors (14), especially parenting style. A supportive and warm parenting style is associated with less NSSI (15), while adolescents under highly controlling parenting who do not perceive parental support are more likely to engaged in NSSI (16, 17).

Notably, parents' attitudes toward NSSI have a significant impact on help-seeking. Prior work has demonstrated that the initial response of parents affects the timing of young people's formal seeking of help (18) and affects the likelihood that they will seek help in the future (19). Unfortunately, many parents do not know the best way to approach NSSI in their children (20). Furthermore, NSSI has a series of serious consequences, not only for adolescents, such as permanent scars, rejection by peers, academic difficulties, and risk of suicide (21, 22), but also for parents and families (17). Compared with other parents, the parents of teenagers with NSSI have higher levels of stress and lower levels of satisfaction. Mothers of adolescents with NSSI also showed more symptoms of depression, anxiety, and stress (23). In addition, parent-child relationships change, posing challenges to the family unit (24). However, the impact of NSSI in adolescents on the family is often ignored (25). Therefore, it becomes particularly important to determine the understanding and the coping styles for NSSI of parents, as well as the impact of NSSI behaviors in teenagers on parents in China.

Currently, despite some progress being made on how the perceptions about NSSI of parents, most of the research on this topic has been performed in developed countries, and research exploring parents' attitudes toward NSSI in adolescents and the seeking of help or support in China is been limited. The culture and the healthcare system in China are different from those in developed countries. The field of mental health in China started relatively late. The total amount of mental health resources has been at a low level for a long time, and human resources are scarce (26). Even two-thirds of counties did not have professional institutions for mental health services and the majority of people are short of mental health awareness (27). We intend to close these research gaps in this study. First, the study focuses on parents' attitudes toward and perceptions of NSSI and its impact on families. We aim to generate information that could have a positive impact on parents and families and to explore the positive and negative significance of parents' attitudes toward teenagers' NSSI. Second, to understand some complex processes, qualitative research is the most appropriate method (28). Finally, the study aimed to provide the experiences of participants which could be used in the follow-up interventions to help other parents in the future.

METHODS

Participants

Purposive sampling was used in the study. Parents of adolescents with NSSI were recruited from the child psychiatric ward of a tertiary hospital in China and were given informed consent forms. All the parents of teenagers meeting the inclusion criteria in the ward were invited. The inclusion criteria were as follows: 1) the participants had a biological child between 12 and 18 years old who were hospitalized for psychiatric disorders with a history of at least two NSSIs; 2) the children of participants do not have severe comorbidities and psychotic symptoms, such as hallucinations, delusion, etc.; 3) the participants were able to complete the interview with normal intelligence. Parents were excluded when they did not know whether the child had a history of NSSI and suffered from serious physical or mental illness and could not participate in the study. If parents were willing to participate in the study, they were given a month to call the researchers by telephone, and their children's clinical data were retrieved. Whether adolescents exhibited NSSI behaviors, including cutting their wrists and thighs with knives and other sharp objects, poisoning themselves, or engaging in other behaviors causing bodily harm, was determined by the clinical data recorded by the psychiatrists during the first consultations. Parental mental state was based on the family history in their children's clinical data.

Twenty-six parents were invited to participate in interviews. In total, 20 participants (16 mothers and 4 fathers) completed an interview. Six parents discontinued participation in the study,

including three parents who suggested that we interview their children, two parents who refused to allow us to record, and one parent who was too emotional to continue the interview.

The study, conducted from August 2019 to December 2019, was approved by the medical ethics committee of the Second Xiangya Hospital of Central South University. All of the participants were informed of the purpose, methods, and privacy of the study and have signed informed consent forms.

Procedures

An in-depth, semi-structured individual interview was conducted in the psychological interview room of the ward, and all of the participants' children were inpatients. In the study, participants underwent an in-depth interview and a psychological consultation, and they received a crayon as a gift. The outline of the self-designed semi-structured interview was developed based on the literature (18, 24) and after discussions with psychiatrists and psychiatric nurses who had encountered adolescents with NSSI. Then, after consulting qualitative research experts, the outline of the interview was finalized. It covered 13 topics, some of which were as follows: 1) How do you know your child had an NSSI? 2) What was your first reaction after learning that your child had an NSSI? 3) What strategies did you use to cope with your child's NSSI? 4) Have you persuaded your child not to hurt him/herself? 5) Are you afraid of outsiders learning about your child's NSSI? Are you feeling shame? 6) Do you understand your child's NSSI? 7) What do you think of your child's hospitalization? and 8) Please describe how you usually get along with your children. Each interview typically lasted 40–50 min. All of the interviews were audio-recorded.

Data Analysis

At the end of each interview, two researchers converted the audio recording into text and coded the data separately. One researcher has a background in psychology, and the other has a background in psychiatry. The general information was extracted in the form of a table. Data coding was performed in NVivo software, version 11. Thematic analysis was used and followed the six-step process by Braun and Clarke (29). Subthemes were formed by extracting the nodes repeatedly. After several discussions, the two researchers reached a consensus on the subthemes, which were agreed upon by all of the staff at the authors' meeting.

TABLE 1 | Participant characteristics.

Age of child (years, SD, range)	14.5 (2.0;12.0–18.0)
Diagnosis of child	
Depression	15 (75%)
Bipolar disorder	3 (15%))
Unspecified behavioral and emotional disorder	2 (10%)
Gender of child	
Female	17 (85%)
Male	3 (15%)
Gender of interviewee	
Female	16 (80%)
Male	4 (20%)
Residence	
City	14 (70%)
Countryside	6 (30%)
Education of child	
Middle school	10 (50%)
High school	10 (50%)
Education of father	
Less than high school	6 (30%)
High school	4 (20%)
More than high school	10 (50%)
Education of mother	
Less than high school	4 (20%)
High school	4 (20%)
More than high school	12 (60%)
Marital status of participants	
Married	14 (70%)
Divorced	5 (25%)
Widowed	1 (5%)
The method of NSSI	
Cutting	13 (10%)
Poisoning	2 (10%)
Head banging	2 (10%)
A combination of methods	2 (10%)

RESULTS

Twenty parents were included in the study. **Table 1** displays the characteristics of the participants and their children. The mean age of the children was 14.5 years old (range: 12.0–18.0 years), and most were girls (85%). The average length of hospitalization was 5.6 d (range: 1–16 d) on the day of interview, including soon after the admission of adolescents (60%), soon after stabilization of symptoms (30%), and approaching the discharge (10%). Reasons for the hospitalization of adolescents were emotional disorders and repeated self-injury. Fifteen adolescents (75%) were diagnosed with nonpsychotic major depressive disorder (F32.2), three adolescents (15%) with nonpsychotic bipolar disorder (F31.4), and two adolescents (10%) with behavioral and emotional disorders with onset usually occurring in childhood and adolescence (F90–F98) according to the International Classification of Diseases 10th Revision (ICD-10). Fifty-five percent of the children with the duration of mental illness is less than one year, 30% of them have been diagnosed for 1–3 years, and 15% of them had more than 3 years. The time when they first engaged in NSSI was almost the same as the time when they received the diagnosis of mental illness. Self-injury methods included cutting (65%), head banging (10%), poisoning (10%), and a combination of methods (10%). Seventy percent of the children lived in towns or cities, and half were junior high school or high school students. It was found that 80% of the adolescents had one or more siblings, of which one teenager's sister has a history of mental illness. Fifty percent of the parents' education level were more than high school. The parenting style of parents are mentioned with parents' authoritarian (40%) and the inter-generational parenting (25%).

Through the thematic analysis, three themes and eight subthemes were extracted: (1) the attitudes to children's NSSI behaviors; (2) coping strategies of parents; and (3) the impacts on family (see **Figure 1**).

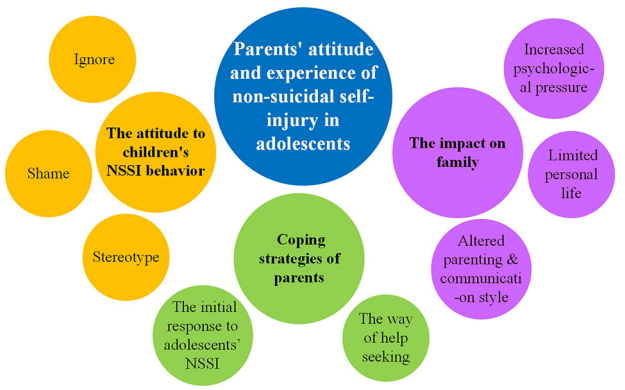

FIGURE 1 | Thematic map of the three themes (middle circle) and eight sub-themes (small circle).

Theme 1: The Attitudes to Children's NSSI Behaviors

Subtheme 1: Ignorance

Many participants reported that NSSI is not very common, especially without a family history. For this reason, when they learned about their child's NSSI, they ignored the behavior.

> *"…Then she told me she wanted to see a psychiatrist, but I didn't even think of it because this didn't happen to any of the older kids in my family, so I didn't care…" (P1)*
> *"…When he told me in junior high school that he was a little mentally abnormal, we didn't care. We asked him why, and he didn't say. We still don't know until now…" (P5)*

Other participants underestimated the severity of the NSSI and believed that their children would recover on their own.

> *"…I know she is sick and very anxious. But I don't think it's a big deal…" (p4)*

Subtheme 2: Shame

Many parents did not know much about mood disorders and NSSI. Many thought that mood disorders were due to a problem with the brain and that their children were like "idiots", the popular understanding being that such people exhibit inappropriate behaviors and language. Therefore, they felt too ashamed to tell others that they had a child with NSSI.

> *"…After all, it is a mental illness, and others may have some bad opinions…" (p2)*
> *"…Not many people know that my daughter is getting sick. I do not want to tell anyone. My family did not know before. I am just afraid that people will find out, and afraid that people will look down on my daughter…" (p1)*

Due to the stigma of mood disorders, some parents were reluctant to seek help from others, such as friends or colleagues. In addition, they worried that it would have a negative impact on their children's further education, employment, and marriage.

> *"…Because I was afraid that it would have an impact on her marriage, even if she recovered…" (p9)*
> *"…I am afraid that being known by others will have an impact on the future…" (p3)*

Subtheme 3: Stereotype

Stereotypes about mood disorders caused misconceptions about them. Most of the parents thought mood disorders were not very serious and were not life threatening. In their opinion, teenagers do not experience any pressures, and they can go out and relax to cure a mood disorder because it is not a mental disease.

> *"…When we took her on a trip, she was in a good mood and did not hurt herself, as if she had recovered from her illness…" (p2)*
> *"…At the beginning, as soon as she said she was in a bad mood, I took her out to play and shop…" (p11)*

Some parents believed that if they did not pay too much attention to their children's self-injury behaviors, their children would become better and their condition would not become more serious.

> *"…Because I am afraid that if I pay too much attention to her self-injury, she will think she is more abnormal, so I dare not pay attention to her…" (p15)*
> *"…I don't think he's a patient. I enlightened him. I never thought he was a patient…" (p3)*

A few parents often confused mood disorders with other mental illness and believed that only someone who is disoriented and has abnormal behaviors has a mental disorder and must go to the hospital for treatment.

> *"…I think if you have this disease, you would not even know your parents and wander around the road. But she said everything clearly and knows everything, so I can't believe that she is ill…" (p13)*
> *"…Sometimes I don't understand what she says to me. For example, she said before, 'Mom, I seem to have depression.' I said, 'What the hell to depression, and depression is psychosis…'" (p16)*

Furthermore, when her granddaughter was in a slightly better mood or had no obvious signs of illness, one grandparent believed that taking drugs was harmful and would subjectively reduce the medication dose.

> *"…Her grandmother thinks it must be bad to take too much medicine. One medicine was taken at night, and the dose was one and a half, and her grandmother threw away half of it…" (p10)*

Theme 2: Coping Strategies of Parents

Subtheme 1: The Initial Response to Adolescents' NSSI

When participants learned that their children had NSSI behaviors, they blamed their children because they were afraid that the child would commit suicide later and felt nervous.

> *"…We blamed him because we were scared that he would commit suicide in the future too…" (p5)*
> *"…At the beginning, I blamed her because I was a little nervous…" (p11)*

Some participants educated their children in their own way to persuade them not to hurt themselves again.

> *"…I was worried and said that 'Don't hurt yourself'. I said,' if you cut your hand again, I would cut it like you…'" (p16)*
> *"We just talked to her a little more for fear that she would hurt herself again…" (p17)*

A few participants felt angry about their children's NSSI behavior, because they believed that children hurt themselves in order to threaten their parents and achieve their own goals.

> *"…She threatened me with cutting her wrists every time. What she wants me to do, if I don't do it, she says she wants to cut her wrists. So I was angry and ignored her…" (p6)*

Subtheme 2: The Way of Help Seeking

Many participants did not know how to cope with the child's NSSI behavior and did not take the child to a psychiatrist in a timely manner. They went to a professional institution for help only after their child or someone else requested it.

> *"…Because none of my other kids had ever done this, I didn't care. Later, she said she wanted to see a psychiatrist, so I took her to see a psychiatrist…" (p14)*
> *"…At the beginning, I felt that she had a very stubborn character, and I just felt that her temper was getting worse, but we didn't pay much attention to it. Later, her teacher also said that she had a bad temper and asked us to see a psychiatrist…" (p11)*

Some of the participants were more likely to take their children for a full-body examination when they find something unusual and the doctor suggested taking their children to a psychiatrist.

"…She said she didn't want to go to school, and said she was uncomfortable, so I took her for an inspection, but nothing was found…" (p1)

> *"…I took her to the largest hospital in my hometown again. The doctor said that if she is always in such situations, it must be a psychological problem…" (p13)*

Theme 3: The Impacts on Family

Subtheme 1: Altered Parenting and Communication Styles

Most of the participants said that they were less likely to lose their temper and were more able to control their emotions. Therefore, they no longer had face-to-face confrontations with their children.

> *"…I am more able to control my emotions, and I will not show that I am annoyed with her…" (p15)*
> *"…Actually, I have a temper, but I didn't let it out. It's better talk to her in a nice way…" (p20)*

Some participants reported being more patient with and paying more attention to their children. Furthermore, they were willing to attempt to communicate with their children as friends rather than as authority figures, like they used to.

> *"…When I speak to her now, my voice is a little lower and softer. I will deliberately pay attention to the content and my way of talking to her…" (p2)*
> *"…I'm a little more patient than before, and most of the time I don't blame her like I used to…" (p11)*

A few participants mentioned that they would develop together with their children and improve themselves. They did not have high expectations for the future and would not pressure their children.

> *"…I think we should grow up together with our children, he should learn the method of catharsis, and we parents should also learn to change the way of education, the way of communication…" (p5)*
> *"…I just hope she can support herself in the future. I have regarded her as a friend rather than a child…" (p6)*

Subtheme 2: Limited Personal Lives

Many participants said that, since they had learned that their child was ill, they had asked for leave or had quit their jobs to stay with their children all the time. A few participants changed jobs, accepting less pay so that they could stay with their children.

> *"…I haven't managed the business in my shop since she was ill…" (p4)*
> *"…I asked for leave from work to accompany her/him…" (p7, 14, 18)*
> *"…I worked in the hotel next to his school, and I got a job in the housekeeping department because I'm afraid he won't eat and take medicine on time…" (p3)*

Other participants mentioned that they spent less time chatting and partying with their friends and spent more time with their children.

> *"…They spend less time chatting and socializing with their friends and spend more time with their children…" (p2)*

Subtheme 3: Increased Psychological Pressure

Most of the participants had high medical expenses, and some of the participants had quit their jobs. Furthermore, most of the children were in the middle and high school, which is a prime period of learning, but the illness can cause academic performance to suffer.

> *"…I'm a little depressed. The child has been excellent since he was a child; suddenly, he said that he would never go to school again. I think it's a pity, so I'm a little depressed…" (p12)*
> *"…In addition to hospitalization and medication costs, sometimes she wants to go out to relax and go out for fun, so the financial pressure is very great…" (p19)*

Other participants mentioned that they sleep less and that their sleep quality has worsened since learning about their child's NSSI. A few participants felt guilty about their child's behavior. Several of the participants reported that they even felt broken and depressed.

> *"…It's the biggest blow to me. I feel like I'm a failure and I think it's my own problem. I feel devastated…" (p7)*
> *"…I didn't go to bed until yesterday. I didn't sleep much the previous few days. I was afraid she would hurt herself." (p20)*
> *"…I'm very depressed. But I was very optimistic and positive in front of her…" (p2)*

A few participants felt that the future was a little bleak because the effect of the treatment was not obvious. In addition, they worried about the recurrence of their child's illness.

> *"…I am afraid that she will have a relapse in the future because the recurrence rate is so high…" (p8)*

DISCUSSION

To our knowledge, the study is the first to investigate parents' attitudes toward and perceptions of adolescents with NSSI behaviors in China. Our research found that parents do not know how to cope with their children's NSSI behaviors and lack relevant knowledge about NSSI in adolescents. Second, the initial response of parents is often not to take their children to the hospital; this option is, in fact, sometimes the last option for parents. In addition, a child's NSSI has some impacts on the parents, altering their parenting, limiting their personal lives and creating a parental burden.

The results showed that most parents lack knowledge about NSSI in adolescents. On the one hand, some of them had never heard of NSSI behaviors before their children engaged in NSSI and underestimate its severity; thus, they ignored it and believed that things will improve spontaneously. This attitude is consistent with Oldershaw and colleagues' study (18). On the other hand, some participants regarded their children's NSSI behavior as shameful, and they were therefore reluctant to mention their child's NSSI history to others. This may be one of the hidden factors influencing parents' lack of knowledge of NSSI. Moreover, many participants have stereotyped conceptions about mental illness. They believe that those suffering from mental illness are "lunatics" and have abnormal speech and behaviors. Therefore, it is difficult for them to equate NSSI with mental illness.

Moreover, in agreement with McDonald's study (20), most of the parents do not know the best coping strategies for children's self-injury behaviors. At the beginning, they tended to confuse self-harm with adolescent rebellion, so they blame and educate to persuade children not to self-harm again. Parents did not address the issue until the child or the teacher or the doctor suggested that the child should go to a psychiatrist for treatment. In addition, we found that there are many barriers to help-seeking for adolescents with NSSI. Some parents fear receiving negative reactions and disrupting academic achievement, employment, and marriage (19, 30), or they simply misunderstand NSSI. As a result, when children mention going to the hospital for treatment, parents' perceptions conflict with their children's perceptions. In this study, we found that most teenagers with NSSI wounds take the initiative to ask for help, which stands in contrast to the findings of Pumpa and colleagues (31), perhaps because our participants were all parents of hospitalized patients.

After learning about NSSI in adolescents, the parents underwent changes. In terms of parenting strategy, they altered their parenting and communication styles due to fear of the child's repeated self-injury. Consistent with Byrne's research (32), some parents reported being more patient and gentle with their children and avoiding conflicts with them. Nevertheless, parents mentioned that communicating with their children, especially about NSSI, was a difficult process. In addition, we found that parents are under great parenting stress. On the one hand, they face a great financial burden. In addition to the expenses of medication, hospitalization, psychological counseling, etc., in order to make their children happy and stop hurting themselves, parents address their children's various desire for shopping, traveling, etc. On the other hand, parents felt increased psychological pressure due to fear that their child would have a relapse and neglect their studies as well as guilt and depression about their child's NSSI.

Regarding existing problems, some interventions have been developed for NSSI behaviors in adolescents consisting of pharmacotherapy and psychotherapies, such as cognitive behavior therapy, interpersonal therapy, and family therapy, etc (33, 34). These interventions have made some progress in reducing the incidence and frequency of NSSI to some extent. However, these studies also have some limitations, such as low participation rates, a lack of a specific focus on NSSI, small sample sizes, and few high-quality randomized controlled trials. According to our findings, considering the characteristics of adolescents with NSSI and their parents, the interventions with low-threshold access, low stigma, and high confidentiality are needed. Online interventions might be more acceptable than in-person interventions. Second, the parents of adolescents with NSSI are under great parenting pressure, and their lives are

impacted by their children's conditions. Intervening parents and children together would be more effective in helping families with adolescents who engaged in NSSI.

Currently, in mainland China, the treatments for inpatients who engaged in NSSI are not optimistic. For one thing, the mental health system in China is understaffed. As of the beginning of 2015, the number of psychiatric beds was approximately 1.71/100,000 population, which was lower than the global average of 4.36/100,000 (27). Psychiatrists and psychiatric nurses are the main professionals providing mental health services, with few clinical psychologists, psychotherapists and social workers involved in China. The resources of mental health services are mostly distributed in cities, with few in rural areas. Moreover, the interventions in China mainly are in the research stage, and there is a lack of intervention programs specially aimed at self-injury (26). As for the treatment methods, pharmacotherapy is the domain approach, supplemented by psychotherapy. Generally, it mainly treats the mental illness first which co-occurs with NSSI, such as depressive disorders or bipolar disorder. Furthermore, there is no national intervention plan addressing suicide and NSSI in children and adolescents.

LIMITATION

In the study, our findings could only be generalized to a certain extent because the participants are all the parents of inpatients. Their attitudes and perceptions might more reflected those of parents whose children have been referred to medical institutions. In addition, most of our participants were mothers because most teenagers were accompanied by their mothers in hospital. This is influenced by the culture, that is, women are the main providers of informal care for family members (35). Therefore, our results might be more representative of mothers' attitudes. Future studies may focus on fathers' parenting, attitudes, and perceptions. Second, we did not go through a rigorous mental health evaluation of parents and did not use validated instruments to measure parenting stress. In future research, quantitative explorations could be undertaken to understand the parenting stress and mental health status of parents. Third, the psychological factors and temperament of the adolescents were not involved. It is suggested to explore the influence of psychological factors and temperament of adolescents on NSSI and parents in the follow-up studies.

CONCLUSIONS

We investigated parents' attitudes toward NSSI in Chinese adolescents and the impacts on their parents in mainland China. The results showed that parents lack the knowledge about NSSI and its treatment and are suffering from great emotional stress. According to these findings, we recommend expanding the popularization of knowledge to increase awareness of NSSI in adolescents and help them to seek professional support in a timely manner. In addition, the well-being of parents of adolescents who have engaged in NSSI require attention, indicating that much research is still needed to improve the well-being of both parents and families. The study supported that online interventions adapted to China's sociocultural climate could be a viable option.

In future research, it would be meaningful to expand the range of participants to family members or the adolescents themselves to understand more perspectives and the impact of NSSI on additional groups. If a community sample could be recruited, a more comprehensive understanding of the attitudes of Chinese parents toward NSSI in adolescents could be obtained. In addition, long-term follow-up studies are necessary to understand the long-term effects of NSSI behaviors in adolescents on families or changes to parent-adolescent relationships.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation, to any qualified researcher.

ETHICS STATEMENT

The study, conducted from August 2019 to December 2019, has been approved by the Medical Ethics Committee of the Second Xiangya Hospital of Central South University. All participants have been informed of the purpose, methods, and privacy of the study and have signed informed consent forms.

AUTHOR CONTRIBUTIONS

JO, YL, and RC designed the study. Data curation: XF, JL, and YP. Formal analysis: XF and JY. Writing—original draft: XF. Writing—review and revising: XL, YS, JO, and YL. XF, JO and YL obtained the funding. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00651/full#supplementary-material

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Association Between Parental Anxiety and Depression Level and Psychopathological Symptoms in Offspring With 22q11.2 Deletion Syndrome

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22q11.2 deletion syndrome (22q11DS) is recognized as one of the strongest genetic risk factors for the development of psychopathology, including dramatically increased prevalence of schizophrenia anxiety disorders, mood disorders, and Attention Deficit Hyperactivity Disorder (ADHD). Despite sharing a homogenous genetic deletion, the psychiatric phenotype in 22q11DS still present significant variability across subjects. The origins of such variability remain largely unclear. Levels of parental psychopathology could significantly contribute to phenotypic variability of offspring psychopathology, through mechanisms of gene x gene (GxG) and gene x environment (GxE) interactions. However, this hypothesis has not been explicitly tested to date in 22q11DS. In the present manuscript, we employed a longitudinal design to investigate bi-directional interactions of parental anxiety and depressive symptoms, estimated with Beck Depression Inventory and Beck Anxiety Inventory, and offspring level of psychopathology assessed with a combination of parentally reported Child Behavioral Checklist, Youth Self Report Questionnaire, and Structured Clinical Interviews for Prodromal Syndromes (SIPS). We tested associations in both typically developing healthy controls (HCs) (N = 88 participants; N = 131 time points) and in individuals with 22q11DS (N = 103 participants; N = 198 time points). We observed that 22q11DS individuals with higher levels of parental anxiety and depression presented significant increases in multiple forms of psychopathology, including higher internalizing and externalizing symptoms, as estimated both by parental and self-report questionnaires, along with higher negative and generalized symptoms as measured with the SIPS. Associations for positive and disorganized dimensions of the SIPS were not statistically significant. Purely longitudinal analysis pointed to bi-directional interactions of parental and child psychopathology, with marginally stronger longitudinal associations between early parental anxiety-depression and subsequent child psychopathology. Interestingly, associations between psychopathology across generations were significantly stronger in 22q11DS individuals

compared to HCs. Our results show that parental levels of anxiety and depression are associated with levels of offspring psychopathology, particularly in individuals with 22q11DS. These findings point to the existence of GxG or GxE mechanisms, that should be investigated in future work. From a clinical perspective, they highlight a strong rational for the management of parental psychological well-being in 22q11DS.

Keywords: 22q11.2, parental psychological distress, gene x environment, offspring, anxiety, depression, psychosis

INTRODUCTION

The 22q11.2 deletion syndrome (22q11DS) is one of the most common recurrent copy number variant disorders occurring in approximately one in 3,000–4,000 live births and up to one in 1,000 pregnancy (1). It is caused by a microdeletion resulting in hemizygosity for approximately 50 genes (2). 22q11DS is associated with a variety of symptoms including physical, social, cognitive, and psychiatric problems (2). In particular, individuals with 22q11DS are characterized by an increased prevalence of neurodevelopmental disorders (25–50%; i.e. attention deficit hyperactivity disorder, autism spectrum disorder, intellectual disability, learning disabilities), anxiety and mood disorders (15–65%), and psychosis spectrum disorders (20–30%) (3, 4). Similar to what has been described in the general population, psychiatric comorbidity is extremely frequent in the context of 22q11DS. For example, it has been shown that individuals with 22q11DS diagnosed with an anxiety disorder are six times more likely to be also diagnosed with a mood and psychosis spectrum disorder compared to those without an anxiety disorder (4). Despite the increased prevalence of psychiatric disorders reported in this population, about 20% of individuals with 22q11DS experience non-clinical levels of psychopathology (5), thus highlighting considerable heterogeneity within the 22q11DS group.

To date, the reasons for this clinical heterogeneity remain unclear and could encompass a complex combination of both gene x gene (GxG) and gene x environment (GxE) interactions. Some studies have recently shown evidence that GxG interactions modulate risk for schizophrenia in 22q11DS (6–8). In particular, Cleynen et al. (6) observed that the presence of common genetic variants outside of the 22q11.2 locus and known to be associated with risk for schizophrenia—also known as the polygenic risk score for schizophrenia—is more frequent in individuals with 22q11DS diagnosed with a psychotic disorder compared to those without psychosis.

With regards to GxE interactions, evidence is more limited but several mice and human studies point toward significant effects (3). For example, a recent study has shown that exposure to stressful life events modulated the risk to experience psychotic symptoms in adolescents and young adults with 22q11DS (9). This study showed also that 22q11DS patients are more sensitive to stressful life events (i.e. which includes parental psychopathology) compared to typically developing offspring, highlight the importance of environmental factors in the pathway to severe mental disorders in 22q11DS. Nevertheless, the study of other important environmental factors, such as specific aspects of the familial environment, has received limited attention. The association between parenting style and behavioral outcome in the offspring diagnosed with 22q11DS has been investigated in two studies (10, 11), both of them showing significant associations. Weisman et al. (12) also investigated dyadic reciprocity during a mother-child interaction and showed significant associations with the level of behavior problems assessed with the Child Behavior Checklist [CBCL (13)].

In the general population, there is substantial evidence that several aspects of the familial environment, such as high family cohesion or a high parental involvement, can act as resilience factors to reduce the risk of psychopathology in vulnerable populations (14). It has also been shown that factors pointing toward lower levels of parental well-being, such as parental stress or the presence of (subclinical) anxiety and depressive symptoms increase the risk of psychopathology in the offspring (15). It should be noted that the vast majority of research focused on parental anxiety and depressive symptoms, which are the most frequent symptoms in the adult population. Several mechanisms have been proposed through which parental anxiety an depressive symptoms might be related to the offspring level of psychopathology [for a review, see (15)]. Notably, several lines of research suggest that there is significant amount of genetic heritability of depression and anxiety (16). On the other hand, the role of environmental exposure has also been highlighted to explain this co-occurrence, notably the fact that parental depression or anxiety places children at increased risk of being exposed to stressful events (e.g. parental conflict), as well as negative cognitions, behaviors, and affects (17). Interestingly, research conducted on genetic syndromes and/or children with developmental disabilities (e.g. autism spectrum disorder, intellectual disability) also highlight that specific characteristics of the children might contribute to explain the emergence of anxiety and depressive symptoms in the parents (18) and that children's symptoms and parental stress might exacerbate each other (19–22).

In summary, current evidence from the general population suggest that parental anxiety and depression and psychopathology in the offspring mutually influence each other through reciprocal interactions that are driven both by genetic and environmental mechanisms. In the current study, we explored for the first time the association between parental anxiety and depression levels and offspring psychopathology in a sample of individuals with 22q11DS and typically developing controls, using a longitudinal design. Specifically, we expected to observe significant associations between parental anxiety and depression levels and a broad

spectrum of psychopathological manifestations in children, as measured with a variety of techniques (parent-reported questionnaire, self-reported questionnaire, and clinician-based semi-structured interview). Secondly and based on existing literature, we expected to observe bi-directional associations between parental anxiety and depression and offspring psychopathology. Finally, we hypothesized to observe stronger associations between parental anxiety and depression and psychopathology in the offspring affected by 22q11DS compared to typically developing offspring, thus offering supporting evidence that GxE interactions contribute to explain the heterogeneity of the clinical phenotype in this population.

METHODS

Cohort

This study was conducted in the context of a large prospective longitudinal study on 22q11DS, which began in 2000 and has been described in previous literature [e.g. (23)]. Recruitment, which is still ongoing, was performed through patient associations and word of mouth. 22q11DS was confirmed using quantitative fluorescent polymerase chain reaction. Healthy controls (HCs) were recruited among unaffected siblings of patients (N=59) and from the Geneva State School System (N=29). Given the reduced prevalence of 22q11DS, currently estimated at 1/3,000–1/6,000 live births (24), age at recruitment varied across subjects. From an initial pool of 167 participants (271 visits) with 22q11DS and 149 HCs (261 visits), only participants aged > 11 years at the time of assessment (i.e. youngest age at which the youth self-report can be collected) with valid self- and parent-reported questionnaires and those for whom information regarding anxious-depressive symptoms, namely the Beck Anxiety Inventory [BAI (25)] and Beck Depression Inventory [BDI (26)], was available for at least one parent were included in the present study (see **Supplementary Figures S1** and **S2** for details for a flow-chart of inclusion/exclusion of participants from the entire Swiss 22q11DS longitudinal cohort). The final sample consisted of 103 (197 visits) participants with 22q11Ds and 88 HCs (129 visits). Maternal BDI and BAI were available for 101 individuals and 194 visits in 22q11DS and for 87 individuals and 129 visits in HCs. Paternal BDI and BAI were available for 88 individuals and 153 visit in 22q11DS and for 73 individuals and 105 visits in HCs.

Once recruited, both patients and HCs were followed up longitudinally every 3.7 ± 0.8 years in HCs and 3.66 ± 0.89 in 22Q11DS. Extent of longitudinal follow-up also varied from one to three visits. Specifically, among individuals with 22q11DS, 39 subjects had one visit, 34 subjects had two visits, and 30 subjects had three visits. Among HCs 55 subjects had one visit, 26 subjects had two visits and seven subjects had three visits. As detailed in the statistical analysis section, mixed models linear regression was employed to deal with the complex structure of the dataset.

Groups were matched for age at first assessment (t=0.353, p=0.73) and sex ($X_{2\ =}$ 0.032, p=0.86) and time between visits (3.68 +/− 1.49 in HCs and 3.65 ± 1 in 22q11DS, p=0.79) (see **Table 1** for the full descriptive characteristics of the sample).

Clinical Instruments

In both 22q11DS individuals and HCs psychopathology was firstly assessed with a combination of the Child Behavioral Checklist [CBCL (13)] before 18 years of age and the Adult Behavioral Checklist [ABCL (27)] after the age of 18, which were filled out by parents, considering the "total problems", "internalizing problems", and "externalizing problems" scales. Additionally, we employed the Youth Self Report Questionnaire [YSR (13)] before 18 years of age and the Adult Self Report Questionnaire [ASR (27)], which was filled out directly by both individuals with 22q11DS and HCs, again considering "total problems", "internalizing problems", and "externalizing problems" scales. In *post-hoc* analyses, the syndrome scales (anxious-depressed symptoms, somatic concerns, thought problems, rule-breaking behavior, aggressiveness, withdrawn symptoms, and attention problems) of the CBCL/ABCL and YSR/ASR were also used. Moreover, we used the Structured Interview for Psychosis-Risk Syndromes [SIPS (28)] only in individuals with 22q11DS, considering the mean positive, negative, disorganized, and generalized symptoms subscales.

Parental anxious-depressive psychopathology was assessed with a combination of the BDI total score [BDI (26)] and BAI total score [BAI (25)]. In order to obtain an average measure of anxious-depressive psychopathology, total BDI and BAI scores were firstly separately z-scored and then averaged for each parent. For visits for which both maternal and paternal psychopathology measures were available, these were averaged across parents in order to obtain an overall estimated of parental anxious-depressive psychopathology (a comparison between maternal and paternal symptoms is described in the **Supplementary Analyses A** and **Supplementary Figure S3**).

Statistical Analyses

We employed mixed-models linear regression (MMLR), to characterize and test the effects of parental anxious-depressive psychopathology in developmental trajectories of child psychopathology, separately in HCs and 22q11DS. Specifically, samples of 22q11DS individuals and HCs were each separately divided in two sub-samples, according to whether parental anxious-depressive psychopathology at the earliest available visit, was higher or lower that the observed mean parental psychopathology. This procedure yielded four samples: high-parental-psychopathology HCs (29 subjects, 44 visits, mean-age 18.6+/−5.3, male/female 13/16) low-parental-psychopathology HCs (59 subjects, 87 visits, mean-age 17.4+/−4.0, male/female 32/27), high-parental-psychopathology 22q11DS (39 subjects, 68 visits, mean-age 19.7+/−5.9, male/female 17/22), and low-parental-psychopathology 22q11DS (64 subjects, 130 visits, mean-age 18.6+/−4.4, male/female 32/32). Sub-samples were matched for age (P=0.13 in 22q11DS, P=0.13 in HCs) and gender (P=0.53 in 22q11DS, P=0.41 in HCs).

We then employed MMLR to compare developmental trajectories of child psychopathology between high vs low parental psychopathology sub-samples in 22q11DS and HCs separately. Indeed, MMLR is ideally suited for longitudinal samples with variable number of visits across subjects and

TABLE 1 | Demographic Table: Description and comparison of demographic features across 22q11DS and Healthy Controls samples and across sub-groups of 22q11DS and Healthy Controls divided on the basis of parental symptoms.

	22q11DS			HCs		
	Total sample	**Low parental symptoms**	**High parental symptoms**	**Total sample**	**Low parental symptoms**	**High parental symptoms**
Nb participants/Nb Visits	103/197	64/130	39/67	88/129	59/85	29/44
Mean Age	16.54 +/- 4.61	16.16+/- 4.11	17.17+/-5.34	16.77 +/- 4.27	16.30 +/- 3.52	17.73 +/-5.45
Male/Female	49/54	32/32	17/22	43/45	27/32	16/13
Participant living with parent(s) (% yes)	97 (94.17)	62 (96.88)	35 (89.74)	77 (87.5)	56 (94.92)	21 (72.41)
Both parents living together (% yes)	80 (78.43)[1]	47 (73.44)	33 (84.62)	71 (80.68)	43 (72.88)	28 (96.55)
Family's annual income (%)	17 (16.67)	8 (12.5)	9 (23.08)	11 (12.5)	2 (3.39)	9 (31.03)
- < 30'000Eu/year	51 (50.00)	30 (46.88)	21 (53.85)	35 (39.77)	27 (45.76)	8 (27.59)
- 30'000 – 75'000 Eu/year	34 (33.33)[1]	26 (40.63)	8 (21.05)[1]	42 (47.73)	30 (50.85)	12 (41.38)
- > 75'000Eu/year						
Maternal level of education (%)	12 (11.88)	6 (9.38)	6 (16.22)	8 (9.09)	5 (8.47)	3 (10.34)
- primary education	34 (33.66)	22 (29.73)	12 (32.43)	31 (35.23)	23 (38.98)	8 (27.59)
- secondary education	55 (45.46)[2]	36 (56.26)	19 (51.35)[2]	49 (55.68)	31 (52.54)	18 (62.07)
- higher education						
Maternal employment (% yes)	78 (77.23)[2]	48 (76.19)[3]	30 (78.95)[3]	64 (72.73)	45 (76.27)	19 (65.52)
Paternal level of education	22 (21.78)	11 (17.46)	11 (28.95)	18 (20.93)	8 (14.04)	10 (34.48)
	29 (28.71)	17 (26.98)	12 (31.58)	22 (25.58)	19 (33.33)	3 (10.34)
	50 (49.50)[4]	35 (55.56)[5]	15 (39.47)[5]	46 (53.49)[9]	30 (52.63)[9]	16 (55.17)
Paternal employment (% yes)	86 (87.76)[6]	60 (96.77)[7]	26 (72.22)[8]	75 (87.21)[9]	53 (92.98)[9]	22 (75.86)
Nb Mothers/Nb Visits	101/194	64/129	37/65	87/129	58/85	29/44
Nb Fathers/Nb Visits	88/153	52/90	36/63	73/105	44/64	29/41

[1]*Missing information for 1 family.*
[2]*Missing information for 2 mothers.*
[3]*Missing information for 1 mother.*
[4]*Missing information for 2 fathers.*
[5]*Missing information for 1 father.*
[6]*Missing information for 4 fathers/1 deceased.*
[7]*Missing information for 1 father/1 deceased.*
[8]*Missing information for 3 fathers.*
[9]*Missing information for 2 fathers.*
For participants with multiple visits, information related to the 1st visit is reported in the table.

ariable age at the first assessment and variable interval between visits (29). Our approach, has been detailed in previous publications from our group (29). Briefly, developmental trajectories for each psychopathological measure we estimated by fitting random slope models of increasing order, from constant to cubic, to the association between age and each variable being tested. Population parameters (age and diagnosis) were modeled as fixed effects and within-subject factors as random effects by using the nlmfit function implemented in MATLAB_R2018a (Mathworks). Subsequently, the Bayesian information criterion (BIC) was employed to select the optimal model order, while avoiding over-fitting. Finally, we applied a likelihood ratio test to evaluate differences in trajectories between groups both in terms of shape differences (curves that do not follow a parallel path for both groups) and intercept differences (curves that follow parallel paths in both groups, but at different intercepts).

As a subsequent analysis, we were interested in comparing the strength the association between child and parental psychopathology across 22q11DS and HCs, in order to test for the existence of potential GxG or GxE interactions. Hence, we computed Pearson correlations between mean parental psychopathology and child total CBCL and YSR scores, which were averaged across multiple visits for each subject, separately for HCs and 22q11DS samples. We then performed Fisher's R to Z transform to test for differences in the strength of the parental-child psychopathology correlation across samples.

As a final analysis were employed our longitudinal sample to attempt to discern the causal directionality of the association between parental and child psychopathology. Hence, we restricted our analysis to families for whom measures of child and parental psychopathology were available for at the least two longitudinal assessments (N=64, mean age at baseline 16.8+/−4.0, mean age at follow-up 20.6+/−4.19). We then computed both the longitudinal association between baseline child psychopathology and parental psychopathology at follow-up and the reverse association between baseline parental psychopathology and subsequent child psychopathology scores at follow-up. Finally, we computed parent-child longitudinal correlation after accounting for the effects of homologous correlations between child-baseline to child-follow-up psychopathology and parent-baseline to parent-follow-up psychopathology, using partial correlations.

RESULTS

Trajectories of Child Psychopathology in High vs Low Parental Psychopathology Sub-Groups

All measures of child psychopathology were stable across age, as indicated by the choice of a constant model order 0, in the mixed model linear regression.

In the 22q11DS sample, children in the high parental psychopathology subgroup presented significantly higher levels of total psychopathology compared to the low parental psychopathology subgroup irrespectively of age, as measured by both the CBCL total score (p=0.0003) and YSR total score (P=0.0007). Such effects were driven by significantly increased levels of both internalizing symptoms (CBCL-internalizing P=0.001, YSR-internalizing P=0.002) and externalizing symptoms (CBCL-externalizing P=0.0008, YSR-externalizing P=0.002) in 22q11DS individuals with high parental psychopathology (see **Figure 1**). As a *post-hoc* analysis, we compared trajectories for individual items of the CBCL-ABCL and YSR-ASR questionnaires. We observed significantly higher scores in the high-parental psychopathology sub-group in most examined items for both YSR-ASR and CBCL-ABCL questionnaires including anxious-depressive score (P-YSR=0.0017, P-CBCL= 0.0012), somatic concerns (P-YSR=0.041, P-CBCL= 0.0011), thought problems (P-YSR=0.0043, P-CBCL= 0.014), rule-breaking behavior (P-YSR=0.0033, P-CBCL= 0.0021), and aggressiveness (P-YSR=0.0007, P-CBCL= 0.0011). Withdrawn symptoms were higher in the high parental psychopathology group only when considering the YSR-ASR (P-YSR=0.01, P-CBCL= 0.187) as were attention problems (P-YSR=0.025, P-CBCL= 0.125). A comparison between the specific effect of maternal vs. paternal psychopathology is described in **Supplementary Analyses B** and **Supplementary Figures S4–S6**.

When examining effects on SIPS sub-scores we did not observe significant differences for SIPS disorganized sub-scale (P=0.11) and only a non-significant trend-level increase in SIPS positive symptom subscale in the high-parental-psychopathology subgroup (P=0.055). However, 22q11DS individuals with high parental psychopathology presented significantly higher levels of SIPS negative symptoms (P=0.03) and SIPS generalized symptoms (P=0.02) compared to the low parental psychopathology sub-group. *Post-hoc* analyses revealed that differences in negative symptoms were driven by more impaired ideational richness (P=0.03) and occupational functioning (P=0.02), whereas differences in the generalized symptoms subscale were driven by more severe dysphoric mood (P=0.006), in the high parental psychopathology sub-group (results for SIPS subscores are presented in **Supplementary Figure S7**).

When dividing HCs according to levels of parental psychopathology we did not observe significant difference in

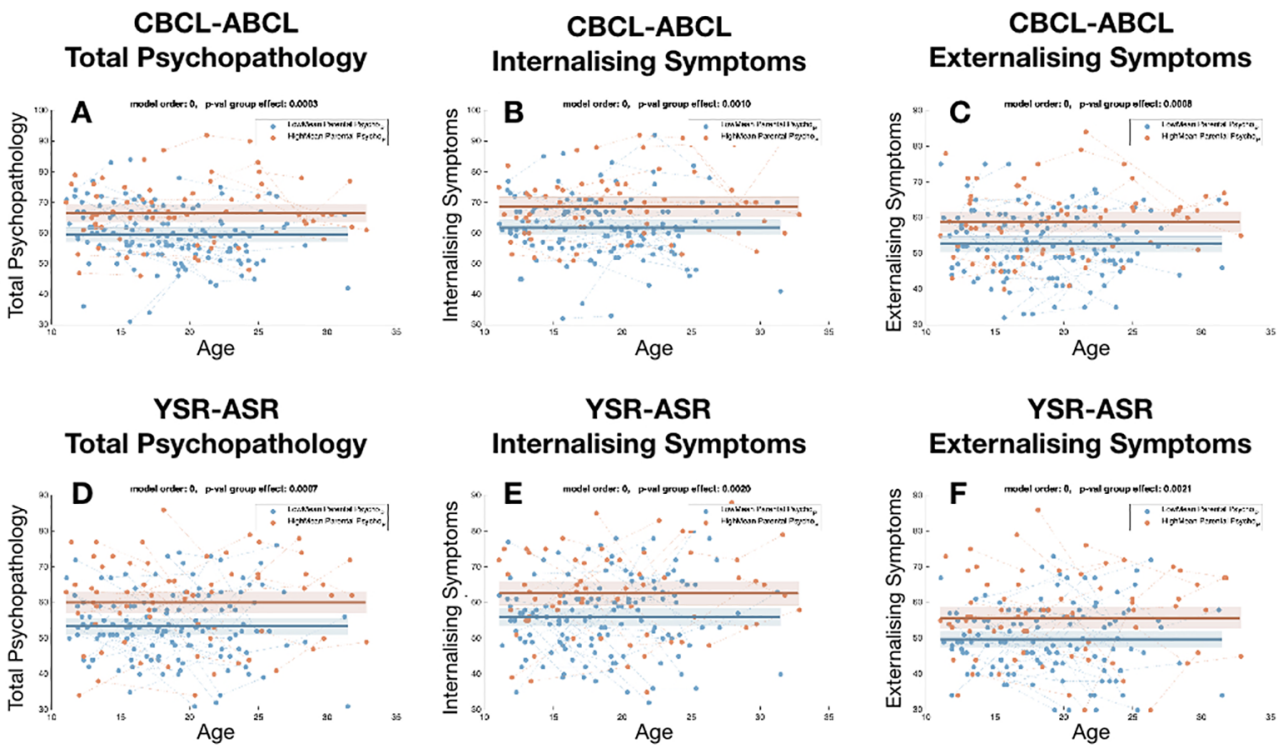

FIGURE 1 | Comparison of the trajectories of child psychopathology across sub-group of 22q11DS individuals, divided according to levels of parental psychopathology. **(A)** Total psychopathology score for CBCL-ABCL. **(B)** Internalizing symptom score for CBCL/ABCL, **(C)** Externalizing symptom score for CBCL/ABCL. **(D)** Total psychopathology score for YSR-ASR. **(E)** Internalizing symptom score for YSR-ASR, **(F)** Externalizing symptom score for YSR-ASR.

levels overall child psychopathology as estimated by both CBCL total score (P=0.144) and YSR total score (P=0.9). Difference were similarly not significant for externalizing symptoms (CBCL-externalizing P=0.19, YSR-externalizing P=0.96). We only observed significantly higher levels of CBCL internalizing scores in HCs with high parental psychopathology (P=0.01) that was however not replicated for YSR internalizing score (P=0.65) (see **Figure 2**).

A summary of the comparisons between subgroups of individuals with 22q11DS and HCs divided according to levels of parental psychopathology can be found in the **Supplementary Table S1**.

Comparison of the Association of Child and Parental Psychopathology Across 22q11DS and HCs

In accordance with previous results in 22q11DS we observed a significant linear association between mean measures of child and parental psychopathology for both CBCL-total-score (R=0.36, p=0.0002) and YSR total score (R=0.31, p=0.001). Correlations between child and parental psychopathology were not significant in HCs for CBCL-total-score (R=0.2, p=0.06) or YSR-total-score (R=0.04, P=0.65) (see **Figure 3**).

A direct comparison of association strength across samples revealed that the CBCL-total score correlation with parental psychopathology was not significantly different across sample (R=0.36 in 22q11DS vs R=0.2 in HCs, P=0.11). However in 22q11DS, we observed a significantly stronger association between parental psychopathology and child YSR-total score compared to HCs (R= 0.36 vs R=0.04, P=0.02) (see **Figure 3**).

Longitudinal Bi-Directional Associations Between Child and Parental Psychopathology in 22q11DS

In 22q11DS we observed a significant association between parental psychopathology at baseline and child YSR psychopathology at follow-up (R-YSR=0.3, P=0.01, R-CBCL=0.35, P=0.003). On the other hand, child psychopathology at baseline did not significantly predict parental psychopathology at follow-up (R-YSR=0.11, P=0.37, R-CBCL=0.21, P=0.09) (see **Figure 4**). However, when we computed partial correlations considering the effects of homologous correlation between Child-baseline to child follow-up and parent-baseline to parent-follow-up, parent-child longitudinal correlations were no longer significant (R-YSR= 0.005, p=0.96, R-CBCL=0.02, P=0.81) (see **Figure 5**).

DISCUSSION

The present study aimed to examine the association between parental levels of anxiety and depression symptoms and

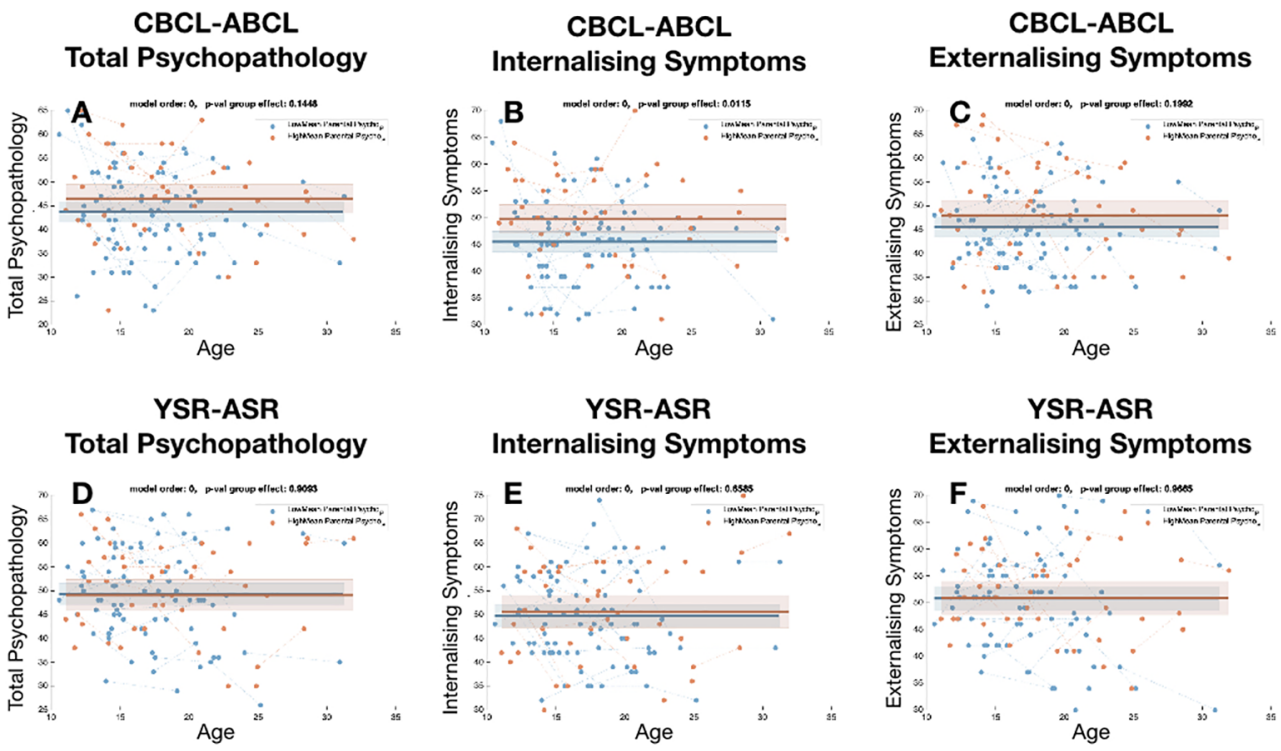

FIGURE 2 | Comparison of the trajectories of child psychopathology across sub-group of healthy controls, divided according to levels of parental psychopathology. **(A)** Total psychopathology score for CBCL-ABCL. **(B)** Internalizing symptom score for CBCL/ABCL, **(C)** Externalizing symptom score for CBCL/ABCL. **(D)** Total psychopathology score for YSR-ASR. **(E)** Internalizing symptom score for YSR-ASR, **(F)** Externalizing symptom score for YSR-ASR.

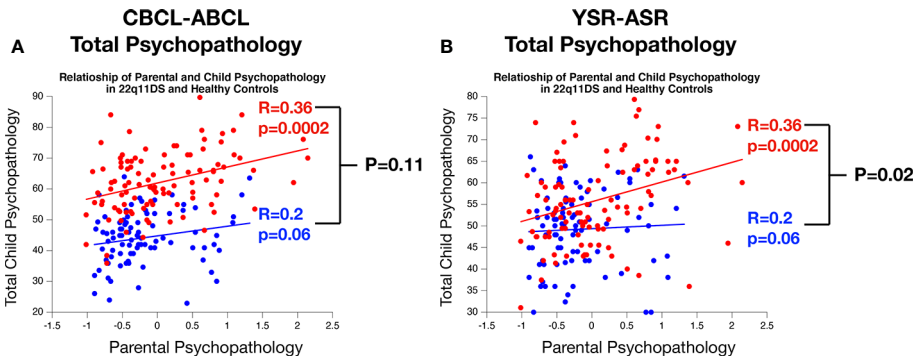

FIGURE 3 | Comparison of the association of parental and child psychopathology in 22q11DS and healthy controls. **(A)** Comparison of the association of parental psychopathology with CBCL-ABCL total psychopathology score. **(B)** Comparison of the association of parental psychopathology with YSR-ASR total psychopathology score.

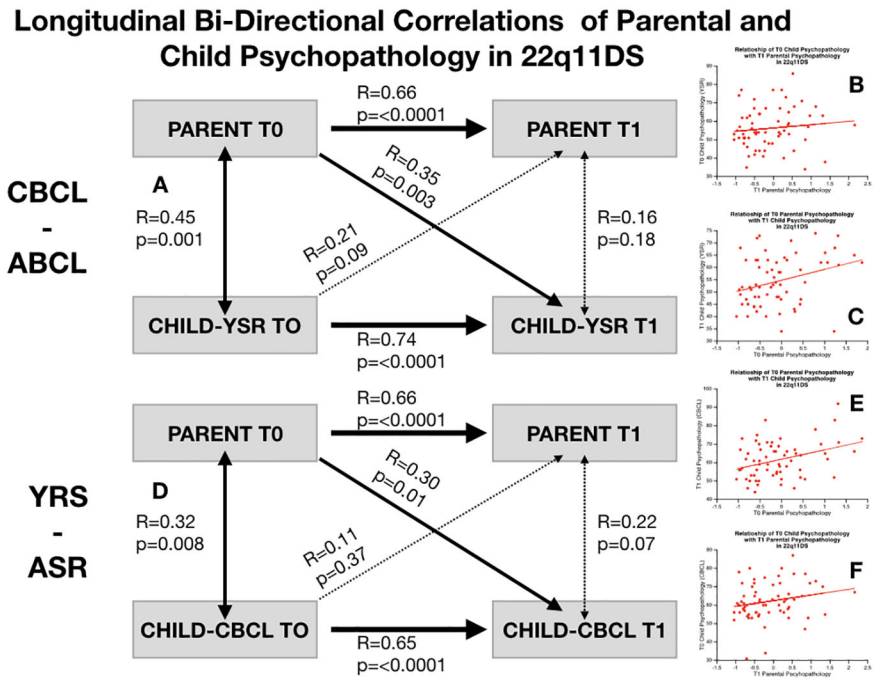

FIGURE 4 | Structure of longitudinal bi-directional correlations of parental and child psychopathology in 22q11DS. **(A)** Structure of longitudinal correlations between parental psychopathology and child CBCL-ABCL total psychopathology score. Bold arrows indicated statistically significant correlations whereas dashed arrows indicate non-statistically significant correlations. **(B)** Correlation of baseline child CBCL-ABCL total psychopathology score with parental psychopathology at follow-up. **(C)** Correlation of parental psychopathology at baseline with child CBCL-ABCL total psychopathology at follow-up. **(D)** Structure of longitudinal correlations between parental psychopathology and child YSR-ASR total psychopathology score. Bold arrows indicated statistically significant correlations whereas dashed arrows indicate non-statistically significant correlations. **(E)** Correlation of baseline child YSR-ASR total psychopathology score with parental psychopathology at follow-up. **(F)** Correlation of parental psychopathology at baseline with child YSR-ASR total psychopathology at follow-up.

psychopathology in their offspring with 22q11DS as well as typically developing controls. Overall, we found significant associations between the two constructs in the 22q11DS group, with parental level of anxiety and depression being related to a widespread increase of psychopathological manifestations measured with both self- and parent-reported questionnaires. Interestingly, associations were significantly stronger in the 22q11DS population compared to the HC group. When

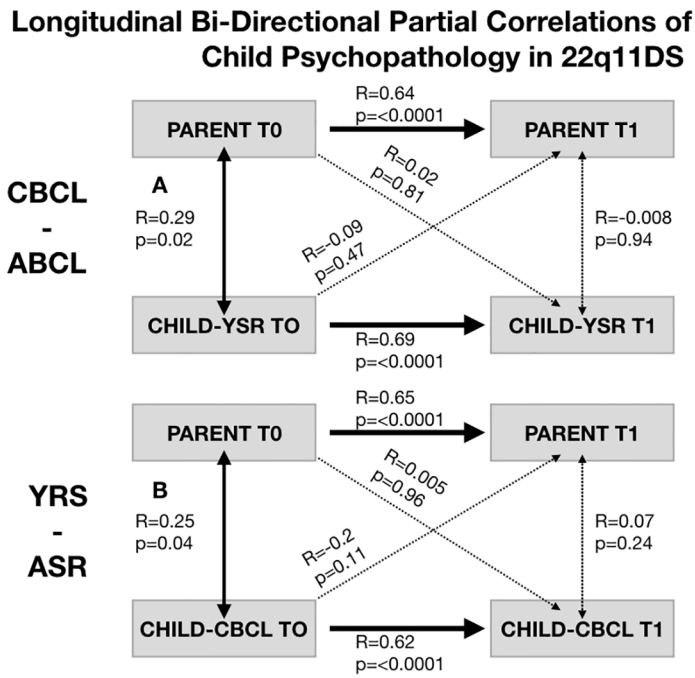

FIGURE 5 | Structure of longitudinal bi-directional partial correlations of parental and child psychopathology in 22q11DS. **(A)** Structure of longitudinal partial correlations between parental psychopathology and child CBCL-ABCL total psychopathology score. Bold arrows indicated statistically significant correlations whereas dashed arrows indicate non-statistically significant correlations. **(B)** Structure of longitudinal partial correlations between parental psychopathology and child YSR-ASR total psychopathology score. Bold arrows indicated statistically significant correlations whereas dashed arrows indicate non-statistically significant correlations.

considering purely longitudinal analyses in the 22q11DS group, we observed a significant association between parental anxiety and depression level at baseline and offspring psychopathology at follow-up, whereas the opposite association was statistically not significant. However, we observed an overall stability of both parental and child psychopathology across longitudinal assessments, leading to strong homologous associations.

The main result of the present study is that higher levels of parental anxious-depressive symptoms are related to the level of psychopathology, specifically in their offspring with 22q11DS. These associations were observed for both internalizing and externalizing dimensions and almost all the CBCL/ABCL and YSR/ASR subscales. That being said, one of the strongest associations was with the anxious-depressed dimension of both the CBCL/ABCL and YSR/ASR. A strength of this study was the simultaneous use of both self- and parent-reported instruments, leading to comparable results. This allows us to discard the fact that those results could be driven by a biased assessment of the offspring's psychopathology by more anxious or depressed parents. Significant associations were also found between parental anxiety and depressive level and the SIPS negative and general dimensions. The results for the SIPS general dimension were mostly driven by an effect of parental anxiety and depression on the offspring's dysphoric mood, which is in line with results obtained with the self- and parent reported questionnaires. Altogether, these results highlight that the strongest associations between parent and offspring with 22q11DS were observed for homologous associations between the affective dimension of psychopathology, similar to what has been described in the general population (15). Decreased occupational functioning (SIPS N6) and impaired ideational richness (SIPS N5) mostly accounted for the results for the SIPS negative dimension. In a previous study by our group (30), those two items were found to load on a different dimension compared to the remaining SIPS negative items, suggesting that they rather reflect aspects of the 22q11DS clinical phenotype that are less directly related to psychosis. On the other hand, "core" negative symptoms of psychosis were found to be not significantly related to parental anxiety and depression. In line with this observation, we found only trend-level associations with the SIPS positive dimension and no effect with the disorganized dimension. This suggests that there is no direct link between parental anxiety and depression and psychosis in 22q11DS.

Several complementary interpretations can be put forth to account for these associations. An important aspect pertains to the directionality of the association. In the present study, we exploited the longitudinal nature of the data to attempt to

address this question of directionality. Overall, we detected a strong stability of both parental and child psychopathology across time and observed that cross sectional correlations of parental and child psychopathology were significantly stronger than longitudinal ones. These results might suggest the existence of bi-directional influences occurring in a short time frame. Indeed, this is highly likely that the long interval between baseline and follow-up assessments (i.e. 3.5 years) did not allow to fully grasp the directionality of complex and dynamic interactions between child and parent psychopathology. Still, we found that parental level of anxiety and depression at baseline predicted offspring psychopathology at follow-up but that the reverse direction was not significant. While such longitudinal correlations were no longer significant after accounting for baseline child psychopathology, these results provide some provisional evidence for a higher sensibility of offspring with 22q11DS to parental psychopathology rather than an opposite parental sensibility to the level of their offspring psychopathology.

In the general population, a large body of literature shows that specific characteristics of the family environment can act either as resilience or risk factors in vulnerable populations. In particular, research indicates that parental anxiety or depression increase the risk of psychopathology in the offspring through complex genetic and environmental mechanisms [for a review, see (15)]. Notably, classical heritability studies show that genetic factors play a significant role regarding the transmission of psychopathology across generations (16). These results have been confirmed using modern Genome Wide Association Studies (GWAS) approaches demonstrating the role of polygenic heritability mechanisms, which have been operationalized by, for instance, polygenic risk scores for depression (31). On the other hand, the role of environmental factors have also been highlighted, notably the fact that parental depression or anxiety places children at increased risk of being exposed to stressful events (e.g. parental conflict), as well as negative cognitions, behaviors, and affects (17). In this regard, probably the most interesting finding from the present study is that the strength of the association between parental anxiety and depression level and offspring psychopathology was significantly stronger in the 22q11DS group compared to typically developing controls. Indeed, this provides at least provisional evidence for the existence of GxG and/or GxE interactions contributing to the emergence of psychopathology in individuals with 22q11DS. As pertains to GxG interactions, recent studies have shown that genetic variants outside of the 22q11.2 locus can significantly modulate the risk for schizophrenia in this population (6). Our results potentially suggest that similar mechanisms could occur for other dimensions of psychopathology. This hypothesis could be explicitly tested using polygenic risk score approaches for affective disturbances. Regarding GxE interactions, recent evidence in 22q11DS has suggested that at least part of the genetic vulnerability to psychopathology—including both psychotic and non-psychotic manifestations—may be mediated by increased vulnerability environmental factors, such as exposure to stressful life events (9).

As mentioned previously, we found no direct link between parental anxiety and depression and psychosis in the sample of participants with 22q11DS, but broad effects on several forms of non-psychotic symptomatology spreading across both internalizing and externalizing dimensions. Recent findings in individuals at clinical high-risk for psychosis (without 22q11DS) have recognized the high prevalence of non-psychotic manifestations, including notably anxiety and depression (32). It is becoming increasingly clear that especially in the early phases, such non-specific manifestation play a role in the pathway toward psychosis and, in general, more severe functional impairments (33). These observations have been conceptualized as either evidence for the existence of common etiology mechanisms shared across all forms of psychopathology (34) or the evidence of the causal role of affective disturbances in the pathway toward psychosis (35). In line with this, the presence of an anxiety disorder has been shown as a significant risk factor for the emergence of psychotic disorders in 22q11DS (36). Altogether, our findings suggest that parental anxiety and depression could be an important upstream variable in the cascade toward more severe forms of psychopathology in this genetically vulnerable group, through a broad increase of non-psychotic manifestations.

From a clinical point of view, these results highlight several considerations. Firstly, it highlights the fact that the conceptualization of psychopathology in 22q11DS should be understood through an integrative approach that also takes the level of parental psychological well-being into account. Indeed, our findings could suggest that despite a strong genetic predisposition, vulnerability to psychopathology in 22q11DS can still be modulated protective environmental factors such as parental well-being. Critically, this implies that parents should not be left alone with the psychological burden of raising a child with 22q11DS. At the practical level, it suggests a rationale for a systematic assessment of parental well-being in the context of 22q11DS. This could be operationalized as a two-step assessment, including a systematic screening and a more in-depth investigation with parents for whom concerns were raised. The management of parental well-being should begin in the very first stages, notably in the communication of the 22q11DS diagnosis. Indeed, several studies have highlighted a more negative diagnosis experience in families of patients with 22q11DS compared to other genetic conditions (37), which could eventually lead to increased stress and the development of (subthreshold) anxiety and depression. In case of concerns regarding parental well-being, a staged approach could be envisioned, starting from family psycho-education about 22q11DS, to practical measures aimed at alleviating parental burden, and extending to family psychotherapeutic interventions.

The present study should be interpreted in light of the following limitations. Firstly, the assessment of parental symptoms only consisted of self-reported measures and focused only on anxiety and depressive symptoms. Secondly, whereas the longitudinal nature of the study can be considered as a strength, the time interval between the two visits was too long to fully address the issue of directionality of the effects between

parental and offspring's symptoms. This could be better addressed in future studies using repeated measures occurring at high temporal resolution, for example through the implementation of experience sampling methodology (ESM) protocols. Finally, the design of the study did not allow to disentangle the role of genetic vs. environmental mechanisms linking levels of psychopathology across generations.

CONCLUSION

In conclusion, we found significant associations between parental levels of anxiety and depression and level of psychopathology in offspring with 22q11DS. This highlights that the conceptualization of psychopathology in 22q11DS should be understood through an integrative approach that also takes the level of parental psychological well-being into account.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Geneva Ethic Committee. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

MA and SE have designed the study and written the manuscript. CS and MS have conducted the statistical analysis and written the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.00646/full#supplementary-material

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Comparing Models of the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS) in an Italian Clinical Sample

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Background: Obsessive-Compulsive Disorder (OCD) is a mental disorder that interferes with daily functioning and may arise during childhood. The current study is the first attempt by Italian researchers to validate the Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS).

Aims: The study's primary aim was to investigate the best CY-BOCS model fit, adopting a Bayesian model comparison strategy, among four different factor models: a one-factor model; a two-factor model based on Obsessions and Compulsions; Storch et al.'s and Mc Kay et al.'s two-factor model based on Disturbance and Severity. The study also aimed to investigate the types of treatments found in a sample of Italian OCD children patients.

Methods: The study sample was made up of 53 children with OCD and 14 children with Tourette Syndrome and TIC.

Results: An analysis of our data demonstrated that the Obsessions and Compulsions model was the most plausible one, as it demonstrated the best fit indices, strong convergent validity, and good reliability. The study results additionally uncovered that 24.5% of the children in the OCD sample had not yet begun any treatment pathway a year after a diagnosis was formulated.

Conclusions: These findings suggest that the Obsessions and Compulsions scales of the CY-BOCS separately represent appropriate instruments to evaluate children with OCD.

Keywords: Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS), Obsessive-Compulsive Disorder, Tourette Syndrome, TIC Disorder, Bayesian model comparison

BACKGROUND

Prevalence and Phenomenology

The estimated lifetime prevalence of Obsessive-Compulsive Disorder (OCD) ranges between 2 and 4% (1–3). On average, symptoms of OCD present at 19.5 years of age (between 10 and 40); in males, the onset is generally before the age of 10, while in females it is during or after adolescence (usually between 20 and 25) (4, 5).

The estimated prevalence of OCD in childhood and adolescence is 0.25%–4%, with those aged between 16 and 18 years old (1%) showing the highest prevalence. The disorder is frequently characterized by gradual onset, a chronic course, and exacerbation of symptoms over a long period of time (the average length of time is 8.9 years over a lifetime) (5–7). Most juvenile OCD patients show a progressive age-related worsening of symptoms, and poor school performance seems to be associated with symptom severity (8). According to several studies, juvenile OCD seems to be mainly characterized by compulsions alone (4, 9, 10) and may be difficult to differentiate from tic-like behaviors.

Garcia etal. (11) more recently reported that 96% of an OCD juvenile patient sample had a mean of four concomitant compulsions, 75% had two concomitant obsessions, and 18% reported having compulsions without obsessions.

Moreover, several researchers put in evidence that juvenile OCD is left unrecognized or untreated and, for this reason, it is characterized by an insidious and progressive course; it can severely disrupt global functioning, negatively affect the lives of patients and their families, and persist in the course of later childhood, adolescence, and adulthood (i.e., 12–15).

Comorbidity

OCD in childhood is frequently associated with other psychiatric conditions such as depression and anxiety disorders, attention deficit hyperactivity disorder (ADHD), tic disorder (TIC), and autism spectrum disorder (in 77-85% of cases), and that can further exacerbate the patient's condition. Some studies have uncovered overlapping comorbidities such as TIC and Tourette Syndrome (TS), which are found in 9-59% of individuals with OCD (16). The presence of OCD has, in turn, frequently been observed in children who have been diagnosed with TIC. One study, in fact, reported that more than 50% of children with TIC also manifested OCD symptoms (17). Bloch etal. (18) pointed out that in approximately 30–50% of the sample of children with TS, it was in comorbidity with OCD. The best estimate of the prevalence of TD in school-age children is approximately 3–8/1000 (19). Boys seem to be more likely than girls to manifest TIC, with a gender ratio ranging between 2:1 and 4:1. The prevalence of TS seems to decrease when children/adolescents grow older, with the highest prevalence found in 7–10-year-olds (20). OCD symptoms associated with TIC generally present at a pre-pubertal age and may predate the onset of TIC (21).

The Psychometric Properties of the CY-BOCS

Several studies have highlighted the importance of investigating childhood-onset OCD, as it represents a serious mental health problem often associated with other conditions that may have important implications for patients' current and future health and quality of life. The Children's Yale-Brown Obsessive-Compulsive Scale (CY-BOCS; 22, 23) is currently the instrument of choice to assess the presence and severity of OCD symptoms in children/adolescents and to monitor treatment. To our knowledge, no attempt has been made to validate the Italian version of the scale. The CY-BOCS is a semi-structured interview made up of 10 items rated on a 5-point Likert scale evaluating the severity of Obsessions and Compulsions across five dimensions, Frequency, Interference, Distress, Resistance, and Control, during the previous week and up to the time of interview. A score above 16 is generally considered indicative of the presence of OCD (16-23 = moderate severity; 24-40 = severe).

The CY-BOCS is similar to the adult version (Y-BOCS), and numerous studies suggest that both can be explained by a two-factor model: Obsessions and Compulsions. In contrast, the validity of a three-factor model (the Obsessions and Compulsions scores and the total severity score) has not been confirmed (24–27).

Other studies have found evidence confirming the validity of a two-factor model based on a Disturbance factor and a Severity factor in an adult (24, 27, 28) and juvenile population (29, 30). Using Confirmatory Factor Analysis (CFA), McKay etal. (29) examined a Severity factor related to general impairment and reflected in Distress, Interference, and Frequency symptoms; the Disturbance factor was linked to the Resistance and Controlling symptoms of both Obsessions and Compulsions. These results were partially replicated by Storch etal. (31), who examined the same two-factor model, the only difference being that the symptom frequency items were loaded onto the Severity factor rather than on the Disturbance one.

In light of conflicting results and in view of the importance of an appropriate assessment of the disorder in juvenile populations, the current study's primary aim was to use a Bayesian model comparison strategy to compare three two-factor models and one single-factor model to determine the best model fit for the CY-BOCS in a sample of Italian children/adolescents diagnosed with OCD.

The single-factor model consisted of only one factor that included all the symptoms related to Obsessions and Compulsions. The second consisted of a two-factor model examining Obsessions and Compulsions. The other two two-factor models were both based on Severity and Disturbance; they differed only with regard to the frequency variable, as in one model, it was loaded onto the Severity factor, while in the other, it was loaded onto the Disturbance one.

Given the shortage of studies examining this disorder in Italian children/adolescents, the study also focused on collecting information regarding the severity of disability and the kind of treatment that is provided in different Italian public health facilities.

METHODS

Participants

The study sample was made up of 67 children/adolescent outpatients/inpatients recruited at different public health facilities located in Northern (n=40), Southern (n=12), and

Central (n=15) Italian towns/cities between 2014 and 2017. All of the children/adolescents were evaluated by Pediatric Neuro-Psychiatrist specialists who formulated their diagnoses on the basis of the patient's score on the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5; 19). Out of the 67-patient population enrolled in the study, 53 were diagnosed with OCD (79.1%), 11 were diagnosed with TS (16.4%), and 3 were diagnosed with TIC (4.5%).

The OCD Group

The OCD study group was made up of 33 boys (62.3%) and 20 girls (37.7%) (mean age = 12.9 years; SD = 3.3 years, range = 6 to 18 years). On average, they were 11.4 years old (SD = 3.1 years, range = 4 to 16 years) when OCD was diagnosed, and they were first evaluated approximately 1.5 years after the first symptoms of the disorder presented (SD = 1.5 years, range = 0 to 6 years).

Comorbid conditions, principally TIC, ADHD/Attentive Disorder, Learning Disabilities, and Anxiety/Emotional Disorder, were present in 52.8% of the sample. Moreover, 15.1% had at least one family member who had been diagnosed with OCD, TIC, or TS. Out of the total patient group being examined, 60.3% were undergoing treatment (26.4% pharmacological treatment, 7.5% psychological treatment, 26.4% both). Out of the total group, 50.9% had never been hospitalized for the disorder, and 24.5% were receiving some type of psychological treatment. As far as school was concerned, 9.5% were receiving some type of educational support, and 3.8% had already left school. Overall, the average number of years of schooling in this group was 7.2 years (DS: 3.5; range: 0 to 13 years).

The Tourette Syndrome and TIC Disorder Group

The second study group was made up of 8 boys (73%) and 3 girls (27%) who were diagnosed with TS and 2 boys (67%) and 1 girl (33%) who were diagnosed with TIC. The mean ages in the TS and TIC subgroups were, respectively, 10.4 years (SD = 2.3, range = 8 to 16 years) and 9 years (SD = 2, range = 7 to 11 years). On average, they were 6.6 years old (SD= 1.5, range=4 to 9 years) when they were diagnosed. The TS patients were evaluated approximately 3.7 years after the first symptoms presented (SD = 2.9 years; range = 1 to 10 years), and the TIC patients were first evaluated less than a year after the first symptoms presented. Comorbid conditions, for the most part, OCD/obsessive-compulsive traits, ADHD, separation anxiety disorder, and generalized anxiety disorder/depressive traits, were present in 82% of the TS patients and in all of the TIC patients.

As far as the TS subgroup was concerned, 55% had a family history of OCD (18%), TIC, or TS (36%). Twenty-seven percent were undergoing treatment (9% pharmacological treatment, 9% psychological treatment, and 9% both). None of the patients in this group had ever been hospitalized for the disorder. Two of the TIC patients had a family history respectively of OCD and TS; none were undergoing treatment, and none had ever been hospitalized for the disorder. As far as school was concerned, one patient was receiving special education assistance. Overall, the average number of years of schooling was 4.2 years (SD: 2.3 years; range: 2 to 10 years) in the TS subgroup and 3 years (SD: 2 years; range: 1 to 5 years) in the TIC subgroup. The participants' demographic data are outlined in **Table 1**.

PROCEDURES

During the first phase of the study, three specialized psychologists were trained in administering the CY-BOCS. The training sessions were audio-recorded and evaluated by the first author of the present study. The assessment phase was carried out at the different mental health facilities respectively located in the north, center, and south of Italy. All the outpatients and inpatients were diagnosed by specialized Pediatric Neuropsychiatrists in those facilities using the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5).

TABLE 1 | Demographic characteristics of the patients studied.

	OCD group N=53	Tourette Syndrome & TIC group N=14
Gender		
(% of male)	33 (62.3%)	10 (71.4%)
Age		
M (SD)	12.9 (3.3) min. = 6; max. = 18	10.1 (2.3) min. = 7; max. = 16
Years of schooling		
M (SD)	7.2 (3.5) min. = 0; max. = 13	3.9 (2.2) min. = 1; max. = 10
Students		
Student	46 (86.8%)	13 (92.9%)
Student with scholastic support	3 (5.7%) 2 (3.8%)	1 (7.1%) 0%
Special course	2 (3.8%)	0%
School drop-out		
Age at diagnosis		
M (SD)	11.4 (3.1) min. = 4; max. = 16	7.1 (1.8) min. = 4; max. = 11
Comorbidity		
(%)	28 (52.8%)	12 (85.7%)
TIC/Tourette	6 (11.3%)	/
Anxiety symptoms	8 (15.1%)	3 (21.4%)
Mood disorder	6 (11.3%)	0
Learning disorder	6 (11.3%)	0
ADHD	2 (3.8%)	4 (28.6%)
OCD traits	/	5 (35.7%)
Familiarity		
(%)	8 (15.1%)	8 (57.1%)
Type of treatment		
Pharmacological treatment (%)	14 (26.4%)	1 (7.1%)
Psychological treatment (%)	4 (7.5%)	1 (7.1%)
Pharmacological and psychological treatment (%)	14 (26.4%)	1 (7.1%)
No treatment after one year from the diagnosis (%)	13 (24.5%)	–
Hospitalized		
(%)	4 (7.5%)	0%
Hospitalized in the past		
(%)	9 (17%)	0%

N, number of group individuals; M, Mean; SD, Standard Deviation; min., Minimum; max., Maximum; OCD, Obsessive-Compulsive Disorder; ADHD, Attention Deficit Hyperactivity Disorder.

The inclusion criterion consisted of a primary diagnosis of OCD and/or TS and/or TIC in a child/adolescent, and all consecutive patients assessed for the first time or during the ongoing monitoring visit were included.

Individuals with neurological disorders or mental retardation based on a previous Pediatric Neuro-Psychiatrist assessment were excluded. Once the patients were identified, they were interviewed individually using the CY-BOCS (or in their parents' presence if they were 7 years old or younger). The interview was carried out by one of the specialized psychologists who was unaware of the patient's diagnoses. The psychologists were simply informed that the patients they would be interviewing could have OCD or/and TIC or/and TS. The interview lasted approximately 40 min.

The Obsessive-Compulsive Inventory-Child Version (OCI-CV) was also administered, with parents if the child was less than 7 years of age.

This study was conducted in accordance with the Declaration of Helsinki and approved by the Ethical Committees of the Department of General Psychology (University of Padova) and all of the mental health facilities participating in the study. All of the children/adolescents participated on an entirely voluntary basis and were enrolled only after their parents had signed consent forms. Their social and demographic information were collected after they were enrolled.

Measures

The *Children's Yale-Brown Obsessive-Compulsive Scale* (22, 23) was the main measure under consideration. Although the original version of the CY-BOCS was translated with the forward translation mode into Italian (32), to our knowledge, to date, no study has investigated its psychometric properties in Italian juvenile patients.

The *Obsessive-Compulsive Inventory-Child Version* (OCI-CV; 33, 34) is a well-established 21-item self-report questionnaire using a three-point Likert scale (ranging from 0 to 2) to assess the frequency of obsessions and compulsions over the previous month. Its six sub-scales concern Doubting/Checking, Obsessing, Hoarding, Washing, Ordering, and Neutralizing. The questionnaire has demonstrated good/modest internal consistency (33, 35). One study by researchers assessing Italian patients reported an excellent/good/acceptable internal consistency both for the inventory's total score and sub-scale scores (34). In our sample of patients, the internal consistency of the total score was found to be good (Cronbach's alpha= 0.84).

The *Child Behavior Checklist 6-18* (CBCL/6-18; 36; Italian version by A. Frigerio - IRCCS EUGENIO MEDEA-LA NOSTRA FAMIGLIA) is a standardized self-report questionnaire used by parents and teachers to screen for psychological problems (emotional and behavioral) and social competencies in children and adolescents. The questionnaire is formed of two sections regarding social competence/adaptive functioning and emotional/behavioral problems. The first section contains 20 items examining social and school activities and specifically the time devoted to sports, games/hobbies, types of activities engaged in, number of friends in general and of close friends, frequency of social interactions, level of self-sufficiency during playtime, problems at school, and academic performance. The second section, termed the "syndrome scale," includes 113 items and uses a three-point Likert scale. The items are grouped into eight categories: anxious/depressed, withdrawn/depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior. Many studies have demonstrated a high rate of reliability between the CBCL scales and the psychological diagnoses formulated (37). The instrument is known to have a good test-retest reliability (ranging from 0.82 to 0.90) and internal consistency (Cronbach's alphas ranged from 0.72 to 0.97). It also has strong criterion-related validity (36).

STATISTICAL ANALYSIS

The Bayesian approach, which presents many practical advantages (e.g., 38–44), was used to analyze our data. A Bayesian model, in fact, provides an adaptive tool that is useful for handling small sample size by including prior information (45). Moreover, it provides a direct representation of the most credible values of the estimated parameter (44, 46) All analyses were performed using R statistical software (47). Each model was fitted using the Bayesian Markov Chain Monte Carlo (MCMC) estimation method implemented in the Just another Gibbs sampler (JAGS) package (48) coupled with the R statistical packages blavaan (49) and runjags (50).

Posterior distributions for each parameter were estimated using four MCMC chains, each running at least for 5000 replicates. MCMC convergence was assessed by calculating the potential scale reduction factor (PSRF) (also called Rhat; 51), which compares the ratio of the average variance of samples within each chain with the variance of the pooled samples across the chains; if all of the chains are at equilibrium, these will be the same, and $\hat{R}$ will be one.

We adopted a model comparison strategy (52) in order to identify the best model by considering the following fit indices: the Bayesian Comparative Fit Index (BCFI), the Bayesian Tucker-Lewis Fit Index (BTLFI), the Bayesian Root Mean Square Error of Approximation (BRMSEA) (53), the Standardized Root Mean Square Residual (SRMR; 54), the Bayes Factor (BF), the Widely-Applicable Information Criterion (WAIC; 55), and the Akaike Weights (AW) (56–58). For each fit index and estimated parameter, we computed the mean of the posterior distributions as the estimate and the 90% credibility interval (also called Highest Posterior Density Interval; HPDI; 58–60).

We adopted the following priors for model parameters: 1) $\nu \sim$ Normal(0, 31.6), for intercepts; 2) $\lambda \sim$ Normal(0.5, 0.58), for factor loadings; 3) $\theta \sim$ Gamma(1, 0.5), for residual variances; 4) $\phi \sim$ Beta(1, 1), for factor correlations. As suggested by Muthén and Asparouhov (45), we included informative small-variance priors for the cross-loadings, $\lambda c \sim$ Normal(0, 0.32). In addition, we considered paired items by including residual covariance with prior distribution Beta(1, 1). The following models were considered: 1) a one-factor model; 2) a two-factor model (Obsessions and Compulsions); 3) Storch etal.'s (30) two-factor model; 4) McKay et al.'s (29) two-factor model (**Figure 1**). We

also used Cronbach alpha and Pearson's r for correlational analysis to assess reliability and construct validity, respectively.

RESULTS

Comparing the CY-BOCS Scale With the Four Factor Models

The Bayesian Comparative Fit Index (BCFI; with 90% hpdi), the Bayesian Tucker-Lewis Index (BTLI, with 90% hpdi), the Bayesian Root Mean Square Error of Approximation (BRMSEA, with 90% hpdi), the Standardized Root Mean Square Residual (SRMR, with 90% hpdi), the Bayes Factor (log) (evidence regarding the worst model, in this case, the one-factor one), the Widely Applicable Information Criterion (WAIC), and the Akaike weight (56–58) were used as fit indices to examine the models. The BCFI, BTLI, and BRMSEA can range between 0 and 1, and values close to 1 on the BCFI and BTLI and close to 0 on the BRMSEA and SRMR indicate a good fit. The BF, which is the likelihood ratio of the marginal likelihood for two competing models, can be interpreted as the relative evidence or plausibility of one model with respect to another. The WAIC is a generalized version of the Akaike Information Criterion (AIC); the smaller the value, the better the model fits the data. Finally, the Akaike Weights represent an estimate of the probability that the model will make the best prediction on new data conditional on the set of models considered (56–58).

The fit indices of the models considered are outlined in **Table 2**. The single-factor model was found to have the worst fit, as it had a BF and an Akaike Weight equal to 0. The model formed by the Obsessions and Compulsions scales was found to be the most plausible, as it had a BF equal to 22.42 and an Akaike weight equal to 0.92. Besides presenting inferior fits in all the indices considered with respect to the Obsessions and Compulsions model, the other two competing models had nearly equivalent BF values (9.86 and 9.99 respectively) and predictions of new

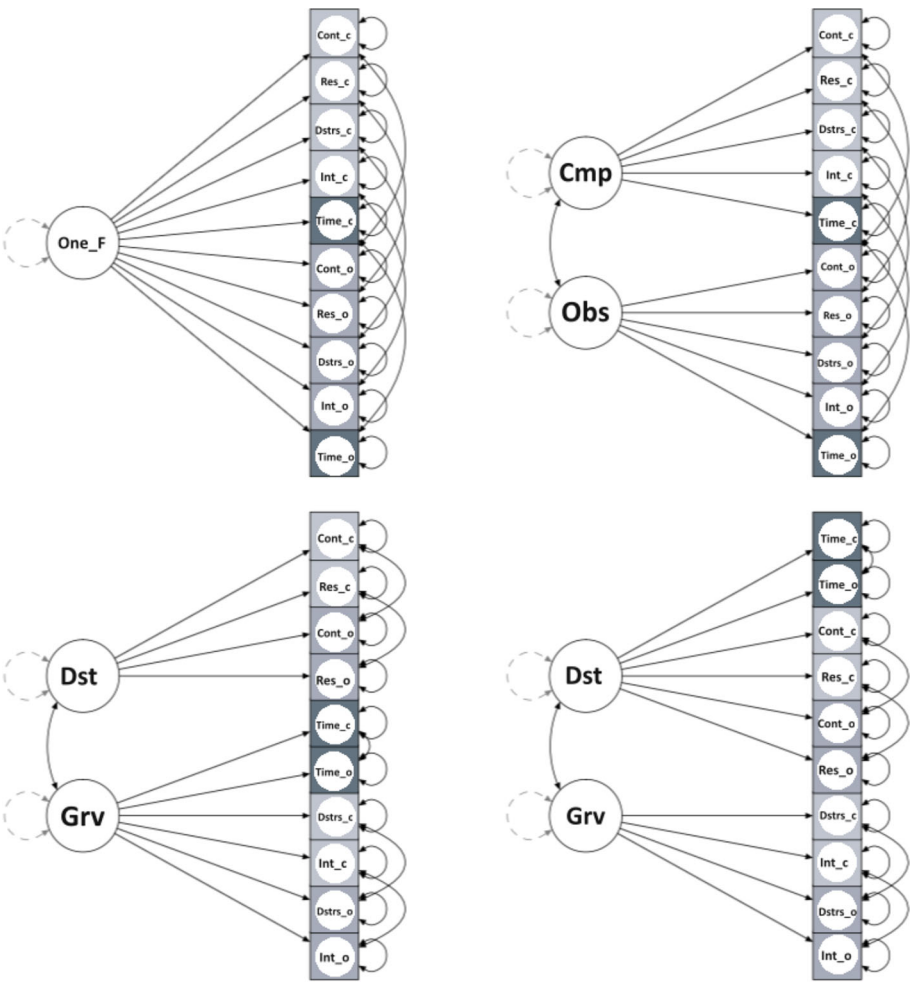

FIGURE 1 | One_F, One-Factor; Cmp, Compulsions; Obs, Obsessions; Dst, Disturbance; Grv, Gravity; Cont_c, Control_compulsions; Cont_o, Control_obsessions; Res_c, Resistance_compulsions; Res_o, Resistance_obsessions; Dstrs_c, Distress_compulsions; Dstrs_o, Distress_obsessions; Int_c, Interference_compulsions; Int_o, Interference_obsessions; Time_c, Time occupied_compulsions; Time_o, Time occupied_obsessions.

TABLE 2 | Comparison of the fit indices of the models considered.

	npar	CC	BCFI	BCFI.hpd	BTLI	BTLI.hpd	BRMSEA	BRMSEA.hpd	SRMR	SRMR.hpd	BF	waic	se_waic	weight
Model 1 one factor	35	100	0,73	(0.54; 0.9)	0,55	(0.24; 0.83)	0,16	(0.11; 0.21)	0,26	(0.25; 0.27)	0	1485,60	(43.9)	0,00
Model 2 Obs & cmp	46	100	**0,98**	(0.92; 1)	**1,13**	(0.76; 1.52)	**0,02**	(0; 0.1)	**0,13**	(0.1; 0.16)	**22,42**	**1437,60**	(38.5)	0,92
Model 3 Storch et al	46	100	0,97	(0.88; 1)	1,04	(0.65; 1.43)	0,04	(0; 0.12)	0,14	(0.11; 0.17)	9,86	1443,63	(40.6)	0,05
Model 4 McKay et al	46	100	0,96	(0.87; 1)	1,04	(0.62; 1.45)	0,04	(0; 0.13)	0,14	(0.11; 0.17)	9,99	1444,37	(40.7)	0,03

Fit indices of the models considered (20000 mcmc posterior samples); NPAR, number of parameters; CC, Convergence criterion (a value less than 100 means that the model does not converge); BCFI, Bayesian Comparative Fit Index (with 90% hpdi); BTLI, Bayesian Tucker-Lewis Index (with 90% hpdi); BRMSEA, Bayesian Root Mean Square Error of Approximation (with 90% hpdi); SRMR, Standardized Root Mean Square Residual (with 90% hpdi); BF, (log) Bayes Factor (evidence with respect to the worst model, in this case, the one-factor model); WAIC, Widely Applicable Information Criterion; WEIGHT, Akaike weight; Obs&Cmp, Obsessions and Compulsions (52, 56, 58).
Bold text highlights the best fit indices.

data (Akaike Weights 0.05 and 0.03). The Obsessions and Compulsions model can be considered 20.42 (0.92/0.05) times more plausible than Storch et al.'s model and 29.57 (0.92/0.03) times more likely to be correct than McKay's model.

Table 3 outlines the estimated factor loadings for the Obsessions and Compulsions model. Every item is grouped in the corresponding scale. Loadings related to the Obsessions were all greater than or equal to 0.70; the loadings related to the Compulsions were all greater than or equal to 0.60. The cross-loadings were proximal to zero, and since the Highest Posterior Density Intervals (HPDs) of all the cross-loadings included zero, we can consider them irrelevant. We can assume, therefore, that they were more likely 95% of the time.

Discriminant Power, the Intercorrelation Between Scales, and Construct Validity

The scores on the CY-BOCS and the patients' diagnoses were compared. The scale's Sensitivity (Se; the proportion of true positives) and Specificity (Sp; the proportion of true negatives) was established by comparing the diagnoses formulated by the Pediatric Neuro-Psychiatrists with the scores on the CY-BOCS (using 16 as the cut-off score). The analysis revealed that it had a high Sensitivity (Se = 0.75) and Specificity (Sp = 1) for OCD.

The internal consistency indices uncovered a good internal consistency for both the Obsessions (α=0.81) and Compulsions scales (α=0.80).

TABLE 3 | The estimated factor loadings for the Obsessions and Compulsions model.

	OBSESSIONS	COMPULSIONS
OBSESSIONS_TIME OCCUPIED	**0,70** (0.45; 0.92)	-0,03 (-0.3; 0.26)
OBSESSIONS_INTERFERENCE	**0,80** (0.5; 1.1)	0,26 (-0.05; 0.57)
OBSESSIONS_DISTRESS	**0,85** (0.6; 1.13)	0 (-0.31; 0.3)
OBSESSIONS_RESISTANCE	**0,70** (0.4; 0.99)	-0,22 (-0.5; 0.08)
OBSESSIONS_CONTROL	**0,83** (0.54; 1.11)	-0,08 (-0.39; 0.23)
COMPULSIONS_TIME OCCUPIED	0,18 (-0.08; 0.44)	**0,60** (0.38; 0.83)
COMPULSIONS_INTERFERENCE	0,17 (-0.11; 0.47)	**0,65** (0.37; 0.9)
COMPULSIONS_DISTRESS	0,06 (-0.26; 0.37)	**0,75** (0.5; 0.99)
COMPULSIONS_RESISTANCE	-0,14 (-0.47; 0.21)	**0,87** (0.57; 1.15)
COMPULSIONS_CONTROL	-0,19 (-0.5; 0.1)	**0,75** (0.52; 0.99)

The best indices are marked in bold. The Highest posterior density interval (HPD) cross-loading parameters for the model are indicated in brackets.

Generally speaking, the correlations between the CY-BOCS subscales were very low (-0.25 < r < 0.22), except for the correlations between the Obsessions and Compulsions items connected to Time (r=0.41; p<0.01), those connected to Interference (r=0.41; p<0.01), and the Interference of the Obsessions item both with the Distress for Compulsions item (r=0.30; p<0.05) and the Compulsions Total score (r=0.33; p<0.05). The correlation between the total scores of the Obsessions and Compulsions scales was also very low (r=0.15; p>0.05) (**Table 4**).

As far as the convergent validity between the CY-BOCS and the OCI-CV was concerned, our analysis showed that both the Obsessions and Compulsions scales of the CY-BOCS were positively correlated with the OCI-CV (r=0.55 and r=0.49, respectively; p<0.01). The Obsessions scale of the CY-BOCS was negatively correlated with the activities scale and the total competence score of the CBCL (respectively, r=-0.29 and r=0.34; p<0.05). Finally, only the Obsessions scale of the CY-BOCS was positively correlated with the total syndrome rating score of the CBCL (r=0.30; p<0.05) (**Table 5**).

DISCUSSION

To our knowledge, this is the first study so far aiming to examine the CY-BOCS best model through the Bayesian approach considering an Italian sample.

Three two-factor models were examined. One was the Obsessions and Compulsions factor model (29) and the other two were the Disturbance and Severity factor models; in the first case, symptom frequency was loaded onto the Disturbance factor (29), and in the other, it was loaded onto the Severity factor (30). We also examined a highly debated single-factor solution that includes all obsessive and compulsive symptomatology (24–27). The Bayesian approach was used in view of its many advantages, including that of allowing the researcher to reach a better prospective likelihood of fit and to study and compare models even in small samples of patients. As far as our juvenile OCD group was concerned, our analyses showed that the two-factor model representing Obsessions and Compulsions was the best factorial structure of the CY-BOCS; the other three models examined showed inadequate fit.

These findings, which further confirmed the validity of the two-factor solution proposed by McKay et al. (29), have relevant

TABLE 4 | Intercorrelations of the CY BOCS sub-scales in the OCD sample studied (N=53).

CY-BOCS	Comp_1 *Time occupied*	Comp_2 *Interference*	Comp_3 *Distress*	Comp_4 *Resistance*	Comp_5 *Control*	Comp *Total*
Obs_1 *Time occupied*	**0.41****	0.12	-0.002	-0.09	-0.12	0.13
Obs_2 *Interference*	0.22	**0.41****	**0.30***	0.13	-0.01	**0.33***
Obs_3 *Distress*	0.13	0.15	0.15	-0.15	-0.16	0.08
Obs_4 *Resistance*	0.12	-0.02	-0.22	0.03	-0.25	-0.04
Obs_5 *Control*	0.16	0.06	0.03	-0.13	-0.01	0.08
Obs *Total*	**0.27***	0.19	0.07	-0.05	-0.14	0.15

CY-BOCS, Children's Yale-Brown Obsessive-Compulsive Scale; Obs, Obsessions; Comp, Compulsions.
Bold text refers to significative correlations at 0.05 or 0.001.

TABLE 5 | Correlations between the CY-BOCS and the OCI-CV and the CBCL in the OCD sample studied (N=53).

	OCI-CV *Total score*	CBCL *Activity*	CBCL *Social*	CBCL *School*	CBCL *School*	CBCL *Competence Total score*
CY-BOCS *Obs*	**0.55****	**-0.29***	-0.23	-0.27	-0.27	**-0.34***
CY-BOCS *Comp*	**0.49****	-0.04	-0.25	-0.07	-0.07	-0.17

CY-BOCS Obs, Children's Yale-Brown Obsessive-Compulsive Scale - Obsessions scale; CY-BOCS Comp, Children's Yale-Brown Obsessive-Compulsive Scale - Compulsions scale; OCI-CV, Obsessive-Compulsive Inventory-Children Version; CBCL, Child Behavior Checklist.
Bold text refers to significative correlations at 0.05 or 0.001.

implications for understanding the disorder, i.e., that Obsessions and Compulsions should be assessed separately. In fact, data analysis showed that a single-factor solution is unsuitable and that using it exclusively could lead to misinterpretation of the severity of the disorder. Not only that, but using it alone in a treatment context could lead to mistakes in interpreting intervention-related changes. Examining the two faces of the disorder separately would seem then to be a better approach to evaluating juvenile OCD.

These results are in line with one retrospective study (4) showing higher scores on the Compulsions scale of the Y-BOCS in those patients presenting an early-onset form of the disorder. They are also consistent with the findings of some studies showing that there tends to be a prevalence of Compulsions in these patients that often precedes the onset of Obsessions. In fact, some have reported that juvenile OCD cases are characterized by an onset of compulsive behavior alone (without obsessions) that may be indistinguishable from TIC (9, 10, 61–63).

As far as validity was concerned, the internal consistency of the CY-BOCS Obsessions and Compulsions scales was high, but in contrast to other studies in which the intercorrelations with the total score were high for both the Obsessions (0.77) and Compulsions (0.82) scales (64), in our sample, it was only moderate, especially for the Obsessions factor (r=0.47 for Obsessions; r=0.72 for Compulsions). Moreover, the intercorrelation between the Obsessive and Compulsive scales was very low (r ranging from -0.22 to 0.41), and only the time spent in compulsions was found to be correlated with the total score of the Obsessions scale (r=0.27). Likewise, the intercorrelation between the Obsessions and Compulsions scales was very low (r=0.15). However, the methodology used here did not enable us to make comparisons with other studies as far as construct validity was concerned: for example, Freeman etal. (64) found an internal consistency of 0.71 for Compulsions and only of 0.64 for Obsessions, while Storch etal. (30) found a moderate relation between Obsessions and Compulsions (r=0.49). Collectively, these findings show that the Obsessions and the Compulsions scales separately provide a clinically useful, reliable, and valid assessment of OCD severity in young children, suggesting that the two factors are distinct OCD constructs. This type of structure is useful to identify the frequent situations in children where obsessions are absent or there is no awareness of their presence. Assessing obsessions and compulsions together would result in an underestimation of OCD diagnosis, which could also lead to a lower probability of access to treatment for those children who would need it. Therefore, this factorial solution, instead, might include data regarding the presence of distinct factors at an early age and could allow early access to treatments, thus interfering with the characteristic tendency for it to become a chronic disorder (i.e., 12–15).

We cannot, however, entirely exclude the possibility that the immaturity of some of the children examined did not allow them access to the cognitive constructs linked to obsessions when, instead, the problem of compulsive behaviors was more evident to them and to others. Future studies with larger numbers of younger children over a wide age range will be able to clarify this point.

The study findings also showed that the Obsessions and Compulsions scales have a good convergent validity with the OCI-CV and confirm its usefulness.

Furthermore, the Obsessions and Compulsions scales were found to be negatively correlated with what parents said about their children's competencies, as evaluated using the CBCL. In

this case, the correlation with the Obsessions factor (r=-0.34) was stronger than that with the Compulsions one (r=-0.17). This was an unexpected result, as parents generally tend to be quite aware of the children's difficulties. We could postulate that the parents' evaluation could be mainly focalized on the cognitive resources indispensable for academic performance and that are affected by Obsessions.

As far as the sensitivity and specificity of the CY-BOCS were concerned, our findings show that they can be considered excellent. In the future, it would be interesting to investigate whether other (separate) cut-offs could be more useful in assessing the disorder's severity and monitoring treatment.

Approximately 24.5% of the children in our sample attending the different mental health facilities participating in our study were not receiving any treatment a year after the diagnosis was formulated, and 26% were receiving only pharmacological treatment. Regardless of the reasons for this choice, treatment guidelines such as the National Institute for Clinical Excellence (65) recommend Cognitive Behavioral Therapy (CBT) for young people with OCD as the first line of treatment even if they have other comorbidities. Again, as far as the children studied here were concerned, 13.2% had left school or was struggling academically and requiring the assistance of a special needs teacher during classes. We are convinced that early assessment and appropriate intervention could lower that percentage (66) and, more importantly, could have a significant impact on the quality of life of the children and their families.

LIMITS

These findings should be considered in light of the study's limitations. First of all, as mentioned above and despite the presence of a parent during the interview, the youngest children participating in our study may not have been able to identify the cognitive aspects linked to obsessions. Moreover, our sample could be biased as we are not aware of how many individuals have refused to participate or have been excluded from the study based on exclusion criteria (e.g., due to having a neurological disorder).

In addition, as the results regarding the scales' sensitivity and specificity are based on the data of a small subgroup of children in the TIC/TS group, the study findings should be interpreted cautiously, and further studies with larger samples are indeed warranted. Future studies could investigate temporal reliability, as it has not been assessed; these data would have important implications in the construct stability, considering this age range. Moreover, we would like to point out that more than half of the children in our sample had comorbidity with another diagnosis and, of 28 individuals (52.8%), 6 (11.3%) had a secondary diagnosis of TIC/Tourette Syndrome disorders. Therefore, it is not possible to exclude that the greater representativeness of the Compulsion aspect with respect to the Obsession one could be partially explained by tic-like behaviors, which often overlap with Compulsions. Finally, although the facilities participating in the study were distributed throughout the country, the sample cannot be considered representative of the Italian population since the sampling was on a voluntary basis. For all of these reasons, future studies are warranted.

CONCLUSIONS

Our analyses showed that the best factorial structure of the CY-BOCS is a two-factor model representing Obsessions and Compulsions and suggest that the two scales of the CY-BOCS separately represent appropriate instruments for evaluating and monitoring the management of children with OCD. In any case, to better support the results of the present research, future studies should focus on a larger sample of children with OCD and without overlapping comorbidities.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by approved by the Ethical Committees of the Department of General Psychology of the University of Padova and of all of the mental health facilities participating in the study. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

CN conceived and planned the study. SP and FC contributed to sample preparation. MP contributed to the analysis of the data. All authors provided critical feedback and helped shape the research, analysis and manuscript.

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Trapped in a Glass Bell Jar: Neural Correlates of Depersonalization and Derealization in Subjects at Clinical High-Risk of Psychosis and Depersonalization–Derealization Disorder

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Background: Depersonalization (DP) and derealization (DR) are symptoms of a disruption of perceptual integration leading to an altered quality of subjective experiences such as feelings of unreality and detachment from the self (DP) or the surroundings (DR). Both DP and DR often occur in concert with other symptoms, for example in subjects at clinical high-risk (CHR) for psychosis, but also appear isolated in the form of DP/DR disorder. Despite evidence that DP/DR causes immense distress, little is known about their neurobiological underpinnings. Therefore, we investigated the neural correlates of DP/DR using pseudo-continuous arterial spin labeling MRI.

Methods: We evaluated the frequency of DP/DR symptoms in a clinical sample (N = 217) of help-seeking individuals from the Early Detection and Intervention Centre for Mental Crisis (CHR, n = 97; clinical controls (CC), n = 91; and first-episode psychosis (FEP), n = 29). Further, in a subsample of those CHR subjects who underwent MRI, we investigated the resting-state regional cerebral blood flow (rCBF). Here, individuals with (n = 21) and without (n = 23) DP/DR were contrasted. Finally, rCBF was measured in a small independent second sample of patients with DP/DR disorder (n = 6) and healthy controls (HC, n = 6).

Results: In the complete clinical sample, significantly higher frequency of DP/DR was found in CHR compared to CC (50.5 *vs.* 16.5%; $\chi^2_{(2)} = 24.218$, $p \leq 0.001$, Cramer's V = 0.359) as well as in FEP compared to CC (37.9 *vs.* 16.5%; $\chi^2_{(2)} = 5.960$, $p = 0.015$,

Cramer's V = 0.223). In MRI, significantly lower rCBF was detected in the left orbitofrontal cortex in CHR with *vs.* without DP/DR (x/y/z = −16/42/−22, $p < 0.05$, FWE corrected). In patients with DP/DR disorder, significantly higher rCBF was detected in the left caudate nucleus (x/y/z = −18/−32/18, $p < 0.05$) compared to HC.

Conclusions: This study shows that DP/DR symptoms are frequently found in CHR subjects. Investigating two separate DP/DR populations with an identical neuroimaging technique, our study also indicates that there may be divergent pathophysiological mechanisms—decreased neuronal activity in the orbitofrontal cortex, but increased activity within the caudate nucleus—leading to a final common pathway with similar psychopathological symptoms. This suggests that both top-down (orbitofrontal cortex) and bottom-up (caudate nucleus) mechanisms could contribute to the emergence of DP/DR.

Keywords: clinical high risk for psychosis, depersonalization, derealization, arterial spin labeling, magnetic resonance imaging, orbitofrontal cortex, caudate nucleus

INTRODUCTION

Altered subjective experiences such as feelings of unreality and detachment from the self or the surroundings are defined as depersonalization (DP) and derealization (DR). Individuals may feel detached from the whole self or from aspects of the self, including feelings, thoughts, body parts or sensations, and from individuals, objects, or all surroundings, often described as being in a fog, dream or bubble, being numb, or as if they are under a glass bell (1–4). DP/DR is a 'physiological' perceptual reaction and psychological phenomenon, especially occurring when stressed, but also when traumatized, very tired, anxious, or intoxicated, however, with sustained insight into the subjective nature of the symptoms. In most cases, these DP/DR experiences are transient, but in some cases, DP/DR may take a chronic course, persisting for days, weeks, or months, with episodic or permanent symptoms. Individuals with DP/DR frequently worry about their mental state and are frightened of becoming crazy or losing their mind (1, 5). DP/DR disorder is characterized by a persistent or recurrent experience of unreality and detachment from oneself or the surrounding, while reality testing remains intact. It is a primary mental health disorder and occurs in the absence or only secondary development of other mental disorders. Symptoms result in significant distress or impairment in functioning (5, 6).

Common age of onset is adolescence, with earlier onset associated with higher severity and poorer prognosis (3, 7). In a systematic review, a prevalence rate of 1.2–2.4% was found for clinically significant DP/DR symptoms in the community and 30–82% in clinical samples (1). DP/DR disorder is often seen in clinical conditions as comorbidity, especially in psychoses (1, 8, 9), depression and anxiety disorders (7), and also after cannabis abuse (10).

Depending on the setting, a review reported DP/DR symptom rates from 7% in outpatients to 36% in inpatients with manifest psychosis (1). Patients with manifest psychosis had higher DP/DR scores according to the 'Cambridge Depersonalization Scale' (CDS) (11) compared to first-degree relatives and healthy controls (12). Furthermore, patients with manifest psychosis were assessed for DP with the 'Bonn Scale for the Assessment of Basic Symptoms' (13) and could be differentiated from those without DP with the paradigm of Basic Symptoms (14). Basic symptoms are subtle, subclinical, self-experienced disturbances in drive, stress tolerance, affect, thinking, speech, perception and motor action. They are experienced with full insight into their abnormal nature. Basic symptoms can be present before, during, and after psychotic episodes (15). Additionally, DP/DR was found to be more frequent, had a longer duration and was stronger in the early, compared to the chronic stages, of psychosis (8). Furthermore, DP/DR symptoms were also reported to occur in ultra-high risk (UHR) subjects for psychosis (16, 17).

The majority of first-episode psychotic disorders are preceded by a prodromal phase in which a multitude of CHR symptoms (including DP/DR), other mental health problems, and psychosocial deficits occur, and during which help may be sought (18–20). This phase offers an excellent starting point for an indicated prevention that aims at reducing CHR symptoms and, thereby, preventing transition to frank psychosis (19). Currently, two major sets of CHR criteria are used to detect a putatively psychosis-prodromal phase: (i) symptomatic ultra-high risk (UHR) criteria, *i.e.*, attenuated (APS) or brief intermittent psychotic symptoms (BIPS); and (ii) basic symptom criteria, *i.e.*, Cognitive Disturbances (COGDIS) and Cognitive-Perceptive Basic Symptoms (COPER) (18, 20).

As DP/DR experiences can occur on a continuum from transient symptoms to chronic ones (1), the question arises whether the symptoms are caused by similar or distinct pathophysiological mechanisms in different clinical groups/diagnoses. Previous studies suggest that different systems such as the fronto-limbic and the temporo-parietal network are responsible for different DP/DR symptoms (21). The theory of the fronto-limbic system proposes that the frontal cortex activity is increased while the limbic system is inhibited (*e.g.* amygdala) causing a reduction of emotional responses (*e.g.* numbing, perceptual detachment) (22), whereas the temporo-parietal system could lead to the emergence of feelings of disembodiment and lack of agency seen in DP/DR patients (21). Different studies confirmed the involvement of both

systems with DP/DR across diverse examination methods such as whole brain magnetic resonance imaging (MRI), fractional anisotropy, and positron emission tomography (23–26).

Further, symptom improvement of DP/DR showed altered insula, visual cortex, and cerebellum activation (27). Treatment of DP/DR with repetitive transcranial magnetic stimulation in patients with DP/DR disorder showed that inhibition applied to the ventrolateral prefrontal cortex and temporo-parietal junction leads to symptom reductions in DP/DR, indicating that both systems have associations with DP/DR (28, 29). Besides the fronto-limbic and the temporo-parietal system, the striatum was also linked to DP/DR (30). These findings, together with the findings of decreased gray matter in the right caudate, right thalamus, and right cuneus as well as of gray matter increases in the left dorsomedial prefrontal cortex and right somatosensory region (23), and alterations in white matter in the left caudate nucleus, the right amygdala and brainstem (24) point towards dysfunctions in different systems.

Taken together, DP/DR symptoms might be linked to brain regions involving the frontal-limbic and temporo-parietal network as well as the striatum (2, 4, 21, 30, 31). For a better understanding of the neuronal mechanisms underlying DP/DR, we used resting state cerebral blood flow (rCBF), a proxy for localized neuronal activity that can be measured with arterial spin labeling (ASL)-MRI (32–34). ASL-MRI measures perfusion using magnetically labeled arterial blood as a tracer. Thereby, ASL-MRI provides a quantifiable measure of regional cerebral blood flow (in ml/min/100 g brain tissue) reflecting the level of glucose metabolism which is associated with neuronal activity of the respective cerebral area (34, 35). We have previously used ASL to successfully capture specific psychopathological symptoms (36–40).

Our aim was to evaluate the frequency of DP/DR symptoms in CHR subjects in a first step and—in a second step—to investigate the neuronal correlates of DP/DR symptoms using the same neuroimaging method in two different clinical samples. First, we assessed the frequency of DP/DR in help-seeking subjects at an early detection service. Second, we assessed rCBF with ASL-MRI in CHR subjects with and without DP/DR symptoms (sample 1). Third, we compared rCBF of a small sample fulfilling criteria for DP/DR disorder with healthy controls (sample 2). We expected to find a high frequency of DP/DR symptoms in CHR and, associated with DP/DR, rCBF alterations in frontal, temporal, or striatal areas in both samples.

MATERIALS AND METHODS

Sample and Assessments

Two independent samples were assessed for this study. The first sample (sample 1) was recruited at the Bern Early Recognition and Intervention Center for Mental Crisis (FETZ Bern; www.upd.ch/de/angebot/erwachsenenpsychiatrie/ambulant-fetz.php) between November 2009 and June 2018. Individuals with various psychiatric symptoms were admitted to the FETZ Bern by physicians, psychosocial institutions, or of their own initiative, whenever there was clinical suspicion for a developing psychotic disorder. The second sample (sample 2) was recruited at the University Hospital of Psychiatry and Psychotherapy in Bern between July 2011 and January 2013 and consisted of patients with DP/DR disorder, exclusively, as well as of healthy controls.

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The human research ethics committee of the Canton Bern approved the study (ID PB_2016-01991, KEK-095/10). All participants gave informed consent, and in minors, parental informed consent was provided.

Psychopathology Assessment of Sample 1

Data from 245 subjects who were examined in the FETZ Bern entered the analyses. The FETZ Bern is the only early detection and intervention center for psychosis in the Canton of Bern, Switzerland, with a catchment area of approximately 1.5 million inhabitants, screening ~80 patients/year (aged 8–40 years) according to the European Psychiatric Association (EPA) guidelines (19, 20). The basic assessment includes a psychopathological evaluation, a cognitive test battery, MRI, and blood screening. Individuals were diagnosed as clinical controls (CC), first episode psychosis (FEP), or CHR (41). CHR and related symptoms were assessed by trained psychologists using semi-structured interviews including the 'Schizophrenia Proneness Instruments Child & Youth and Adult' (SPI-CY and SPI-A) to evaluate basic symptoms (42, 43), the 'Structured Interview for Prodromal Syndromes' (SIPS) (44), and the rating from the Comprehensive Assessment of At-Risk Mental States (CAARMS earlier version than 2006) (45) to evaluate UHR and related symptoms.

The SPI-A and later the SPI-CY were developed based on the BSABS. They assess the same concepts and are semi-structured interviews. However, the SPI-CY/SPI-A assesses the symptoms on a quantitative 7-point rating scale, as opposed for the BSABS which rates the symptoms qualitatively for their presence or absence only (13, 46). For more information about the various assessments, we refer to the EPA guidelines (20).

DP/DR symptoms can be assessed either with the SIPS and/or the SPI-CY/SPI-A. The SIPS rates DP/DR items (P1 and N4) in a lifetime; however, we focused on symptoms measured *via* SPIA/SPICY as we aimed to capture present symptoms (symptoms that were present within the last three months). Therefore, DP/DR was assessed within the last three months using operationalized items from the SPI-CY/SPI-A. Derealization (SPI-CY: item B7; SPI-A: item O8) was assessed from age 13 onwards (requires self-reflection and higher metacognitive processes) and is defined as a change in how the person relates emotionally to the world, *i.e.* by an 'as if'-feeling that the world is not real or of oneself being estranged from it while knowing at the same time that it is real, and they are a part of it (see **Supplementary Text S1** for a detailed description). Depersonalization is rated in the SPI-CY from age 13 onwards with the items somatopsychic depersonalization (B8.2), *i.e.*, feeling estranged from one's own body and autopsychic depersonalization (C6), *i.e.*, feeling estranged from one's own actions, feelings or emotions, in any case, while being fully aware that it is them. In the SPI-A, only somatopsychic depersonalization (F6) can be assessed (see **Supplementary Text S1**).

The SPI-CY/SPI-A ranks items on a severity scale according to the maximum frequency of their occurrence within the past three months ranging from '0' (absent = symptom has not occurred in the past 3 months) to '6' (extreme = symptom has occurred daily over sometime within the past 3 months). Symptoms may also be rated as '7' (symptom has always been present in same severity; trait), '8' (symptom is definitively present, but its frequency of occurrence is unknown), and '9' (the presence of the symptom can neither be unambiguously ruled in nor out). To dichotomize subjects into either having DP/DR symptoms or not, subjects scoring in any of the items from 1 to 6 or 8 were rated as having DP/DR, while subjects with no symptoms (0), unclear symptoms (9), or symptoms as traits (7) were considered to have no DP/DR.

Due to five abortions of the clinical assessments, 13 persons being younger than 13 years and 10 missing values for DP/DR due to incomplete interviews, complete behavioral data was accessible from 217 subjects. The CC did not fulfill any CHR criterion nor did they have a history of past or present psychosis, but they were help-seeking individuals fulfilling other psychiatric diagnoses (see **Table 1**). FEP fulfilled a past or present psychosis and CHR subjects did not fulfill a past or present psychosis but the CHR criterion.

Additionally, the Mini-International Neuropsychiatric Interview for adults (MINI) (47) and its version for children (MINI-Kid) (48) were used to assess diagnoses. Psychosocial functioning was evaluated with the 'Social and Occupational Functioning Assessment Scale' (SOFAS) (49).

MRI Sample 1 of CHR Subjects

We further selected all CHR subjects of sample 1 with available ASL-MRI scans and after artifact rejection (n = 2). In total, of 44 (45.3%) participants (MRI scans were not mandatory) out of 97 CHR subjects, ASL data was available. These 44 CHR subjects were analyzed to investigate differences in rCBF comparing CHR subjects with (n = 21, 21.6%) and without (n = 23, 23.7%) DP/DR symptoms.

MRI Sample 2 of DP/DR Disorder Patients and Healthy Controls

From six patients (not being part of the other study) with DP/DR disorder according to ICD-10 (five males) aged between 16 and 34 (24.3 ± 7.9 years) and six healthy subjects (three males; 27.0 ± 1.8 years) ASL-MRI scans were analyzed. To assess DP/DR in patients, the CDS (11) was used in the German version, which was found to be reliable (α = .95) (50). This self-rating questionnaire consists of 29 items assessing characteristics of depersonalization and derealization (11). Five factors could be extracted from the CDS numbing of emotions, altered body perception, feeling unreal, distorted sense of time, and an unreal seeming environment (51). For each DP/DR experience, the duration and frequency during the last six months were assessed by means of a Likert scale. All patients fulfilled the clinical diagnosis of DP/DR disorder according to ICD-10 (F48.1) assessed through trained interviewers and had CDS scores of 70 ± 39 *(Mdn* = 63), indicating mean to high levels of DP/DR symptoms. A convenience sample of six healthy controls did not met the criteria for any ICD-10 diagnosis. As none of this sample had been suspected to develop psychosis and, therefore, referred to the FETZ Bern, this sample was not examined for CHR criteria.

MRI Data Acquisition and Processing

The 3.0-Tesla whole-body Siemens MRI system (Magnetom Verio, Siemens Medical Systems, Erlangen, Germany) produced high-resolution structural MRI scans and ASL data in one single session while the subjects were laying alert but with their eyes closed in the MRI. In addition, T1-weighted 3D modified driven equilibrium Fourier transform (MDEFT) images were generated as templates (number of slices, 176; matrix, 256 × 256; slice thickness, 1 mm; voxel size, 1 × 1 × 1 mm^3) to enable subsequent co-recording of functional data (52). For the pseudo-continuous ASL, interleaved images with and without labeling were obtained in gradient-echo echo-planar imaging sequence (field of view, 220 mm^2; matrix, 64 × 64; flip angle, 25°; tagging duration, 1,600 ms; post-labeling delay, 1,250 ms; TR/TE, 4,000 ms/13 ms; 100 volumes) (32, 33). The entire brain was contained by the fourteen axonal slices (6 mm thickness and 1.5 mm gap), which were positioned alongside the anterior–posterior commissure line. Matlab (MATLAB and Statistics Toolbox 2012a) and Statistical Parametric Mapping (SPM 8; Wellcome Department of Imaging Neuroscience, London) were used for MRI analysis. The calculation of ASL data was conducted using the aslm toolbox for SPM8 (ASL Imaging Toolbox) (53). Data were visually screened for motion (>3 mm in x, z, or z direction or >3° rotation) and scanner artifacts. Voxelwise mean rCBF for each subject was calculated from flow-time series, subtracting labeled and non-labeled images (54). After realignment and co-registration to the gray matter (GM)-segmented T1 images, normalization was conducted using the SPM Montreal Neurologic Institute T1 template. Spatial smoothing was done with an 8-mm full-width at half maximum kernel. Mean rCBF data were finally normalized [z = (voxel rCBF − global GM rCBF)/SD across individual brain voxels] and GM corrected using GM segments as inclusive masks.

Statistical Analyses

Behavioral data were analyzed using SPSS (IBM SPSS Statistics for Windows, released 2016, Version 24.0., IBM Corp., Armonk, NY, United States).

For behavior and sample characteristics, frequencies were compared by chi-square tests and continuous or ordinal data with Kruskal–Wallis H tests. Fisher's exact tests were used when any cells from the chi-square tests contained less than five observations.

For MRI analyses, two-sample t-tests were conducted to compare rCBF between CHR subjects with and without DP/DR (MRI sample 1) and between subjects with DP/DR disorder and healthy controls (MRI sample 2). The results of MRI sample 1 are reported family wise error (FWE), whole brain, corrected at $p < 0.05$. For MRI sample 2, results are reported following small volume correction for the region of interest (ROI: frontal, temporal and/or striatal areas) and with FWE corrected at $p < 0.05$. This less conservative approach was used for MRI sample 2 because of its small sample size.

TABLE 1 | Sociodemographic and clinical characteristics of the complete sample 1 (CHR, FEP, CC).

	Total N = 217		CHR n = 97		FEP n = 29		CC n = 91		Statistical values[a]
Age in years									
mean ± SD	19.2 ± 4.6		18.8 ± 3.9		20.5 ± 6.4		19.2 ± 4.7		H=0.758, p=0.684, df=2, ϵ^2 = 0.004
Median	17.8		17.6		18.5		17.8		
Range	13–40		13–35		13-40		13-37		
SOFAS score									
mean ± SD	61.0 ± 12.0		60.1 ± 11.0		55.1 ± 11.3		63.7 ± 12.7		H=10.841, p=**0.004**, df=2, ϵ^2 = 0.050[b]
Median	61.0		61.0		55.0		65.0		
Range	32–89		35–83		35-75		32-89		
Gender, male (n, %)	126	58.1	52	53.6	16	55.2	58	63.7	$\chi^2_{(2)}$=2.093, p=0.351, V=0.098
Current partnership, yes (n, %)	48	22.1	17	17.5	9	31.0	22	24.2	$\chi^2_{(2)}$=3.384, p=0.184, V=0.131
Nationality, Swiss (n, %)	189	87.1	86	88.7	23	79.3	80	87.9	$\chi^2_{(2)}$=0.099, p=1.000, V=0.011
Highest education (n, %)									$\chi^2_{(4)}$=3.399, p=0.463, V=0.149
ISCED 1 (6 school years)	5	2.3	1	1.0	0	0.0	4	4.4	
ISCED 2 (9–10 school years)	138	63.6	62	63.9	22	75.9	54	59.3	
ISCED 3 (12–13 school years)	58	26.7	28	28.9	6	20.7	24	26.4	
Currently employed or in training/school (n, %)[c]	185	85.3	84	86.6	22	75.9	79	86.8	$\chi^2_{(2)}$=0.301, p=0.920, V=0.026
Current alcohol misuse, present (n, %)	10	4.6	5	5.2	1	3.4	4	4.4	$\chi^2_{(2)}$=0.197, p=1.000, V=0.012
Current drug misuse, present (n, %)	16	7.4	10	10.3	0	0.0	6	6.6	$\chi^2_{(2)}$= 2.385, p=0.288, V=0.121
Any current ICD-10 diagnosis (n, %)									
Any affective disorder (F30–F39)	74	34.1	44	45.4	8	27.6	22	24.2	$\chi^2_{(2)}$=9.207, p=**0.010**, V=0.220
Any anxiety disorder (F40–F41)	37	17.1	25	25.8	3	10.3	9	9.9	$\chi^2_{(2)}$ =7.449, p=**0.021**, V=0.198
Any eating disorder (F50)	3	1.4	2	2.1	0	0.0	1	1.1	$\chi^2_{(2)}$=0.536, p=1.000, V=0.056
OCD (F42)	12	5.5	5	5.2	1	3.4	6	6.6	$\chi^2_{(2)}$ =0.373, p=0.908, V=0.042
PTBSD (F43.1)	1	0.5	1	1.0	0	0.0	0	0.0	$\chi^2_{(2)}$=1.669, p=1.000, V=0.075
DP/DR disorder (F48.1)	18	8.3	12	12.4	0	0.0	6	6.6	$\chi^2_{(2)}$=4.803, p=0.080, V=0.153
DP/DR symptoms, present (n, %)	75	34.6	49*	50.5	11	37.9	15*	16.5	$\chi^2_{(2)}$=24.212, $p \leq$ **0.001**, V=0.334
DP symptom, present (n, %)	29	13.4	18	21.2	5	19.2	6	6.8	$\chi^2_{(2)}$=8.136, p=**0.016**, V=0.196
DR symptoms, present (n, %)	64	29.5	43*	44.3	10	34.5	11*	12.4	$\chi^2_{(2)}$=23.048, $p \leq$ **0.001**, V=0.327
Psychotic disorders (F20–F29) (n, %)					29	100.0			
Schizophrenia or -like psychotic disorder					16	55.2			
Acute psychotic disorder					4	13.8			
Delusional schizophrenia					2	6.9			
Psychotic disorder unspecified					4	13.8			
Major depression with psychotic symptoms					2	6.9			
Bipolar disorder with psychotic symptoms					1	3.4			
Any CHR criteria									
APS (n, %)			68	70.1					
BLIPS (n, %)			2	2.1					
COPER (n, %)			59	60.8					
COGDIS (n, %)			37	38.1					

CHR, Clinical High Risk; FEP, First Episode Psychosis; CC, Clinical Controls; SOFAS, Social and Occupational Functioning Assessment Scale of DSM-IV; ISCED, International Standard Classification of Education; OCD, Obsessive-compulsive Disorder; PTBSD, Post Traumatic Stress Disorder; DP/DR, Depersonalization/Derealization; UHR, Ultra-High Risk; BS, Basic Symptoms; APS, Attenuated Positive Symptoms according to SIPS, Structured Interview for Psychosis-Risk Syndrome and/or CAARMS, Comprehensive Assessment of At-Risk Mental States; BLIPS, Brief Limited Intermittent Psychotic Symptoms; COPER, Cognitive-Perceptive Basic Symptoms; COGDIS, Cognitive Disturbances

[a]Effect sizes reported as Cramer's V for χ^2-tests and Fisher's exact tests; 0.1 equals a small effect, 0.3 a medium effect and 0.5 a large effect.

[b]FEP vs. CC (z=–3.191, p=0.004, r=0.299, n=114).

[c]Includes sheltered employment, temporary employment, and regular full- and part-time employment (incl. schooling, academic studies, occupational training, full-time house work).

**Standardized cell residuum higher or lower than 1.96.*

Bold means that the results are significant.

RESULTS

Demographics and Psychopathology of Sample 1

The three groups (CHR, FEP, and CC) differed regarding their SOFAS score due to a significantly lower score in FEP compared to CC (see **Table 1**). Further, CHR subjects more often qualified for affective and anxiety disorders and presented more DP/DR symptoms than FEP and CC. There was a significant difference in individuals reporting DP/DR symptoms between CHR and CC (50.5 *vs.* 16.5%; $\chi^2_{(2)} = 24.218$, $p \leq 0.001$, Cramer's V = 0.359) as well as between FEP and CC (37.9 *vs.* 16.5%; $\chi^2_{(2)} = 5.960$, p = 0.015, Cramer's V = 0.223), indicating moderately higher scores in FEP and CHR as compared to CC (see **Table 1**).

Demographics of MRI Sample 1

The CHR subjects with DP/DR symptoms differed regarding age, education, and ICD-10 DP/DR disorder from those without DP/DR symptoms (see **Table 2**).

Demographics of MRI Sample 2

There were no differences in age (H = 0.232, p = 0.630, ϵ^2 = 0.021) nor sex ($\chi^2_{(2)}$ = 1.500, p = 0.545, Cramer's V = 0.354) between the group with DP/DR disorder and healthy controls.

rCBF in MRI Sample 1

A significantly decreased rCBF was found in the left orbitofrontal cortex, Brodmann Area 11, (x/y/z = −16/42/−22, t = 5.3, cluster size = 226, FWE whole brain corrected, p = 0.029) in CHR subjects compared to those without DP/DR symptoms (**Figure 1**).

rCBF in MRI Sample 2

A significantly increased rCBF was discovered in the left caudate nucleus (x/y/z = −18/−32/18, t = 7.6, cluster size = 95) and in the left inferior temporal gyrus (x/y/z = −60/−44/−20, t = 6.7, cluster size = 87) in patients with DP/DR disorder compared to healthy controls. The increase of rCBF in the left caudate nucleus survived FWE (p < 0.05) and small volume correction for the region of interest (**Figure 2**).

DISCUSSION

This study found a high frequency of DP/DR symptoms in CHR subjects (50.5%) and applied ASL-MRI to investigate DP/DR symptoms for the first time. Using an identical neuroimaging approach, the present study investigates resting state neuronal activity in two different clinical samples, one sample of CHR subjects with a known high prevalence of DP/DR symptoms and an independent sample with DP/DR disorder, exclusively. We found two different brain regions involved with symptoms of

TABLE 2 | Sociodemographic and clinical characteristics of clinical high risk (CHR) subjects for psychosis with and without DP/DR with available MRI scans.

	CHR Total N = 44		CHR with DP/DR n = 21		CHR without DP/DR n = 23		Statistical values[a]
Age in years							
mean ± SD	19.8 ± 4.4		20.9 ± 3.9		18.8 ± 4.7		H=4.476, p=**0.034**, df=1, ϵ^2 = 0.104
Median	18.4		21.1		17.4		
Range	13-35		15–26		13–35		
SOFAS score							
mean ± SD	63.1 ± 10.4		64.7 ± 9.9		61.7 ± 10.9		H=0.830, p=0.362, df=1, ϵ^2 = 0.019
Median	65.0		70.0		65.0		
Range	43–82		48–82		43–75		
Gender, male (n, %)	24	54.5	11	52.4	13	56.5	$\chi^2_{(1)}$ =0.076, p=0.783, V=0.042
Current partnership, yes (n, %)	9	20.5	4	19.0	5	21.7	$\chi^2_{(1)}$ =0.212, p=0.719, V=0.072
Nationality, Swiss (n, %)	39	88.6	20	95.2	19	82.6	$\chi^2_{(1)}$=1.738, p=0.348, V=0.199
Highest education (n, %)							$\chi^2_{(2)}$=13.685, $p \leq$ **0.001**, V=0.561
ISCED 1 (6 school years)	1	2.3	0	0.0	1	4.3	
ISCED 2 (9–10 school years)	27	61.4	8	38.1	19	82.6	
ISCED 3 (12–13 school years)	15	34.1	13*	61.9	2*	8.7	
Currently employed or in training/school (n, %)[b]	39	88.6	20	95.2	19	82.6	$\chi^2_{(1)}$=1.738, p=0.348, V=0.199
Current alcohol misuse, present (n, %)	3	6.8	2	9.5	1	4.3	$\chi^2_{(1)}$=0.463, p=0.599, V=0.103
Current drug misuse, present (n, %)	3	6.8	1	4.8	2	8.7	$\chi^2_{(1)}$=0.267, p=1.000, V=0.078
Any current ICD-10 diagnosis (n, %)							
Any affective disorder (F30–F39)	21	47.7	13	61.9	8	34.8	$\chi^2_{(1)}$=2.968 p=0.085, V=0.269
Any anxiety disorder (F40–F41)	10	22.7	4	19.0	6	26.1	$\chi^2_{(1)}$=0.222, p=0.728, V=0.072
Any eating disorder (F50)	0	0.0	0	0.0	0	0.0	
OCD (F42)	1	2.3	0	0.0	1	4.3	$\chi^2_{(1)}$=0.934, p=1.000, V=0.146
PTBSD (F43.1)	0	0.0	0	0.0	0	0.0	
DP/DR disorder (F48.1)	5	11.4	5	23.8	0	0.0	$\chi^2_{(1)}$=6.178, p=**0.019**, V=0.375
DP/DR symptoms, present (n, %)	21	47.7	21	100	0	0.0	
DP symptom, present (n, %)	8	18.2	8	38.1	0	0.0	
DR symptoms, present (n, %)	19	43.2	19	90.5	0	0.0	
Any CHR criteria							
APS syndrome (n, %)	34	77.3	16	76.2	18	78.3	$\chi^2_{(1)}$=0.27, p=1.000, V=0.025
BLIPS syndrome (n, %)	0	0.0	0	0.0	0	0.0	
COPER (n, %)	29	65.9	15	71.4	14	60.9	$\chi^2_{(1)}$=0.545, p=0.460, V=0.111
COGDIS (n, %)	20	45.5	10	47.6	10	43.5	$\chi^2_{(1)}$=0.076, p=0.783, V=0.042

*MRI scans were not mandatory for subjects in the CHR group. The MRI subsample was made out of the whole CHR subject group (see **Table 1**) with available MRI scans.*

MRI, Magnet Resonance Imaging; CHR, Clinical High Risk; DP/DR, Depersonalization/Derealization; SOFAS, Social and Occupational Functioning Assessment Scale of DSM-IV; ISCED, International Standard Classification of Education; OCD, Obsessive-compulsive Disorder; PTBSD, Post Traumatic Stress Disorder; UHR, Ultra-High Risk; BS, Basic Symptoms; APS, Attenuated Positive Symptoms according to SIPS, Structured Interview for Psychosis-Risk Syndrome and/or CAARMS, Comprehensive Assessment of At-Risk Mental States; BLIPS, Brief Limited Intermittent Psychotic Symptoms; COPER, Cognitive-Perceptive Basic Symptoms; COGDIS, Cognitive Disturbances.

[a]*Effect sizes reported as Cramer's V for χ^2-tests and Fisher's exact tests; 0.1 equals a small effect, 0.3 a medium effect and 0.5 a large effect.*

[b]*Includes sheltered employment, temporary employment, and regular full- and part-time employment (incl. schooling, academic studies, occupational training, full-time house work).*

**Standardized cell residuum higher or lower than 1.96.*

Bold means that the results are significant.

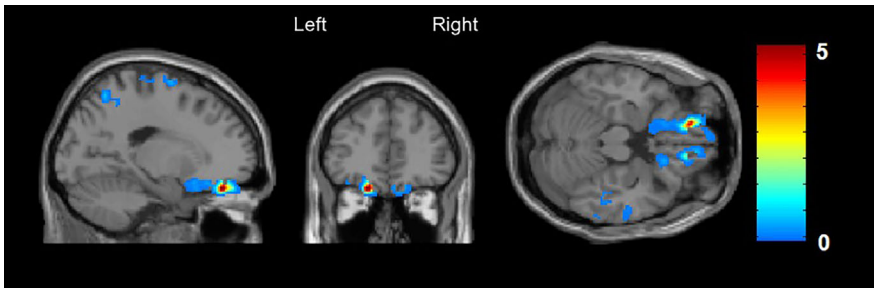

FIGURE 1 | Arterial Spin Labeling analysis for gray matter regional cerebral blood flow (rCBF), whole brain, T-contrast in CHR subjects with (n = 21) *vs.* without (n = 23) DP/DR, uncorrected at $p < 0.001$ (x/y/z = −16/42/−22, t = 5.3). Red areas indicate significantly decreased CBF in the left orbitofrontal cortex in the CHR group with DP/DR.

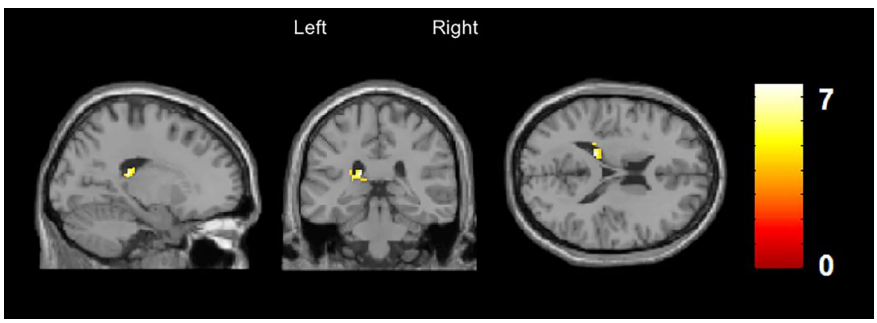

FIGURE 2 | Arterial Spin Labeling Analysis for gray matter regional cerebral blood flow (rCBF), whole brain, T-contrast in DP/DR disorder patients (n = 6) *vs.* healthy controls (n = 6), uncorrected at $p < 0.001$ (x/y/z = −60/−44/−20, t = 6.7). Yellow areas indicate significantly increased CBF in the left caudate nucleus in DP/DR as compared to controls.

DP/DR, namely the orbitofrontal cortex and the caudate nucleus. The left orbitofrontal cortex showed a lower rCBF in CHR subjects with DP/DR symptoms than without, whereas the left caudate nucleus demonstrated a higher rCBF in patients with DP/DR disorder than healthy controls.

The two significant brain regions differ with regard to their structural connections and functions. The orbitofrontal cortex (Brodmann area 11) is heavily connected to the limbic areas, *e.g.* amygdala, hippocampus, and temporal cortex, and the striatum. It receives visual inputs from the temporal cortex and auditory inputs and somatosensory inputs from somatosensory cortical areas and the insula and sends outputs to the temporal cortex, cingulate cortex, and caudate nucleus. The orbitofrontal cortex plays a major role in the computation of expected values and outcome values and their difference and is implicated in positive prediction error signaling *via* dopaminergic neurons in the striatum (55, 56). Other functions of the orbitofrontal cortex are somatosensory integration *e.g.* pleasant/painful touch, visual inputs, *e.g.* face discrimination, reward representation, and cognitive enhancement of the value of affective stimuli (55). Thus, it is important for emotional, perceptional, and cognitive processing-functions that might be disturbed in DP/DR. Moreover, orbitofrontal cortex dysfunction has been implicated in various psychiatric disorders such as borderline personality disorder, posttraumatic stress disorder, major depression, panic disorder or manifest psychosis (57) that can also show DP/DR symptoms (6). Finally, structural and functional findings within the orbitofrontal cortex have been associated with manifest psychosis (58, 59), and psychosis risk findings from the NAPLS study (N = 274 UHR subjects, including 35 converters) indicated that converters experienced a steeper rate of gray matter loss in the medial orbitofrontal cortex (60).

The caudate nucleus is connected with the motoric, sensory, and dorsolateral prefrontal cortex and the lateral orbitofrontal cortex (61, 62). The caudate nucleus is important for the inhibition of motoric impulses and basal learning processes (62) and also for higher cognitive functions including goal-directed actions. It contributes to behavior through the excitation of correct action schemas and the selection of appropriate sub-goals (63) and also to emotions and motivation (64). Dysfunction of the caudate nucleus supported the role as a regulator of fronto-striatal circuits (61) and has been functionally and structurally involved in the pathogenesis of psychosis (65, 66).

Importantly, the orbitofrontal cortex and the caudate nucleus are interconnected and interact with each other through a

cortico-striatal circuitry. Top-down and bottom-up processing has become an influential concept in cognitive neuroscience, signifying a highly interactive information exchange where incoming information in lower level sensory regions (*e.g.* auditory input) is modified by higher level cognitive processes (*e.g.* frontal cortex) and *vice versa* (55, 64, 67, 68). The orbitofrontal cortex is involved in top-down and the caudate nucleus in bottom-up processing (69, 70). In predictive coding, sensory perceptions are combined with prior beliefs, thus depending on the successful interaction of bottom-up and top down processes. Prediction errors are defined as the difference between expectations based on the past and the actual outcome (71–74). In psychosis, defective prediction errors may lead to symptoms such as delusions and hallucinations.

Our data suggest that cerebral areas involved in both bottom up and top down processes can be disturbed and therefore lead to DP/DR symptoms. Dysfunctions of the orbitofrontal cortex could change perception "top down" *via* cognition and faulty error prediction in CHR subjects, whereas dysfunctions within the caudate nucleus could change perception "bottom-up" *via* sensory information in patients with DP/DR disorder.

In particular, the caudate nucleus and also the orbitofrontal cortex have previously shown to play a role in DP/DR symptoms (23, 24, 30, 31). Whole brain MRI analyses of gray matter volume in patients with DP/DR and healthy controls showed a decrease in gray matter in the right caudate nucleus that was associated with DP/DR symptom severity (23). Research investigating white matter brain connectivity, using network-based statistics, found a trend supporting the fronto-limbic hypothesis (24). Lower fractional anisotropy in patients with DP/DR than in healthy controls was found in the left caudate nucleus, brainstem, and right amygdala, whereas higher anisotropy was found in the left superior frontal gyrus and right medial orbitofrontal cortex (24). Importantly, one study reported a hypoperfusion of the orbitofrontal cortex (Brodmann area 11) and the left caudate nucleus in a patient group with DP/DR symptoms compared to healthy controls (31). The theory of the fronto-limbic system assumes that the frontal cortex activity is increased (22), but we found a lower rCBF in the orbitofrontal cortex in subjects with DP/DR symptoms. ASL-MRI has many advantages (75–77); however, the nature of cells (excitatory or inhibitory) that contribute to the signal remains unresolved (78). Therefore, brain regions can increase or decrease according to the major cell types (*e.g.* glutamatergic *vs.* GABAergic) that contribute to the signal.

Finally, a PET study reported decrease [11C]raclopride receptor binding potential in the caudate nucleus and putamen bilaterally followed by an increase in the endogenous dopamine availability simultaneously with the emergence of DP/DR symptoms after intake of psilocybin (30).

Hence, imaging studies examining DP/DR reported findings in the caudate nucleus and the orbitofrontal cortex but also mentioned other brain regions, like the temporo-parietal network or the involvement of the limbic system (21, 28). Our own data did not clearly demonstrate changes in the temporo-parietal network or the limbic system. The lack of the involvement of the temporo-parietal network might be explained by the different symptoms of DP/DR. Feelings of disembodiment and lack of agency are explained by this system (21, 79), whereas emotional numbing and perceptual detachment are explained by the fronto-limbic system. This study did not differentiate the type of DP/DR to test those systems.

Several disorders show symptoms of DP/DR like posttraumatic stress disorder, depression, anxiety (1, 7) but also in psychosis (12, 14) and in our study, in CHR subjects. In patients clinically suspected to develop psychosis, DR as well as both auto- and somatopsychic DP occurred in roughly 16% of cases, but only DR was found to be psychosis-predictive (46, 80). An explanation of the DP/DR symptoms in psychosis is that an impairment of multisensory integration could lead to incoherent self-experiences, which then leads to DP/DR. It is hypothesized that the brain's efforts to fix that perceptual incoherence could result in hallucinations and delusions because the focus lies on the DP/DR and no longer on the real outside world (81); therefore, DP/DR was also considered as a predelusional state (82). Self-disturbances in CHR subjects, such as DP/DR, might be potential markers of psychosis (83–85). Self-disturbances are generally described as anomalies of subjective experiences such as disruption of the stream of consciousness, distortion of sense of presence, corporeality or difficulties in self-demarcation (83). Self-disturbances or self-disorders are conceptualized as a constellation of interrelated anomalies of subjective experience gravitating around pervasive distortions of the "minimal" or "core self" (86). Self-disturbances are usually self-recognized in CHR subjects due to intact self-monitoring, whereas in patients transitioning to psychosis those disturbances are no longer recognized.

Self-disturbances can be measured with the Examination of Anomalous Self-Experience scale (87) or through some of the basic symptoms as they are defined as self-experienced disturbances (15, 86).

DP/DR symptoms were found to be more frequent, had a longer duration, and were stronger in the early stages of psychosis than in the chronic stages. Therefore, it was proposed that the symptoms would predate the onset of psychosis as they were more often in the early stages than in the chronic ones (8). The orbitofrontal cortex and caudate nucleus have also been associated with psychosis (58, 59, 65, 66). Therefore, in future longitudinal studies, the role of DP/DR symptoms and involved brain regions (orbitofrontal cortex and caudate nucleus) with regard to a conversion to psychosis should be investigated. With this, the potential value of DP/DR symptoms as an additional predictor for psychosis in CHR subjects could be further evaluated.

Strengths and Limitations

One strength of this study is the investigation of two different samples with the same method. The first sample with CHR subjects with or without DP/DR symptoms and the second sample with DP/DR disorder and healthy controls. The ASL-MRI signal is directly linked to resting-state rCBF and provides a quantitative and absolute measure of rCBF, reflecting the level of neuronal activity (34, 35) plus providing the potential to measure changes in striatal neuronal activity (88–90).

Despite the strengths of our study, some limitations must be considered. The small sample size with DP/DR disorder is a major limitation. Further studies should involve larger samples to increase the statistical power of the analyses. However, we still wanted to highlight the findings from this small sample as we believe the inclusion of this group is of scientific value. The majority of studies with DP/DR using MRI investigated DP/DR symptoms in disorders such as major depression, posttraumatic stress disorder, drug abuse, or borderline personality disorder, whereas this study investigated pure DP/DR disorder without comorbidities. Pure DP/DR disorder patients without concomitant additional diagnoses are difficult to find and hard to motivate for study participation. With regard to sample size, several published studies are comparable to our study [*e.g.* (27, 91)]. Another limitation is the classification of DP/DR. In sample 1, DP/DR was narrowly assessed in a clinical interview through the SPI-CY/SPI-A and transformed into a binary variable. In the SPI-A the autopsychic DP was not collected, whereas in the SPI-CY it was. That could lead to a small bias of CHR with and without DP/DR symptoms. In sample 2, DP/DR was more broadly assessed, and participants were grouped into DP/DR or healthy controls. Because DP/DR is reported to lie on a continuum, analyses would ideally involve DP/DR on an ordinal scale.

There was no differentiation in symptoms of DP/DR in this study. Despite that they are subsumed as DP/DR, future studies should differentiate the symptoms of DP/DR in different subgroups as this could give more comprehension in the neurobiological correlations and consider the comorbidities and developmental aspects such as age. A further limitation is the direct comparison of the two samples in this study as they were not assessed with the exact same clinical instruments. Future studies should use the same instruments to detect psychiatric disorders and CHR symptoms as well as DP/DR. With the CDS DP/DR could be assessed on a scale and differentiated, and other disorders or CHR symptoms could be used as covariates.

Conclusion

To summarize, DP/DR symptoms are frequent in CHR subjects. Investigating two separate DP/DR populations with an identical neuroimaging technique, we found decreased neuronal activity in the orbitofrontal cortex but increased activity in the caudate nucleus.

As the orbitofrontal cortex is involved with psychiatric disorders that are associated with DP/DR symptoms (1, 7, 57), we conclude that the area is important for the emergence of DP/DR. According to its function in somatosensory integration, it is reasonable that DP/DR can be seen as a failure in somatosensory integration, which could turn into numbing of emotions, altered body perception, feeling unreal, distorted sense of time, or perceiving an unreal environment.

The caudate nucleus as part of the striatum is connected to prefrontal areas (36) and is important for cognitive functions, emotions, and motivation and could play a role in the control function from fronto-limbic system and therefore produce DP/DR symptoms.

Our results indicate that there seem to be divergent mechanisms that finally lead to the same/similar symptoms. This suggests that top-down (orbitofrontal cortex) and bottom-up (caudate nucleus) mechanisms might contribute to a different extent to the emergence of DP/DR, depending on the manifestation/phenomenology of the symptoms.

DATA AVAILABILITY STATEMENT

The datasets generated for this study are available on request to the corresponding author.

ETHICS STATEMENT

All procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2013. The human research ethics committee of the Canton Bern approved the study (ID PB_2016-01991, KEK-095/10). All participants gave written informed consent, and in minors, parental written informed consent was provided to participate in this study.

AUTHOR CONTRIBUTIONS

JB wrote the first draft of the manuscript and did the statistical analysis. CM and JK rewrote sections of the manuscript. AF and MH provided MRI knowledge. SK and BS were responsible for the design of the DP/DR disorder sample. FS-L was leader of the FETZ. FS-L, DH, SW, and MK gave meaningful inputs for the manuscript. All authors contributed to the article and approved the submitted version.

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ORIGINAL RESEARCH
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Association Between Major Depressive Disorder and Sleep Disturbances Through Inflammation in Adolescents

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Background: Although approximately 13% of adolescents suffer from Major Depressive Disorder (MDD), and many adolescents have reported sleep disturbances, the relationship between sleep disturbances and MDD in adolescents is poorly understood. Thus, our objective was to study how adolescent MDD was related to sleep disturbances in a cross-sectional study, and the potential role of inflammation linking adolescent MDD to sleep disturbances.

Methods: Ninety-two female and male, African American and White, adolescents aged 15 to 18 years completed the study. Adolescents were diagnosed with MDD according to the Diagnostic and Statistical Manual of Mental Disorders-5 as confirmed by the MINI International Diagnostic Interview. The severity of depression was assessed using the Quick Inventory of Depressive Symptomatology. Sleep disturbance was measured using the Pediatric Sleep Questionnaires (PSQ). Blood sample was collected from each participant for measuring the inflammatory factors.

Results: Compared with the controls (n=39), adolescents with MDD (n=53) had greater PSQ scores (0.32 ± 0.02 vs. 0.10 ± 0.02). In adolescents with MDD, PSQ scores were correlated with the severity of depressive symptoms (r=0.31, $p<0.05$). In addition, tumor necrosis factor-α levels were greatly elevated in the MDD group (2.4 ± 0.1 vs. 1.8 ± 0.1 pg/ml) compared with the controls. Severity of depressive symptoms was best predicted by PSQ scores, medications, and childhood experiences.

Conclusions: Sleep disturbance measured by the PSQ is associated with severe depressive symptoms in adolescents, and one potential pathway may be through elevated tumor necrosis factor-α. Further research is warranted to probe a cause and effect relationship among sleep disturbances, MDD, and chronic inflammation.

Keywords: adolescents, major depression, sleep disturbance, inflammation, cytokine

INTRODUCTION

Recent data by National Institute of Mental Health suggests that an estimated 3.2 million adolescents aged 12 to 17 years in the U.S. have had at least one major depressive disorder (MDD) episode, which represents 13.3% of the U.S. population aged 12 to 17 years. Studies have shown that adolescent depression increases the risk for subsequent depression and anxiety disorders in adulthood (1). Adolescents with MDD are at much higher risk of poor performance at school, using illicit drugs and alcohol, and bingeing (2). Furthermore, depressed adolescents tend to have suicidal ideation (2). In addition, up to 40% to 70% of children and adolescents with MDD also suffer from other psychiatric disorders, and many youngsters have two or more comorbid diagnoses (3). Although the Treatment for Adolescents with Depression Study, a large multi-site clinical research study funded by the NIMH, showed a response rate of 71% on a combination of fluoxetine and cognitive behavioral therapy after 12 weeks, and even 85% response rate at 18 weeks, treatment resistance to both antidepressants and psychotherapy is high in children and adolescents with MDD (4–6). Besides treatment resistance, adherence to treatment is always challenging. It is reported that about 30% to 50% are non-compliant, resulting in poor prognosis and functioning levels in adolescents (7). Thus, high prevalence of MDD in adolescents, limited response rate and high non-compliance indicate that preventive strategies are warranted.

A meta-analysis of longitudinal studies demonstrated that sleep disturbance is one of the primary risk factor for depression (8). It is well-established that one of the core symptoms in adolescent MDD is sleep disturbances, including daytime sleepiness and insomnia (9). The prevalence of insomnia in adolescents is as high as 23.8% (10). Some studies also suggest a significant relationship between sleep disturbances and completed suicide in adolescents (11). Recent studies focusing on sleep architecture using electroencephalogram in depressed adolescents have yielded heterogeneous results. Some studies found less stage 1 and 2 sleep, more sleep awakenings and a shorter latency to rapid eye movement sleep (12). However, majority of studies show no difference in sleep architecture between depressed and non-depressed adolescents (2). In contrast, electroencephalogram sleep findings are much more consistent among different studies in adult depression (12). Therefore, a good understanding of sleep problems in adolescents with MDD is critical.

Prior studies in adults found that chronic inflammation is associated with MDD, and several studies also reported that inflammatory factors are related to the sleep-wake cycle in humans (13–16). Both interleukin (IL)-1β and tumor necrosis factor-α (TNF) were reported to play an important role in the regulation of sleep (17). Similarly, IL-6 was also found to relate with lower sleep efficiency and daytime napping (18, 19). Thus, inflammatory factors may be a link between MDD and sleep disturbances quality in adolescents.

While sleep problem is a core symptom in adolescents with MDD, more studies are needed to precisely understand the relationship between sleep disturbances and MDD in adolescents. Therefore, the current study was designed to determine the relationship between sleep disturbances and adolescent MDD. A secondary aim was to explore the potential pathway by examining the role of inflammatory factors in the relationship between adolescent MDD and sleep disturbances.

Abbreviations: MDD, major depressive disorder; TNF, tumor necrosis factor; DSM-5, Diagnostic and Statistical Manual of Mental Disorders-5; PSQ, Pediatric Sleep Questionnaire; IL, interleukin; QIDS-A_{17}-SR, Quick Inventory of Depressive Symptoms-Adolescent-Self Report; ANCOVA, analysis of covariance; BMI, body mass index.

METHODS

Participants

This was a cross-sectional study design. All study procedures were reviewed and approved by the University of Alabama at Birmingham (UAB) Institutional Review Board before enrolling the first participant. Participants were recruited through the community, Birmingham, AL, or the UAB outpatient Psychiatric and Pediatric settings. Study flyers were posted in these areas, and families interested in participation called our office, where study staff explained the study and answered questions. Afterward, interested families and adolescents were invited to come to the laboratory for the enrollment. Both guardians and adolescents provided their written informed consent. Participants included males and females, Whites and African Americans, ages 15 to 18 years and were physically healthy or had stable medical conditions (**Table 1**). Of 99 males and females enrolled in the study, 92 participants completed all study procedures for data analysis. Of the 7 subjects that were excluded, 4 were excluded for sleep disorders, substance use, mania or diabetes, and 3 refused the blood draw. None had evidence of systemic inflammatory diseases or were taking medications known to affect immune system or any antibiotics. Participants with a history or a diagnosis of sleep disorders, including sleep apnea, were excluded. Participants were also excluded from the study if they were pregnant or lactating. Demographic data, medical history, medications, and family information were recorded by self-report. After they were

TABLE 1 | Participant characteristics.

	Control	MDD	*p* values
N	39	53	
Gender, female/male, N	22/17	33/20	0.36
Race, C/AA, N	12/26	40/13	0.00
Age, years	16.1 ± 0.16	16.2 ± 0.13	0.58
QIDS scores	4.7 ± 0.5	13.2 ± 0.8	0.00
Body mass index, kg/m^2	23.9 ± 1.0	27.8 ± 1.2	0.02
Family income, K	58 ± 9.4	61 ± 7.2	0.80
Childhood trust events scores	2.9 ± 0.4	7.8 ± 0.6	0.00
Guardian education status, ≥ 12 years, N	31	36	0.41
Smoking status, N	2	7	0.17
Antidepressants, N	1	36	0.00

MDD, major depressive disorder; C, Caucasians; AA, African Americans; QIDS, Quick Inventory of Depressive Symptoms.

consented, Structured Clinical Interview for DSM-5 or the Mini International Neuropsychiatric Interview for children and adolescents V6.0. was used to diagnose MDD, and administered in each participant (20). Participants who met the criteria for MDD were in the MDD group, and participants who did not meet the criteria for MDD were in the non-MDD or control group. Due to safety concern, adolescents endorsed acute suicidal ideation would be referred for further psychiatric assessment, and would not be enrolled.

Measures

Depressive symptoms in each adolescent were measured using the Quick Inventory of Depressive Symptoms-Adolescent-Self Report (QIDS-A_{17}-SR) (21). The scoring system of the QIDS-A_{17}-SR comprises 9 domains of depressive symptoms. Each domain weights 0 to 3 and the total score ranges from 0 to 27.

The Pediatric Sleep Questionnaire (PSQ) was used in the current study because it has been extensively studied and shows adequate psychometric properties (22). Scales for PSQ assess for different sleep disturbances, including sleep-related breathing disorder, snoring, daytime sleepiness, and inattentive/hyperactive behavior, and is composed of 22 items that could be completed by their guardians in about 5 min. The 22 items of the scale are each answered yes=1, no=0, or don't know=missing. The number of items endorsed positively ("yes") is divided by the number of items answered positively and negatively; the denominator therefore excludes items answered as don't know (missing responses). Participants in the current study were required to answer all 22 items. The result is a proportion that ranges from 0.0 to 1.0. Score of PSQ greater than 0.33 is suggestive of a diagnosis of sleep-related disorder.

The Childhood Trust Events Survey is a self-report screening survey to assess a child's exposure to traumatic events (23, 24). It includes 8 categories of adverse events, including physical abuse, emotional abuse, sexual abuse, alcohol exposures, family member in prison, ill caregiver, domestic violence, and loss/separation from caregivers. Each category will receive a score of 1 or 0. If any question in the category is answered yes, then the score for that category will be 1. If all questions in the category are answered no, then the score for that category will be 0. Add all of the numbers in the score column up to receive the total trust events score. Total scores range from 0 to 8, and higher scores reflect less trust.

Blood Collection and Serum Measurement

Participants presented to the laboratory between 8:00 and 10:00 AM, and were not requested to fast before blood collection. Fifteen milliliters of blood were drawn from each participant and centrifuged at 3000*g* for 10 mins. Sera were immediately divided into aliquots, and frozen at −80°C until analysis. The analysis for inflammatory factors, including IL-6, IL-8, IL-10, C-reactive protein (CRP), and TNFα was performed using a Meso Scale Discovery multiplex assay and analyzed with MPSQ Discovery Workbench software (Gaithersburg, MD). Concentrations for IL-6, IL-8, IL-10, and TNFα were expressed in pg/ml, and CRP was expressed in mg/L. All samples were run in duplicate, and the mean of the duplicate samples was reported.

Statistical Analysis

All analyses were completed with SPSS version 25, and p value was set at <0.05 as significant. All variables were tested for normality of distribution by means of Kolmogorov-Smirnoff tests, and would be log-transformed for distribution normality. Data are presented as means ± standard error. Differences between the two groups in variables of interest were compared using Chi-square test for categorical data, including gender, race, smoking status, highest education in guardians, and use of antidepressants and sleeping medications. Independent T-test was used for continuous data, including age, BMI, family income, QIDS scores, childhood trust events scores, PSQ global and subscales scores. Comparisons of PSQ subscales were also conducted after adjusting for race, BMI, antidepressants, and childhood trust events scores. Analysis of covariance (ANCOVA) adjusted for age, race, gender, BMI, childhood trust events scores, and use of antidepressants and sleeping medications was used to determine differences in the inflammatory factors between the two groups. Partial Pearson correlation analysis was used to determine the correlation between sleep disturbances and the severity of depression after controlling for all aforementioned variables in total sample. Mediation analysis was conducted using PROCESS. Stepwise multiple linear regression analysis was used to identify the independent variables that best predicted depression in total sample (n=92). Variables that may contribute to depression were entered into the model, including age, race, gender, PSQ global and subscale scores, BMI, childhood trust events scores, and all measured inflammatory factors.

RESULTS

Participants Characteristics

A summary of the 92 participants is presented in **Table 1**. Participants were stratified into MDD (n=53) and non-MDD (controls, n = 39) groups, and there were no significant differences in age, gender, smoking status in adolescents, family income, and guardian's education status. However, there were more Whites, greater BMI, and childhood trust event scores in the MDD group than in the controls. As expected, depressive scores measured by the QIDS were much greater in the MDD group, and there were 36 adolescents in the MDD group taking antidepressants. Sleep disturbance assessed using the PSQ is reported in **Table 2**. The mean total score on the PSQ was 0.32 ± 0.02 in the MDD group with higher scores

TABLE 2 | Comparisons of sleep disturbances.

	Control	MDD	*p* values
PSQ scores	0.10 ± 0.02	0.32 ± 0.02	0.001
Snoring	0.64 ± 0.22	1.26 ± 0.19	0.479
Sleepiness	0.49 ± 0.13	2.28 ± 0.20	0.000
Inattentive/hyperactive behavior	0.77 ± 0.20	2.30 ± 0.24	0.010
Sleep medication, N	1	6	0.131

MDD, major depressive disorder; PSQ, pediatric sleep questionnaire.

indicating sleep disturbances. Additionally, subscales for PSQ were also compared between the two groups. Adolescents with MDD had greater sleep snoring, sleepiness, and hyperactivities in daytime. After controlling for race, BMI, childhood trust event scores, and antidepressants, sleep snoring was not significant although sleepiness and hyperactivities in daytime remained significant between the groups.

Relationship Between Sleep Disturbances and Depression

After controlling for age, race, gender, BMI, childhood trust events scores, use of antidepressants and sleeping medications, Pearson correlation analysis in 92 adolescents showed a significant relationship between PSQ scores and depressive scores (r=0.31; p=0.006), indicating poor disturbance is related to more severe depression (**Figure 1**). PSQ subscales correlation with depressive scores also showed positive relationships with a greatest relationship between hyperactivities on daytime and depression severity (r=0.31; p=0.005).

Relationships Between Sleep Disturbances, Depression, and Inflammation

ANCOVA adjusting for race, BMI, and childhood trust event scores indicated that adolescent MDD group had significantly elevated TNFα levels compared to the control group (**Figure 2**). However, other measured inflammatory factors did not differ between the 2 groups. Pearson correlation analysis after adjusting for race, BMI, and childhood trust event scores showed significant correlations between PSQ scores and TNFα levels (r=0.24; p=0.047), as well as hyperactivities and TNFα levels (r=0.34; p=0.004). Mediation analysis showed that TNFα had an indirect effect of 12.4% on the link of MDD with sleep disturbance in adolescents. Stepwise multiple linear regression analysis indicated that the severity of depressive symptoms was best predicted by medications, PSQ scores, and childhood trust event scores (**Table 3**).

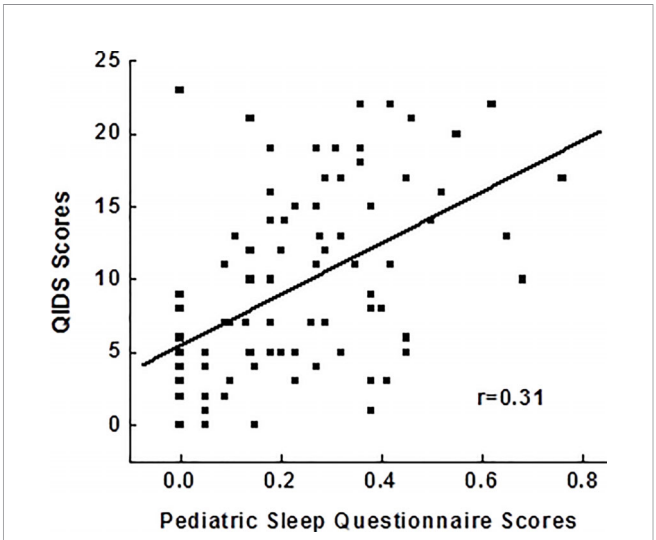

FIGURE 1 | Correlations between pediatric sleep questionnaires and the severity of depressive symptoms. QIDS, Quick Inventory of Depressive Symptoms.

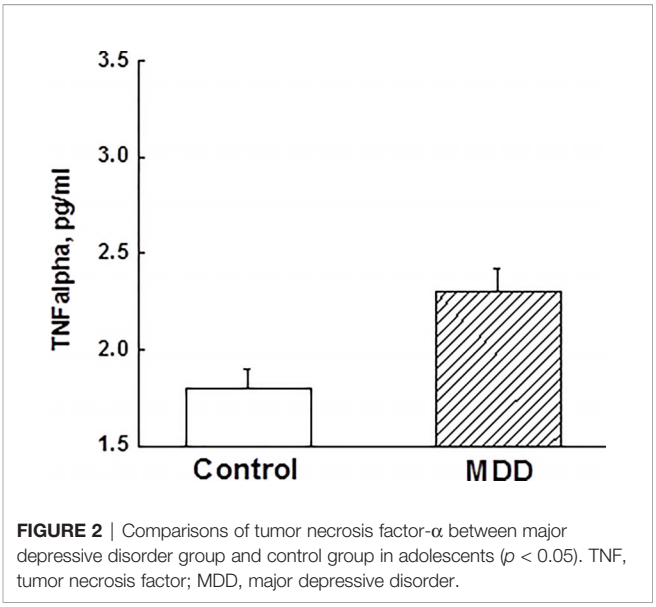

FIGURE 2 | Comparisons of tumor necrosis factor-α between major depressive disorder group and control group in adolescents ($p < 0.05$). TNF, tumor necrosis factor; MDD, major depressive disorder.

DISCUSSION

In this study we explored the relationship between sleep disturbances and MDD in adolescents, as well as a potential underlying pathway by studying the role of chronic inflammation. Our study clearly shows that sleep disturbance is associated with MDD in adolescents. Our data further suggests that as the sleep disturbance gets greater, the symptoms of MDD get worse. Mechanistic study revealed that TNFα was significantly elevated in adolescent MDD compared to controls, positively associated with PSQ scores, and play an indirect role in the association between MDD and sleep disturbance. To our knowledge, this is the first study to explore the relation between sleep disturbances, MDD, and the role of inflammation in adolescents.

TABLE 3 | Stepwise linear regression analysis predicting depression.

Dependent variable	Significant predictors	B	R^2
QIDS scores	PSQ scores	5.83	0.44
QIDS scores	PSQ scores, medications	4.48	0.49
QIDS scores	PSQ scores, medications, childhood trust event scores	3.36	0.53

Independent variables included age, race, gender, body mass index, smoking status, PSQ scores, measured inflammatory factors. QIDS, quick inventory of depressive symptoms; PSQ, pediatric sleep questionnaire.

Recent literature shows increasing evidence of relationship between sleep disturbance and MDD in adolescents (2). Literature review also suggests sleep disturbance in adolescents is likely to predict depression (2). Studies show that adolescents with depression have problems with sleep-onset, being unable to return to sleep after waking prematurely, and hypersomnia (25, 26). There is strong evidence of consequences of sleep disturbances in adolescents including depression, anxiety, increased risk of suicidal ideation, and also increased risk of obesity (27). In our study, we showed that adolescents with MDD scored much higher in PSQ scale with snoring, sleepiness, and increased hyperactivity during the day. Thus, our findings are consistent with the literature that not only there is sleep disturbances at night in adolescents who have depression but also there is functional impairment during the day (18, 28). The association of sleep disturbances with MDD also indicates that early and adequate treatment of sleep disturbances, including insomnia, might contribute to the treatment for MDD in adolescents. The relationship between all the above has not been well studied in well-designed longitudinal studies utilizing sleep-focused therapy to explore the impact of addressing sleep disturbances on MDD, and is an area that needs further investigation.

Our previous study and many other studies have shown that adults with MDD show increased circulating levels of inflammatory markers like IL-6 and TNFα (13, 29). Pro-inflammatory cytokines like TNFα can induce indoleamine 2-3-dioxygenase, an enzyme that results in catabolism of tryptophan resulting in decreased serotonin levels. In addition, TNFα can also influence the hypothalamic-pituitary-adrenal axis by increasing corticotrophin releasing hormone release and disturbing the function of the glucocorticoid receptor (30). Thus, there is evidence in different studies of TNFα's role in depression, and we postulate a similar role for TNFα in relation to MDD in adolescents as evidenced by elevated levels in our study.

As compared to inflammatory markers in adults with MDD, there is limited data with significant variation in inflammatory markers in adolescents with MDD (31, 32). The small number of studies and sparse data could be one of the main reasons preventing researchers from reaching a conclusion on the role of inflammatory markers in adolescent depression. In addition, TNFα levels were compared only in adolescents with MDD and suicidal ideation, which also showed variations (31). Unique to our study is the fact that we looked at adolescents with only MDD and no suicidal ideation, and they had significantly elevated TNFα levels compared to the control group which is consistent with findings in multiple adult studies (29). However, other inflammatory markers, including IL-6, IL-8, IL-10, and CRP, did now show significant differences between controls and MDD group in our study. Numerous factors have been postulated causing the differences in inflammatory markers in adolescent MDD and adult MDD. Some of them have been attributed to changes in neuronal development, hormonal changes, stress, trauma, and differences in immunity in adults as compared with adolescents (31).

There is strong evidence in literature that TNFα plays an important role in sleep regulation in both animal and human studies (15, 17). In pediatric obstructive sleep apnea patients, TNFα levels increase, and are closely related to sleepiness (33). Also, TNFα levels and sleepiness in these patients decreased after surgery (33). In healthy young men, during sleep, plasma TNFα decreases (34). Consistently, in humans with sleep deprivation, circulating levels of TNF-receptor increase (35). Thus, TNF system may play an important role in normal circadian regulation (14). In the present study, we found increased TNFα levels in adolescents with MDD who displayed sleep disturbances. Thus we explore the possibility of interplay of sleep disturbances and TNFα in MDD in adolescents which has not been explored before.

There are a few limitations that are needed to note when our results are interpreted. Frist, our sample size is relatively small, though it is still bigger than some of previous studies for inflammatory markers in adolescents. Second, it is a cross-sectional study design, so a causal-effect relationship could not be established. Third, the assessment of sleep disturbance was based on a validated but self-reported questionnaire, which has been widely used in clinical research when polysomnography is not feasible (22). However, there may not be perfect overlap between self-reported questionnaires and objective measures from polysomnography. Finally, more studies are needed to explore the role of other inflammatory markers in adolescents with MDD and sleep disturbances. However, our findings indicate that timely treatment of sleep problems in adolescents will help address MDD earlier and help with academic performance, prevent drug abuse and help with inter personal relationships (2). Our paper brings attention to the possibility of treating MDD in adolescents by addressing both sleep and inflammation at the same time.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors following the National Institutes of Health guidelines.

ETHICS STATEMENT

All study procedures were reviewed and approved by the University of Alabama at Birmingham (UAB) Institutional Review Board before enrolling the first participant. Written informed consent to participate in this study was provided by the participants' legal guardian.

AUTHOR CONTRIBUTIONS

AR analyzed the data, drafted, edited, and approved the final manuscript. MT drafted, edited, and approved the final

manuscript. LL designed and performed the study, analyzed the data, and edited and approved the final manuscript.

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Looking at Intergenerational Risk Factors in Schizophrenia Spectrum Disorders: New Frontiers for Early Vulnerability Identification?

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Offspring of individuals with serious mental illness (SMI) constitute a special population with a higher risk of developing psychiatric disorders, which is also highly prevalent among referrals to child and adolescent mental health services (CAMHS). They often exhibit more or less subclinical conditions of vulnerability, fueled by mutually potentiating combinations of risk factors, such as presumed genetic risk, poor or inadequate affective and cognitive parenting, and low socio-economic status. Despite this evidence, neither specific preventive programs for offspring of parents with SMI are usually implemented in CAMHS, nor dedicated supportive programs for parenting are generally available in adult mental health services (AMHS). Needless to say, while both service systems tend to focus on individual recovery and clinical management (rather than on the whole family system), these blind spots add up to frequent gaps in communication and continuity of care between CAMHS and AMHS. This is particularly problematic in an age-range in which an offspring's vulnerabilities encounter the highest epidemiological peak of incident risk of SMI. This paper offers a clinical-conceptual perspective aimed to disentangle the complex intertwine of intergenerational risk factors that contribute to the risk of developing SMI in offspring, taking schizophrenia spectrum disorders as a paradigmatic example.

Keywords: genetic risk, offspring, serious mental illness, schizophrenia, intergenerational transmission

INTRODUCTION

Consider the case of M.D., an 11-year-old male offspring of a parent with schizophrenia, whose psychopathological assessment reveals an attenuated psychosis syndrome laying on a schizotaxic subjective substrate of cognitive deficits and pervasive distortions of subjective experiences (aka anomalous self-experiences, ASE) (1, 2). Also, consider the case of C.Z., a 6-year-old female

offspring of a parent with schizoaffective disorder, weakly exposed from birth to socially-deprived contexts and taken away from close relatives, that manifests a severe selective mutism when attending kindergarten (from 5 years of age) and subsequently primary school.

In the first case, the psychopathological manifestation of the offspring appears in clear, so-called homotypic, continuity with the psychopathological condition of the parent: i.e., a schizophrenia parent conferring a familiar risk for schizophrenic manifestations, early expressed phenotypically in the offspring in terms of schizotaxia (3), self-disorders (4), and attenuated psychosis syndrome (5). In the second case, i.e., so-called heterotypic continuity, the psychopathological manifestations do not appear in strict continuity across generations (i.e., schizoaffective disorder in the parent, selective mutism in the offspring do not formally align in the same psychopathological cluster), suggesting other pathomorphic factors over and above the putative genetic risk (e.g., environmental factors such as a hypo-stimulating parenting or poor development of social scaffolding).

Starting from these brief vignettes extrapolated from real-world daily clinical practice, it is intuitive how in the mental health domain, the intergenerational transmission of risk is a complex, multi-factorial, and multi-directional phenomenon. Many studies dealt with this phenomenon focusing on specific phenomena such as violence, abuse, child maltreatment, and criminal tendencies (6–10) or on moderating factors as parenting and attachment (11, 12). A more complex issue is represented by the intergenerational transmission of vulnerability for specific psychopathological pictures, characterized by a higher inter and intra categorical heterogeneity in the balance between presumed genetic risk, environment, and their interaction (GxE). In this perspective depression and anxiety have been the most studied conditions (13–16), with most studies focusing on the effects of postpartum depression on parenting and longitudinal offspring mental health.

While common and specific genetic structures of psychopathology have been progressively discovered [e.g., (17, 18)] and unspecific (19–22) and disease-specific (23–26) environmental risk factors (i.e., significant associations) for mental health have been progressively described, pathophysiological mechanisms induced by the interaction between genetic risk and environmental exposure are far from being fully understood and described in humans. Indeed, the complexity of GxE interactions is, for example, represented by the different magnitude scales of putative environmental risk factors, i.e., from micro [such as air pollution and neuroendocrine disruptors: (21, 22)] to macro (such as stress exposure, maltreatment, or parenting). A further layer of complexity resides in epigenetic processes [i.e., the combination of mechanisms that confer short-term and long-term changes in gene expression without altering the DNA code (27)]. These processes become even more critical along neurodevelopment, especially in early years (20), thereby making the intersection between genetic risk and environmental risk factors more complex to decipher and discern. Indeed, epigenetic processes not only mediate the effects of environmental risks in neuropsychiatric disorders but also interact with their genetic load (28–30).

Considering the vastness of the field of intergenerational transmission of risk, this paper offers a clinically digested scoping review focused on schizophrenia spectrum disorders (SSD), a group of severe and chronic mental disorders whose etiology is likely to be multifactorial, with multiple small-effect and fewer large-effect susceptibility genes interacting with environmental risk factors (31).

EARLY VULNERABILITY TO SCHIZOPHRENIA

Genetics

The earliest approach to genetic risk in schizophrenia has been historically based on the study of offspring, i.e., subjects with first-degree relatives with SSD diagnosis (Familial High Risk): the risk of schizophrenia rises from the 4–6% in second-degree relatives, to 10% in the children of a schizophrenic parent (regardless of whether it is the father or the mother), to 40% in children of both schizophrenic parents up to almost 50% in homozygous twins of schizophrenic subjects (32).

Decades of studies on offspring of individuals diagnosed with schizophrenia robustly showed that they present early endophenotypic alterations detectable at different levels of analysis (e.g., neural, motor, cognitive, emotional, social, and behavioral), placing them in a phenotypical intermediate position between SSD subjects and healthy controls (33–39).

A more recent approach to characterize such genetic risk in quantitative, probabilistic terms is represented by the Polygenic Risk Scores (PRS), i.e., proxy values generated combining multiple genetic markers into a single score indicative of specific lifetime risk for a disease (40); within psychiatry, PRS define cumulative risk profiles based on the identification of genetic variants related to psychiatric disorders, obtained through genome-wide association studies (GWAS) (41, 42). Applied to the general population in developmental years, schizophrenia PRS shows multiple associations with phenotypic expressions through a broad range of soft (i.e., non-psychotic) neurocognitive and behavioral features [for review, (43–46)]. For example, Jansen et al. (47) indicated a selective association between the schizophrenia PRS and higher internalizing tendencies at all ages, as well as with higher externalizing tendency at age 3 and 6; moreover, looking at the syndromic subscales, s-PRS was positively associated with higher emotional reactivity at age 3, with emotional reactivity, anxiety/depression, somatic complaints, withdrawal at the age 6, and with problems of thought at age 10. Another study by Riglin and colleagues (48) reported an association of schizophrenia PRS with performance IQ, speech intelligibility and fluency, and headstrong behavior at age 7–9 years, and with social difficulties and behavior problems at age 4 years.

Overall, studies on schizophrenia PRS suggested that genetic liability is not silent in childhood but is endophenotypically expressed through mild alterations in several domains of

functioning. Although intriguing due to the innovative PRS-based approach, these findings substantially replicate and refine those derived from previous familial-high-risk studies on offspring of schizophrenic patients (39), which inspired the original conceptualization proposed by Meehl of schizotaxia, i.e., a broad predisposition to develop SSD due to a genetically predisposed premorbid neurobiological condition (3, 49).

The importance of genetic risk in the neurodevelopmental articulation and clinical unfolding of liability to schizophrenia has been recently reinvigorated by the early detection approach, inspired by the clinical staging model of psychosis (5, 50, 51). Indeed, in addition to attenuated psychotic symptoms and brief limited/intermittent psychotic symptoms, the clinical criteria defining a *Ultra High-Risk* (UHR) of developing psychosis, include a third group, defined by a combination of presumed genetic risk (i.e., family history of psychosis or individual schizotypal personality disorder) associated with a decline in functioning or sustained low decline. This subgroup, termed "*genetic risk and deterioration syndrome*" (GRDS), has a meta-analytical prevalence of 5% among UHR samples (52) and, if not combined with other UHR criteria (i.e., APS or BLIPS), has a relatively lower risk of longitudinal transition to psychosis in comparison with other UHR subgroups.

In sum, the genetic approach to schizophrenia, from earliest studies on offspring to recent PRS studies, globally shows that the presumed genetic load is early expressed in the phenotype but at the same time is not deterministic, conferring a vulnerability that only in the interaction with environmental risk factors may progressively evolve to psychosis and SSD (53), as already classical studies on adopted children pointed out.

Environment

The Finnish Adoptive Developmental Study (54, 55) followed longitudinally a sample of 185 offspring of schizophrenic mothers who were adopted within the 4th year of life, and compared to a control sample of similar composition in which the adopted children had no biological parents diagnosed with schizophrenia. Findings highlighted an interaction between genetic risk factors and protective factors, with a dimensional distribution of the risk of developing schizophrenia: children raised in adoptive families without severe mental health problems in the adoptive parents, regardless of the genetic risk (presence or absence of schizophrenia in the biological mother), have shown minimum levels of psychopathology over time; the level of psychopathology increased in the presence of an adoptive parent with mental disorders and more in the case of both parents, so much so that of the 35 subjects who had developed longitudinally schizophrenia, 32 had been adopted by problematic and disturbed families.

Similar findings emerged from the Rochester Longitudinal Study (56), which followed up along a 4-year period a group of children of chronically ill schizophrenic women. Mothers varied on mental health dimensions of diagnosis, severity of symptomatology, and chronicity of illness. Other factors included in the analyses were socioeconomic status (SES), race, sex of child, and family size. Curiously, a specific maternal diagnosis of schizophrenia had the least impact on global functioning of children; on the contrary, both SES and severity/chronicity of illness showed a greater impact on development, with children of more severely or chronically ill mothers and lower SES performing most poorly.

The disentanglement of environmental factors impacting on the development of vulnerability to SSD is certainly more complex and nuanced as compared to the investigation of primarily genetic factors. Indeed, as mentioned before, environmental risk factors occur on different scales of magnitude [e.g., from air pollution and neuroendocrine disruptors (19–22) through prenatal/perinatal events as maternal infection and obstetric complications (57–59) to harmful childhood adversities as physical and/or emotional neglect or maltreatment (60, 61) as well as sociodemographic characteristics as urbanicity and immigrant status (62–65)] and are widely dispersed across temporal frames (e.g., from punctiform perinatal events to prolonged exposures in developmental years). Crucially, however, aggregate scores of environmental risk factors (e.g., cannabis use, urbanicity, season of birth, paternal age, obstetric and perinatal complications, childhood adversities), weighted by specific odds ratios for association with psychosis in the literature, may predict transition to psychosis in subjects at familial high genetic risk (66).

Overall, environmental risk factors for SSD are mainly obtained from significant associations in observational studies and their relative weight (odd ratio) may emerge more clearly in meta-analytical studies (24); therefore, especially for environmental risk factors involved in the *developmental origins of health and disease* (DOHaD) hypothesis applied to mental health (20), a necessary step forward to translate scientific insight into tangible preventive strategies is more rigorous experimental designs. Those indeed are essential to properly establish causal inferences and confirm (or disconfirm) the role of putative risk factors (67, 68), such as in the case of the recently confirmed causal role of cannabis use by a mendelian randomization study (69).

With respect to the characterization of combined genetic and environmental risk factors causing the neurodevelopmental pathways leading to increased SSD-proneness, some recent advances are particularly promising. First is the discovery that the schizophrenia PRS score is 5 times greater in those subjects that had experienced perinatal complications, suggesting that a higher genetic risk may increase the likelihood of experiencing prenatal or perinatal adversities (70); second is the preliminary characterization of epigenetic modifications in SSD, as both molecular scars of environmental exposure and source of phenotypic variability (71).

Modifiable Risk Factors

Within the early intervention paradigm in psychiatry (72), special attention is paid to modifiable risk factors (73, 74), i.e., factors that can be manipulated by early specific and preventive interventions moderating their longitudinal role in contributing to the risk of psychosis and schizophrenia (75). With respect to intergenerational liability, one of the most important modifiable risk factors includes parenting, whose quality is strongly correlated with severity and chronicity of mother mental illness

(76, 77), including SSD (78–81). In particular, troubled or high-risk parenting related to serious mental illness may be implicated in increased rates of insecure or disorganized attachment patterns (82–84); these specific attachment patterns, combined with an underlying neurobiological (schizotaxic) vulnerability, may exert a non-protective role for the development of SSD (85–87). However, despite the increasing amount of evidence on the potential role of mental illness on parenting (and therefore on offspring's later risk of mental illness), there is a relative paucity of high-quality studies addressing interventions to reduce the risk of developing mental illness in offspring of parents with mental illness (88). A recent meta-analysis (89) of randomized controlled trials quantified effects of preventive interventions for this at-risk population, reporting small though significant Effect Sizes (ES) for programs enhancing the mother-infant interaction (ES = 0.26) as well as mothers' (ES = 0.33) and children's (ES = 0.31) behavior, that proved to be stable over the 12-month follow-up. Interventions for children/adolescents resulted in significant small effects for global psychopathology (ES = 0.13), as well as internalizing symptoms (ES = 0.17), and increased significantly over time, with externalizing symptoms reaching significance in the follow-up assessments (ES = 0.17). Not surprisingly, interventions addressing parents and children jointly produced overall larger effects than interventions separately focused on offspring or on parents.

CLINICAL TRANSLATIONAL IMPLICATIONS

As exemplified by the clinical staging model of psychosis (5, 50, 51), severe mental illnesses do not generally arise out of the blue, but rather emerge progressively on the background of complex neurodevelopmental interactions of genetic and environmental factors, often producing early, unspecific premorbid phenotypic alterations, followed along the years by progressively more disturbing prodromal manifestations that finally acquire specific psychopathological and clinical connotations (90). Within this context, children of parents with severe mental illness (such as SSD or mood disorders) represent a peculiar at-risk category, combining presumed genetic liability with an increased likelihood of environmental adversities (from maternal unhealthy lifestyle during pregnancy through prenatal/perinatal complications to exposure to poor parenting).

Modifiable environmental risk factors should be the focus of planned preventive interventions, for example, supporting parents' healthy lifestyle and parenting. These interventions should be integrated within the more general early detection and intervention paradigm, whose focus has gradually become more inclusive, moving from psychosis to trans-diagnostic manifestations of early risk of severe mental illness. Indeed, the prediction of mental illness is moving toward the definition of progressively more accurate risk calculators, combining aggregate scores of multiple risk factors (24, 66, 91). However, as exemplified by the low prevalence of the GRFD subgroup among UHR individuals transitioning to psychosis, the use of genetic liability to establish an a priori risk of mental illness in already help-seeking, putatively prodromal subjects, could be a rather tardive preventive strategy. Instead, the psychopathological risk conferred by such genetic liability should be better deployed to drive psychosocial interventions in those earlier premorbid stages (92, 93), characterized by an increased plasticity and possibility to reduce longitudinal risk.

In this perspective, given the widespread, increasing effort to refine risk phenotypes in order to intervene as soon as possible in a hypothetical primary prevention approach (94), it is paradoxical that, beyond the realm of empirical research, children of parents with mental illness (i.e., a childhood population with an established higher risk for the development of lifetime psychopathology and related risk of biopsychosocial decline) are still only marginally considered in the guidelines and operative policies ruling real-word mental health departments. Indeed, despite this evidence, neither specific preventive programs for offspring of parents with severe mental illness are usually implemented in child/adolescent mental health services, nor dedicated supportive programs for parenting are generally available in adult mental health services. While both service systems tend to focus on individual recovery and clinical management (rather than on the whole family system), these blind spots add up to frequent gaps in communication and continuity of care between these mental health services (95–97). Moreover, the fear of stigmatizing young subjects in relation to possible increased risk for mental illness, although not explicitly acknowledged, characterizes both empirical research and clinical practice (98, 99). Overall, this is reflected in the limited availability of preventive trials and clinical guidelines, as well as in a certain widespread clinical style that—despite formal complacency—widely tolerates a lack of natural or systematic communication between families and clinicians on the stigmatizing issue of mental illness and mental illness risk. For example, clinicians of adult parents will mental illness rarely investigate with the due detail the development and mental health of their offspring; similarly, pediatricians and parents' clinicians seldomly cooperate on the systematic sharing of a comprehensive intervention plan, despite both being aware of the impact of severe and chronic mental illness on families. Notably, despite obvious analogies the attitude is radically different when the parental risk is, for example, linked to a genetic-dependent organic condition (e.g., cardiovascular or oncological diseases). On the contrary, in mental health there is still an ongoing debate on the clinical management of help-seeking subjects at UHR (100, 101), including the opportunity of communicating the risk of psychosis. While respectable, such debate seems to elude an obvious medical fact, that is, although not necessarily transitioning to psychosis, UHR help-seekers usually have a lower level of functioning, poorer quality of life, and a higher proclivity for an array of other mental health disorders. On this background it is crucial to highlight the problem of unmet needs and insufficient managing of early signatures of risk of mental illness in offspring of parents with SMI (102).

In conclusion, a more in-depth (and clinically oriented) appreciation of the intergenerational components building up

the predisposition to the development of SMI, exemplified in this perspective paper focusing on SSD, could be an essential step forward toward the next generation of early preventive interventions.

AUTHOR CONTRIBUTIONS

The article was jointly conceptualized, wrote, and revised by all authors.

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Basic Symptoms Are Associated With Age in Patients With a Clinical High-Risk State for Psychosis: Results From the PRONIA Study

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In community studies, both attenuated psychotic symptoms (APS) and basic symptoms (BS) were more frequent but less clinically relevant in children and adolescents compared to adults. In doing so, they displayed differential age thresholds that were around age 16 for APS, around age 18 for perceptive BS, and within the early twenties for cognitive BS. Only the age effect has previously been studied and replicated in clinical samples for APS. Thus, we examined the reported age effect on and age thresholds of 14 criteria-relevant BS in a patient sample at clinical-high risk of psychosis ($N = 261$, age 15–40 yrs.), recruited within the European multicenter PRONIA-study. BS and the BS criteria, "Cognitive Disturbances" (COGDIS) and "Cognitive-perceptive BS" (COPER), were assessed with the "Schizophrenia Proneness Instrument, Adult version" (SPI-A). Using logistic regressions, prevalence rates of perceptive and cognitive BS, and of COGDIS and COPER, as well as the impact of social and role functioning on the association between age and BS were studied in three age groups (15–18 years, 19–23 years, 24–40 years). Most patients (91.2%) reported any BS, 55.9% any perceptive and 87.4% any cognitive BS. Furthermore, 56.3% met COGDIS and 80.5% COPER. Not exhibiting the reported differential age thresholds, both perceptive and cognitive BS, and,

at trend level only, COPER were less prevalent in the oldest age group (24–40 years); COGDIS was most frequent in the youngest group (15–18 years). Functional deficits did not better explain the association with age, particularly in perceptive BS and cognitive BS meeting the frequency requirement of BS criteria. Our findings broadly confirmed an age threshold in BS and, thus, the earlier assumed link between presence of BS and brain maturation processes. Yet, age thresholds of perceptive and cognitive BS did not differ. This lack of differential age thresholds might be due to more pronounced the brain abnormalities in this clinical sample compared to earlier community samples. These might have also shown in more frequently occurring and persistent BS that, however, also resulted from a sampling toward these, i.e., toward COGDIS. Future studies should address the neurobiological basis of CHR criteria in relation to age.

Keywords: psychosis, clinical high risk, basic symptoms, age, brain maturation

INTRODUCTION

Despite their low lifetime prevalence of between 0.2 and 3.5% (1), schizophrenia-spectrum and other psychotic disorders are among the most severe and costly neuropsychiatric diseases (2–4). Schizophrenia is the 9th most important cause for disability-adjusted life-years (DALYs) already in 10–14-year-old boys, and the 2nd most important in all 15–19-year-olds (5), although full-blown psychoses rarely manifest in children and adolescents (6). However, because the majority of psychoses develop slowly over several years, their first prodromal symptoms will frequently show in childhood and adolescence; and prodromes with such an early onset tend to be longer and to be associated with poorer outcome (7, 8). Thus, the early detection and prevention of psychosis, which aims to reduce the burden of the disorder (9–11), has increasingly moved from adult patients into ever younger patient groups. However, this has been done without full consideration of potentially influential developmental issues (6, 12, 13).

In the early detection of psychoses, two complementary approaches to define the clinical high-risk (CHR) state for psychosis are currently followed (9, 14). One is the ultra-high-risk (UHR) approach that was developed to detect an imminent risk of psychosis. It includes (1) the attenuated psychotic symptoms (APS) syndrome characterized by recently developed or worsened symptoms that resemble positive symptoms of psychosis, yet with still some insight being maintained; (2) the brief limited intermittent psychotic symptoms (BLIPS) syndrome with frank positive psychotic symptoms that spontaneously remit within a couple of days; and (3) the genetic risk plus functional decline (GRFD) syndrome that combines a significant recent functional decline with a genetic risk factor of psychosis, i.e., a first-degree relative with psychosis or a schizotypal personality disorder in the patient (9, 14).

The second approach is the basic symptoms (BS) approach that was developed to detect emerging psychosis as early as possible (9, 14). It includes two alternative criteria, "Cognitive disturbances" (COGDIS) and "Cognitive-perceptive BS" (COPER) (**Table 1**). BS have been described as the earliest subtle and subjectively experienced symptoms of psychosis (16–19). BS are subclinical disturbances in the affected individual's own mental processes, such as thinking, speech, (body) perception, motor action, drive, affect, and stress tolerance, that are primarily recognized by the affected individual and are only rarely directly observable by others (16–19). BS were named "basic" as they had been assumed to be "substrate-close," i.e., the most immediate psychopathological expression of the neurobiological aberrations underlying the development of psychotic disorders. At this, BS are assumed to be the basis on

TABLE 1 | Basic Symptom (BS) criteria.

Cognitive disturbances (COGDIS)
Presence of ≥ 2 of the following 9 basic symptoms of at least moderate severity (≥3)[a] within the last 3 months
Inability to divide attention
Thought interference
Thought pressure
Thought blockages
Disturbance of receptive speech
Disturbance of expressive speech
Unstable ideas of reference
Disturbance of abstract thinking
Captivation of attention by details of the visual field
Cognitive-perceptive basic symptoms (COPER)
Presence of ≥ 1 of the following 10 basic symptoms of at least moderate severity (≥3)[a] within the last 3 month and first occurrence ≥12 months ago
Thought interference
Thought perseveration
Thought pressure
Thought blockages
Disturbance of receptive speech
Decreased ability to discriminate between ideas/perception, fantasy/true memories
Unstable ideas of reference
Derealization
Visual perception disturbances *(excl. blurred vision and hypersensitivity to light)*
Acoustic perception disturbances *(excl. hypersensitivity to sound/noises)*

[a] *Assessed by the Schizophrenia Proneness Instrument (SPI-A) (15).*

which (attenuated) psychotic symptoms develop as a result of dysfunctional coping (16, 18). By definition, BS are experienced with immediate and full insight and, thus, are distinct from APS, BLIPS and frank psychotic symptoms, which, at least initially, are experienced as being real and/or reasonable (10, 16, 17, 19).

As a result of the above, models of the early course of psychosis commonly assume that BS and BS criteria develop first, and are followed by UHR symptoms and criteria before more persistent psychotic symptoms set in (9, 10, 14, 16, 17). This sequence, however, was only partially supported by retrospective analyses of first-episode psychosis patients (7, 20). However, the temporal sequence 'BS-APS-positive symptoms' was particularly frequent in first-episode psychosis patients with an onset of first prodromal symptoms before age 18 (7).

UHR and BS criteria have been associated with pooled long-term conversion rates into full-blown psychosis between 37 and 61%, with higher conversion rates in BS-defined samples compared to UHR samples at observation periods of three or more years, and with significantly lower conversion rates in child and adolescent compared to adult samples (14). Next to this lower psychosis-predictive value of CHR criteria in children and younger adolescents, in particular of the APS syndrome (14, 21), accumulating evidence suggests that age and developmental aspects might also alter the general clinical relevance and the prevalence rate of CHR symptoms. Again, this evidence has mainly accumulated for APS and BLIPS (13, 14, 21–28), in doing so indicating an age threshold around the age of 16 below which these symptoms are more frequent, but less clinically relevant in terms of their association with functional deficits and/or non-psychotic mental disorder, and less psychosis-predictive (21–23, 28, 29). In doing so, the interaction of APS with age played a particular role in predicting psychosocial functioning, with APS being increasingly associated with functional deficits with advancing age in the community (29). The only exception was disorganized communication at APS-level for that, in interaction with age, no stable association with functional deficits was revealed. Non-psychotic mental disorders, however, were mainly predicted independently by female sex and presence of APS (29). Again, disorganized communication was an exception in that it predicted mental disorder by its interaction with age rather than its sole presence. In doing so, participants without disorganized communication were commonly younger than those with it; this age effect being more pronounced in those with mental disorder (29).

As regards BS and BS criteria, the impact of age and developmental aspects has been less studied. Two studies on the dimensions of BS indicated differences between children and adolescents, and adult patients (19, 30). Yet, only one Swiss community study has so far studied age effects on the prevalence and clinical relevance of BS (29, 31). It reported age thresholds of around 18 years of age for perceptive BS and of within the first half of the twenties for cognitive BS, indicating a higher prevalence and a lesser clinical relevance, i.e., a lesser association with functional impairment, below these age thresholds (29, 31). As in APS, age played a major role in moderating the association between BS and functional deficits, while female sex was an independent predictor of mental disorder (29). In doing so, the association of BS and psychosocial functioning increased with age. Only in case of perceptual BS, their interaction with age was additionally moderated by sex, indicating that the effect of the interaction between age and perceptual BS on psychosocial impairment was more pronounced in males (29). In case of non-psychotic mental disorders, in addition to the general sex effect, age only moderated the effect of cognitive BS, indicating that a mental disorder was less likely when participants with cognitive BS were younger (29). Thus, in both APS and BS, age commonly moderated their association with functional deficits but not their association with mental disorder (29).

In light of current models and the assumed sequence of BS before UHR symptoms in the at-risk or prodromal stage of psychosis (9, 10, 14, 16, 17), the higher age thresholds of BS (31) compared to APS (22) in the Swiss community study were surprising, because a lower or at least similar age threshold of BS compared to APS had been expected (31). Yet, the two age thresholds of perceptive and cognitive BS seemed to follow known brain maturation processes (29, 31). Consequently, the higher prevalence of BS below these thresholds in concert with the fact that BS mostly occurred too infrequently to meet the BS criteria's frequency requirement of "at least once per week" (**Table 1**) was explained by ongoing brain maturation processes (31). According to the suggested model (**Figure 1**), the prevalent yet rarely occurring BS below the respective age thresholds were proposed to signal subtle, transient disruptions of mental processes that occur as part of the ongoing transformations at the cerebral level, and thus to support the proposed substrate-closeness of BS (31). The age threshold of APS, however, seemed to reflect the age at which most cognitive abilities have been acquired (31, 37). As a result, APS that were more prevalent below this threshold and also mainly occurred more rarely than the required frequency of "at least once per week" (22) were explained as the expression of not yet fully matured cognitive abilities, including coping strategies, which makes the young person more prone to develop inadequate explanatory models (**Figure 1**) (31).

In light of these considerations that may have major impact on future research into the neurobiological underpinnings of symptoms of psychosis (15, 31) and the future development of both age-adapted early detection and age-adapted early interventions (6, 12, 31), and in light of the limited studies on age effects on BS, we investigated the age effects on and age thresholds of BS in a CHR sample. In line with the replication of age effects on APS in clinical samples (23, 25), we expected that age thresholds would follow those earlier reported from the Swiss community study (29, 31). Additionally, in light of the moderating effect of age on the association of BS with functional impairment, which was weaker in younger subjects (29, 31), we also examined if the effect of age on BS might be influenced by the presence of functional impairments.

METHODS

Sample

The sample consisted of 261 patients with a CHR state who were recruited as part of the EU-funded Personalized Prognostic Tools

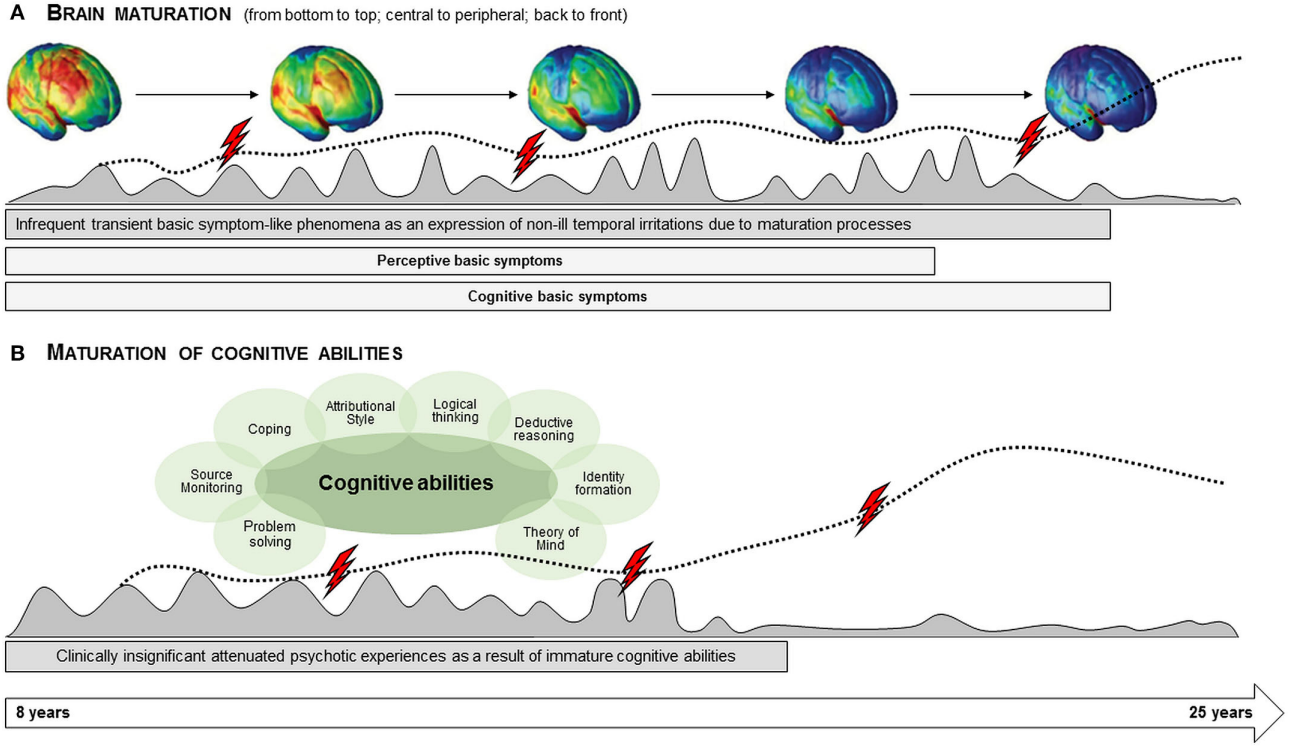

FIGURE 1 | Model of the possible relationship between basic symptoms and brain maturation, and between attenuated psychotic symptoms and maturation of cognitive abilities (31). This model assumes that **(A)** subtle subclinical disturbances in cognitive and perceptive processes that are phenomenologically identical to basic symptoms (BS) might occur during childhood and adolescence as infrequent temporary expressions of insignificant passing dysfunctions in the wake of brain maturation processes (gray-shaded curve). However, if these disturbances, i.e., BS, occur more frequently (i.e., meet the frequency requirements of the BS criteria) and are persistent (dotted line), they might be a sign of disturbances in brain maturation processes, which, in line with a neurodevelopmental model of psychosis (32, 33), might predispose to the development of psychosis. A genetic predisposition, childhood adversities or other risk factors (indicated by flashes) including stressful life-events and cognitions promoting the development of attenuated psychotic symptoms (APS), such as poor coping, externalization biases or poor source monitoring (34), might further sustain and/or amplify the development and persistence of information processing disturbances. On the other hand, the model assumes that **(B)** unusual perceptual experiences or thought contents phenomenologically identical to APS might occur during childhood and early adolescence as an expression of not yet fully matured cognitive abilities (gray-shaded curve). If their maturation is impaired by risk factors or stressors (flashes) or neurodevelopmental disturbances in information processing (that might be experienced as BS), APS might persist or progress (dotted line), potentially leading to positive and potentially benign schizotypal traits (35), an Attenuated Psychosis Syndrome (36), and/or psychosis.

for Early Psychosis Management (PRONIA) study [www.pronia.eu (38)] at ten early-detection centers in five European countries between February 2014 and November 2017 (**Table 2**). In each center, the study was approved by the local ethics committee, and all participants or participant's parents/guardians gave their written informed consent prior to study inclusion.

The inclusion criteria of the CHR sample were age between 15 and 40 years, sufficient knowledge of the local language, in which the assessments were conducted, and meeting any one of the slightly adapted UHR criteria (**Supplementary Table 1**) and/or COGDIS (**Table 1**). Participants were excluded in case of a past or present diagnosis of psychosis and of treatment with any antipsychotic medication at or above the minimum dosage threshold defined by the DGPPN S3 Guidelines for the treatment of first-episode psychosis (2006) (39) for either more than 30 days or within the past 3 months before baseline assessment (**Supplementary Table 2**). Further exclusion criteria were an IQ below 70, alcohol or polysubstance dependence within the past 6 months, current or past head trauma with loss of consciousness for more than 5 min, or any neurological or somatic disorder having a potential effect on the brain.

Assessments

For the assessment of the UHR criteria, the Structured Interview for Psychosis-Risk Syndromes (SIPS) (40) was used. The BS criteria COPER and COGDIS were assessed with the Schizophrenia Proneness Instrument – Adult version (SPI-A) (41). Following the procedures of the Swiss community study (22, 23, 31), cognitive and perceptive BS were distinguished: Cognitive BS comprised at least any one of the following 12 BS: inability to divide attention; thought interference, pressure, blockages and perseveration; disturbances of receptive and expressive speech, of abstract thinking, or of discriminating between ideas and perceptions; unstable ideas of reference; capturing of attention by details of the visual field and derealization. Perceptive BS included at least any one of the various visual or acoustic perception disturbances. Additionally, BS were distinguished according to meeting or not meeting

TABLE 2 | Sociodemographic characteristics and prevalence of at least one of the 14 basic symptom (BS), irrespective of BS criteria's frequency and novelty requirements.

Characteristic	Subjects with ≥ 1 of 14 BS (n = 238)		Subjects without any of 14 BS (n = 23)		Total sample (n = 261)		Statistics[a]			
	Mdn	Mean (SD)	Mdn	Mean (SD)	Mdn	Mean (SD)	*U*		*p*	ES
Age	21.5	23.0 (± 5.3)	26.0	25.0 (± 6.4)	22.0	23.3 (± 5.5)	1,934.5		0.020	0.144
Educational years	13.0	13.5 (± 2.7)	14.0	13.9 (± 3.1)	13.0	13.5 (± 2.7)	1,299.5		0.253	0.076
	N	%	*N*	%	*N*	%	x^2	*df*	*p*	ES
Age group (n)							5.087	2	0.079	0.140
15–18 yrs.	40	95.2[b]	2	4.8[b]	42	16.1[b]				
19–23 yrs.	110	94.0[b]	7	6.0[b]	117	44.8[b]				
24-40 yrs.	88	86.3[b]	14	13.7[b]	102	39.1[b]				
Center							8.280	9	0.506	0.178
LMU Munich	83	34.9	11	47.8	94	36.0	1.527	1	0.217	0.076
UBS Basel	23	9.7	0	0.0	23	8.8	2.437	1	0.118	0.097
UKK Cologne	34	14.3	3	13.0	37	14.2	0.027	1	0.870	0.010
University Birmingham	16	6.7	2	8.7	18	6.9	0.127	1	0.721	0.022
University Turku	27	11.3	0	0.0	27	10.3	2.910	1	0.088	0.106
University Udine	17	7.1	3	13.0	20	7.7	1.032	1	0.310	0.063
University Milan	20	8.4	2	8.7	22	8.4	0.002	1	0.962	0.003
University Münster	11	4.6	2	8.7	13	5.0	0.735	1	0.391	0.053
University Bari	1	0.4	0	0.0	1	0.4	0.097	1	0.755	0.019
University Düsseldorf	6	2.5	0	0.0	6	2.3	0.593	1	0.441	0.048
Gender: male	114	47.9	10	43.5	124	47.5	0.164	1	0.685	0.025
Migratory background[c]	28	11.8	2	8.7	30	11.5	0.194	1	0.659	0.027
Any current non-psychotic axis-I disorder	151	63.4	8	34.8	159	60.9	7.237	1	0.007	0.167
Any major depressive disorder	117	49.2	5	21.7	122	46.7	6.335	1	0.012	0.156
1st-degree biological relative with psychosis	36	15.1	1	4.3	37	14.2	2.003	1	0.157	0.088
Schizotypal personality disorder	17	7.1	2	8.7	19	7.3	0.075	1	0.784	0.017
Any UHR-criterion	172	72.8	15	65.2	187	71.6	0.513	1	0.474	0.044
BLIPS syndrome	5	2.1	0	0.0	5	1.9	0.493	1	0.483	0.043
APS syndrome	154	64.7	13	56.5	167	64.0	0.610	1	0.435	0.048
GRFD syndrome	36	15.1	3	13.0	39	14.9	0.072	1	0.789	0.017
COGDIS	147	61.8	0	0.0	147	56.3	32.523	1	0.001	0.353
COPER	210	88.2	0	0.0	210	80.5	103.858	1	0.001	0.631
impaired GF *social*[d] ≤ 6	122	51.3	8	34.8	130	49.8	2.278	1	0.131	0.093
impaired GF *role*[e] ≤ 6	130	54.6	13	56.5	143	54.8	0.031	1	0.861	0.011

[a] *Test statistics: Mann-Whitney U-test for non-normally distributed continuous variables with Rosenthal's r as effect size (ES), chi-squared test for categorical variables with Cramer's V as effect size (ES).*

[b] *% of age group not of BS group sample.*

[c] *any other white/Asian/black/mixed background.*

[d] *GF social = Global Functioning social scale a value of ≤ 6 indicates presence of "moderate impairment in social/interpersonal functioning."*

[e] *GF role = Global Functioning (GF) role scale a value of ≤ 6 indicates presence of "moderate impairment of role functioning."*

the novelty requirement (i.e., BS constitutes a disruption in the person's "normal" self and has a distinct time of first occurrence) and the frequency requirement (i.e., BS occurs at least once per week within the past 3 months) of the BS criteria.

Furthermore, the Structured Clinical Interview for DSM-IV-TR (SCID) (42) was performed to rule out past or present psychosis and to assess other mental disorders. Moreover, the Global Functioning: Social (GF: S) (43) and Global Functioning: Role (GF: R) (43) as well as the Global Assessment of Functioning (GAF) (44) were used to measure level of psychosocial functioning both globally and specifically. Impaired psychosocial functioning was assumed when the global GAF score was 70 or lower and when a GF score was 6 or lower.

All interviewers were trained in the assessments. Additionally, weekly supervision within each research center and monthly CHR case conferences on the CHR criteria relevant for inclusion by phone with an expert in early detection of psychoses (F.S.-L.) were carried out to ensure excellent and reliable data quality across centers.

Statistical Analyses

Using SPSS 25.0, frequencies were compared by chi-squared test for categorical variables, and non-normally distributed interval and ordinal data were analyzed with the Mann-Whitney U test.

As in previous studies of age effects (22, 23, 29, 31), binary logistic regression analysis with "enter" as method were used to evaluate effects of defined age ranges on prevalence rates of "at least any one of the 14 BS," "at least any one cognitive BS" and "at least any one perceptive BS" as well as of the related novelty and frequency requirements in the total CHR sample ($N = 261$). Because our age range differed from earlier studies (22, 23, 29, 31) by not including the age range of 8–14 years, we aligned the definition of our age groups with the results on BS in the community (29, 31) and defined three age groups: 15–18 years for the age threshold around age 18 reported for perceptive BS, 19–23 years because of the age threshold of within the first half of the twenties reported for cognitive BS, and 24–40 years. Also roughly in line with the previous studies (22, 23, 31), the age group of 19–23 years was used as the reference group in regression analyses. This age group was chosen, because the peak onset of first-episode psychosis was reported to be between the ages of 20 and 24 years (45) and, thus, this age group can be expected to show the highest rate of CHR symptoms and criteria. The reliability of the regression results was internally examined using bootstrapping ($N = 1{,}000$).

Furthermore, stepwise logistic regression analyses (Wald method) were employed to test effects of age and of functional deficits in both social and role functioning as well as of their interaction on the respective presence of BS and the BS criteria requirements. More specifically, "age group," "GF: S $\leq$ 6" or "GF: R $\leq$ 6" and "age group" $\times$ "GF: S $\leq$ 6"/"GF: R $\leq$ 6" were entered as potential predictors and the respective BS variable entered as dependent variable. To ensure stable results, the effects were only considered as significant when the same predictors were selected in both forward and backward selection.

RESULTS

Presence of at least one of the 14 BS within 3 months prior to the interview was reported by 238 patients (91.2%) (**Table 2**). Out of these, 87.4 % reported cognitive BS and 55.9 % reported perceptive BS. Furthermore, the COGDIS criterion was met by 147 (56.3%) and the COPER criterion by 210 patients (80.5%); naturally, all of them were members of the group with BS (**Table 2**). Any UHR criterion was reported by 187 participants (71.6%), mainly by meeting the APS syndrome (64.0%). There was no difference in frequency of UHR criteria between those with and without BS. Patients with BS were on average 2 years younger than those without any BS and more frequently presented with any non-psychotic axis-I disorder, in particular major depressive disorder (**Table 2**). No significant difference was seen between those with and without BS with regard to educational years, recruitment site, sex, migration background, family history of psychosis, presence of schizotypal personality disorder or of functional impairment (**Table 2**).

Logistic regression analyses indicated a lower frequency for both perceptive and cognitive BS, and the related requirements, in those of age 24 and over compared to the two younger groups, i.e., the 15–18-year-olds and the reference group of 19–23-year-olds (**Table 3**). Overall, this age effect was slightly more pronounced for perceptive BS compared to cognitive BS, with Odds Ratios [i.e., Exp (ß)] being between 0.073 and 0.004 points lower. For all 14 BS together, this difference only reached the level of a statistical trend for overall prevalence and the frequency requirement (**Table 3**).

As regards BS criteria, COPER revealed a statistical trend toward being least frequent in the oldest age group (**Table 4**). COGDIS was significantly more frequent in the youngest age group, i.e., in 15–18-year-olds (**Table 4**).

Regarding the potential influence of the functional level on the presence of BS or BS criteria, the results indicated that only age rather than impaired social or role functioning or their interaction with age was a predictor of the presence of BS and BS criteria (**Tables 5**, **6**). Yet, compared to univariate analyses of age effects, age was less frequently selected as a significant predictor in the multivariate analyses (**Tables 5**, **6**).

DISCUSSION

This is the first study to examine the effect of age and developmental aspects in a CHR sample, alternatively defined by UHR criteria and COGDIS. Within our clinical CHR sample, 91.2% reported the presence of any of the 14 BS included in the definition of COGDIS and COPER. Expectedly and largely independent of functional deficits, our analyses showed a significant lower prevalence of BS in the older age group, i.e., in patients of and above age 24, with the relative probability of reporting BS decreasing by roughly 35–40%.

The previously described age thresholds for perceptive BS around late adolescence (i.e., around age 18) and for cognitive BS in the early twenties (31) that seemed to follow brain maturation processes were considered as further support of the assumption that BS were the most immediate psychopathological expressions of neurobiological aberrations underlying the disorder, i.e., that they were "substrate-close" (29, 31). Hence, the higher prevalence of usually infrequently occurring BS in younger age groups in the community was regarded as indicating that low-frequency BS might occur in childhood and adolescence as an infrequent and temporary non-pathological expression of insignificant and transient dysfunctions in the wake of normal brain maturation (31). Thus, given an undisturbed, "normal" brain maturation, these non-pathological BS would spontaneously remit – or grow out again – over the course of further maturation processes (31) (**Figure 1**). In the Swiss community sample (31), however, BS had not only been less frequent than in our sample (18.1 vs. 91.2%), they had also been reported as meeting frequency requirements of BS criteria, i.e., as occurring at least once per week, at a far lower rate (in only 33.7 vs. 90.7% of those with BS). Whereas, the rate of those meeting the novelty requirement had been only slightly lower in the community (in 77.8 vs. 98.7% of those with BS). A higher frequency of BS along with a higher persistence,

TABLE 3 | Effects of age on the report of the 14 BS irrespective of novelty and frequency (a), when meeting novelty requirement (b) and when meeting frequency requirement (c); binary logistic analysis with method "enter" and 19–23-year-olds as the reference age group.

Age group (years)	*ß*	SE	Wald (*df* = 1)	*p* after bootstrap	Exp (*ß*)	95% CI	*n* present	% present
(A) PREVALENCE OF BS IRRESPECTIVE OF NOVELTY AND FREQUENCY								
≥ 1 BS (in 19–23 years: *n* = 110, 94%)								
15–18	0.241	0.823	0.086	0.769	1.273	0.25–6.38	40	95.2
24–40	***–0.916***	***0.485***	***3.577***	***0.059***	***0.400***	***0.16–1.03***	88	86.3
≥ 1 cognitive BS (in 19–23 years: *n* = 107, 91.5%)								
15–18	–0.119	0.621	0.037	0.848	0.888	0.26–2.99	38	90.5
24–40	**–0.896**	**0.417**	**4.612**	**0.032**	**0.408**	**0.18–0.93**	83	81.4
≥ 1 perceptive BS (in 19–23 years: *n* = 77, 65.8%)								
15–18	0.147	0.387	0.145	0.703	1.159	0.54–2.47	29	69.0
24–40	**–1.093**	**0.281**	**15.105**	**< 0.001**	**0.335**	**0.19–0.58**	40	39.2
(B) PREVALENCE OF BS *MEETING NOVELTY* AND IRRESPECTIVE OF FREQUENCY REQUIREMENT								
≥ 1 BS (in 19–23 years: *n* = 109, 93.2%)								
15–18	0.384	0.812	0.223	0.636	1.468	0.3–7.20	40	95.2
24–40	**–0.930**	**0.456**	**4.153**	**0.042**	**0.394**	**0.16–0.97**	86	84.3
≥ 1 cognitive BS (in 19–23 years: *n* = 104, 88.9%)								
15–18	–0.078	0.56	0.019	0.889	0.925	0.31–2.78	37	88.1
24–40	**–0.845**	**0.378**	**5.010**	**0.025**	**0.429**	**0.21–0.90**	79	77.5
≥ 1 perceptive BS (in 19–23 years: *n* = 75, 64.1%)								
15–18	0.223	0.385	0.333	0.564	1.249	0.59–2.66	29	69.0
24–40	**–1.018**	**0.28**	**13.242**	**< 0.001**	**0.361**	**0.21–0.63**	40	39.2
(C) PREVALENCE of BS *MEETING FREQUENCY* AND IRRESPECTIVE OF NOVELTY REQUIREMENT								
≥ 1 BS (in 19–23 years: *n* = 101, 86.3%)								
15–18	0.409	0.591	0.479	0.489	1.505	0.47–4.79	38	90.5
24–40	***–0.609***	***0.359***	***2.881***	***0.090***	***0.544***	***0.27–1.10***	79	77.5
≥ 1 cognitive BS (in 19–23 years: *n* = 97, 82.9%)								
15–18	0.423	0.536	0.621	0.431	1.526	0.53–4,36	37	88.1
24–40	**–0.656**	**0.329**	**3.964**	**0.046**	**0.519**	**0.27–0.99**	73	71.6
≥ 1 perceptive BS (in 19–23 years: *n* = 55, 47%)								
15–18	0.120	0.360	0.111	0.739	1.127	0.56–2.28	21	50.0
24–40	**–0.663**	**0.283**	**5.504**	**0.019**	**0.515**	**0.30–0.90**	32	31.4

Significant predictors ($p < 0.05$) are in bold type, predictors with significance at statistical trend ($p < 0.10$) in bold italics.

TABLE 4 | Effects of age on the report of BS criteria COPER and COGDIS; binary logistic analysis with method "enter" and 19–23-year-olds as the reference age group.

Age group (years)	*ß*	SE	Wald (*df* = 1)	*p* after bootstrap	Exp (*ß*)	95% CI	*N present*	% present
Cognitive-perceptive BS (COPER; in 19–23 years: *n* = 98, 93.8%)								
15–18	0.151	0.507	0.089	0.766	1.163	0.43-3.14	36	85.7
24–40	***–0.568***	***0.338***	***2.818***	***0.093***	***0.567***	***0.29–1.1***	76	74.5
Cognitive disturbances (COGDIS; in 19–23 years: *n* = 60, 51.3%)								
15–18	**0.751**	**0.382**	**3.874**	**0.049**	**2.119**	**1.0–4.48**	**29**	**69.0**
24–40	0.225	0.272	0.682	0.409	1.252	0.73–2.14	58	56.9

Significant predictors ($p < 0.05$) are in bold type, predictors with significance at statistical trend ($p < 0.10$) in bold italics.

which had not been examined in both the community and the present study, has been assumed to indicate disturbances in brain maturation that might predispose to the development of psychosis (31) (**Figure 1**). Consequently, our present results from a more mentally unwell clinical sample suggest that they might not exhibit the same differential age thresholds for perceptive and cognitive BS for the very reason that the frequent occurrence of BS already signals aberrant neurodevelopment. If this was true, BS should also be more persistent in clinical samples; thus, the course of BS needs to be examined in future studies. For this reason, future psychopathological and neurobiological studies should not only assess the age-of-onset of BS but also examine

TABLE 5 | Age effects on BS considering impaired global social functioning (GF social ≤ 6).

	Significant predictor	ß	SE	Wald (*df* = 1)	*p* after bootstrap	Exp (ß)	95% CI
Prevalence of BS irrespective of novelty and frequency requirements							
≥ 1 BS	No significant predictor						
≥ 1 cognitive BS	No significant predictor						
≥ 1 perceptive BS	**Age**	**–0.684**	**0.191**	**12.838**	**< 0.001**	**0.505**	**0.35–0.73**
Prevalence of BS meeting novelty irrespective of frequency requirement							
≥ 1 BS	*Age*	***–0.637***	***0.334***	***3.633***	***0.057***	***0.529***	***0.28–1.02***
≥ 1 cognitive BS	No significant predictor						
≥ 1 perceptive BS	**Age**	**–0.664**	**0.190**	**12.262**	**< 0.001**	**0.515**	**0.36–0.75**
Prevalence of BS meeting frequency irrespective of novelty requirement							
≥ 1 BS	No significant predictor						
≥ 1 cognitive BS	**Age**	**–0.571**	**0.241**	**5.628**	**0.018**	**0.565**	**0.35–0.91**
≥ 1 perceptive BS	**Age**	**–0.403**	**0.182**	**4.908**	**0.027**	**0.668**	**0.47–0.96**
Prevalence of BS criteria							
COPER	No significant predictor						
COGDIS	No significant predictor						

Binary logistic analysis with method "forward" and "backward" using the respective BS as dependent variable; Age group, GF social ≤ 6 and "age group x GF social ≤ 6" entered as predictors. Only stable models are reported (both methods revealed significant effects). Significant predictors (p < 0.05) are in bold type, predictors with significance at statistical trend (p < 0.10) in bold italics.

TABLE 6 | Age effects on BS considering impaired global role functioning (GF role ≤ 6).

	Significant predictor	ß	SE	Wald (*df* = 1)	*p* after bootstrap	Exp (ß)	95% CI
Prevalence of BS irrespective of novelty and frequency requirements							
≥ 1 BS	No significant predictor						
≥ 1 cognitive BS	No significant predictor						
≥ 1 perceptive BS	**Age**	**–0.684**	**0.191**	**12.838**	**< 0.001**	**0.505**	**0.35–0.73**
Prevalence of BS meeting novelty irrespective of frequency requirement							
≥ 1 BS	*Age*	***–0.668***	***0.340***	***3.853***	***0.050***	***0.513***	***0.26–1.0***
≥ 1 cognitive BS	No significant predictor						
≥ 1 perceptive BS	**Age**	**–0.664**	**0.190**	**12.262**	**< 0.001**	**0.515**	**0.36–0.75**
Prevalence of BS meeting frequency irrespective of novelty requirement							
≥ 1 BS	No significant predictor						
≥ 1 cognitive BS	**Age**	**–0.571**	**0.241**	**5.628**	**0.018**	**0.565**	**0.35–0.91**
≥ 1 perceptive BS	**Age**	**–0.248**	**0.107**	**5.389**	**0.020**	**0.780**	**0.63–0.97**
Prevalence of BS criteria							
COPER	No significant predictor						
COGDIS	No significant predictor						

Binary logistic analysis with method "forward" and "backward" using the respective BS as dependent variable; age group, GF role ≤ 6 and "age group x GF role ≤ 6" entered as predictors. Only stable models are reported (both methods revealed significant effects). Significant predictors (p < 0.05) are in bold type, predictors with significance at statistical trend (p < 0.10) in bold italics.

differences between subjects with an onset of BS before and those with an onset after the likely conclusion of major brain maturation processes in the early twenties.

Furthermore, from the community results it was assumed that an onset before the early twenties may reflect aberrant brain maturation, while an onset at an older age may reflect neurodegenerative processes (31). The possibility to distinguish between aberrant neurodevelopmental and neurodegenerative processes might well-impact on the choice of treatment, for example between neuroprotective and anti-inflammatory interventions (46–48). Thus, a simple reliable and valid marker to guide this distinction, such as age-at-onset and course of BS, might greatly enhance the development of benign psychopharmacotherapy in CHR states.

Next to the clinical status, sampling differences might have also caused the missing differential age thresholds, in particular the selection bias in favor of cognitive BS that meet novelty and frequency criteria, the more restricted age range of the PRONIA study with no inclusion of 8–14-year-olds, the low number of patients below age 19 (16.1%), and the dominance of

the reference age group of 19–23-year-olds (44.8%). These biases resulted in low numbers of cases without any BS and without any cognitive BS and, relatedly, higher standard errors (SE; **Table 3**) in the youngest group, which increase the confidence intervals and the probability (*p*) to falsely accept the null hypothesis of equality between the youngest and the reference group. Thus, from a statistical point of view, the oldest age group that had a more favorable ratio between positive and negative cases, offered a higher likelihood to detect differences between age groups. Compared to cognitive BS, a higher likelihood to detect differences between age groups was also given for perceptive BS that are not part of COGDIS (**Table 1**) and that, consequently, were not directly influenced by the inclusion criteria. Because COPER and COGDIS tend to frequently co-occur because of their shared cognitive BS (49, 50), and our results might reflect a slightly more "natural" and robust variance in relation to age in perceptive BS compared to cognitive BS that was thus maintained in the multivariate models including functional deficits. In contrast, in the community sample, the perceptive BS had shown less pronounced age effects as compared to cognitive BS (31). In light of these differences in sampling and clinical status between the earlier community (29, 31) and our clinical sample, the missing difference between the age thresholds does not seem surprising. Rather, overall, our findings seem to support the notion that criteria-relevant BS occur more frequent before the conclusion of brain maturation in the first half of the twenties. The assumed close link of BS to the "substrate," of course, requires validation in future neurobiological studies, for example in structural imaging studies for that a decrease in gray matter volume (GMV) would be expected to be related to BS groups as a result of potential aberrant brain maturation leading, for example, to an excess in pruning (18, 51, 52) or to neurodegenerative, for example, inflammatory processes (53, 54). In respect to the model on both BS and UHR symptoms (**Figure 1**), however, an increase in GMV would be expected to be related to UHR symptoms as a result of excessive compensatory – though inadequate – neurocognitive coping processes in response to other symptoms or environmental stressors (34, 55).

Thus, the combined assessment of BS and symptomatic UHR criteria might help to better understand brain imaging results in UHR samples reporting both GMV decrease (in the right gyrus rectus, the right superior frontal gyrus, and the left superior frontal gyrus) and GMV increase (in the bilateral median cingulate, the right fusiform gyrus, the left superior temporal gyrus, and the right thalamus) (56). The GMV-increased primary auditory and neocortical language regions, superior temporal gyrus, and insula were reported as the core regions responsible for the positive symptoms, such as delusions, hallucinations, and disorganized speech (57–59) and, in longitudinal studies, progressive GMV reduction of the superior temporal gyrus was linked to low improvement in positive psychotic symptoms (60, 61). These GMV increases are still subject to debate and discussed in relation to different pathophysiological processes in the early phase, age, other demographic differences, genetic predisposal, and different MRI scanners or parameters employed in the method section (56). In light of the model in **Figure 1**, however, the increase in regions already related specifically to positive symptoms might well be perceived as a result of excessive neurocognitive and psychological processes, i.e., intensive cognitive activities, that might have also become evident by the increase in thalamic structures responsible for the emotional experience and expression, and cognitive functions, such as memory, attention, and sensory-guided actions (56). On the other hand, all three regions with GMV reductions are involved in cognitive processes that might be reflected by criteria-relevant cognitive BS (**Table 1**). These processes are: (1), working memory (62), possibly impaired in thought blockages; (2) complex attention (63), possibly impaired in inability to divide attention and captivation of attention, (3) response inhibition (64), possibly impaired in thought interference, pressure and perseveration, disturbance of abstract thinking and unstable ideas of reference; and (4) language and memory recall (65), possibly impaired in disturbances of receptive and expressive speech, and disturbance in distinguish between memory and phantasy. These possible relations between APS and BS and GMV aberrations should be studied in future imaging studies using fine-grained psychopathological measures (15).

Strengths and Limitations

Our study has several strengths and limitations. Among the strengths are clearly the large sample size and the high-quality assessment of BS. Next to the discussed limitations related to sampling, a clear limitation is the related impossibility to reanalyze the age effect on APS for lack of patients below the suggested age threshold of 16 years. Yet, this age threshold has already been replicated in clinical samples (23) and, thus, can be assumed to work in the present sample. Furthermore, the fact that the age thresholds in BS reported from the Swiss community sample (29, 31) could be replicated in this clinical sample, despite the differences in age range, suggest that these findings may generalize to other samples.

Outlook

As the early detection of psychosis is increasingly applied to ever younger age groups, the need to re-evaluate the validity and clinical significance of current CHR criteria and symptoms in younger age groups should be addressed in future studies to improve understanding of what properties (such as age-at-onset, frequency and persistence) convey their clinical relevance at different developmental levels. In doing so, their association with objective measures, such as imaging-based tools, should be given additional attention to gain further insight into the pathogenesis of psychosis and its early symptoms. Such studies have the potential to gain insights into useful targets for interventions and, thus, to improve outcomes prior to the first manifestation of psychosis.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by local research ethics committees of each location. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

HW wrote the first draft under supervision of FS-L and they had full access to the data and take responsibility for the integrity of the data and the accuracy of the data analysis. HW, NK, LK-I, SR, MR, AR, KC, JK, TH, FS-L, AR-R, RU, JH, CP, SW, PB, and SB: acquisition, analysis, or interpretation of data. HW, FS-L, LA, and AP: statistical analysis. NK, LK-I, SR, AR-R, RS, CP, PB, SB, and SW: obtained funding. NK, MR, AR, KC, TH, RU, JH, EM, PB, and SB: administrative, technical, or material support. FS-L, NK, LA, and AP: supervision. All other authors critically revised the manuscript for important intellectual contents and approved of the final version of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.552175/full#supplementary-material

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BRIEF RESEARCH REPORT
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Auditory Mismatch Negativity in Youth Affected by Autism Spectrum Disorder With and Without Attenuated Psychosis Syndrome

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The present study investigates the differences in auditory mismatch negativity (MMN) parameters given in a sample of young subjects with autism spectrum disorder (ASD, $n = 37$) with or without co-occurrent attenuated psychosis syndrome (APS). Our results show that ASD individuals present an MMN decreased amplitude and prolonged latency, without being influenced by concurrent APS. Additionally, when correlating the MMN indexes to clinical features, in the ASD + APS group, we found a negative correlation between the severity of autistic symptoms and the MMN latency in both frequency (f-MMN $r = -0.810$; $p < 0.0001$) and duration (d-MMN $r = -0.650$; $p = 0.006$) deviants. Thus, our results may provide a more informative characterization of the ASD sub-phenotype when associated with APS, highlighting the need for further longitudinal investigations.

Keywords: autism spectrum disorder, attenuated psychosis syndrome, mismatch negativity, EEG, pediatric

INTRODUCTION

Autism spectrum disorder (ASD) is a neurodevelopmental condition characterized by an early onset of social communication deficit associated with a restricted and repetitive pattern of behaviors (1). Since socio-communication impairment is known as a core symptom of ASD, several studies are investigating the role of language difficulties on the central auditory process that, in turn, may be linked to an atypical processing of auditory stimuli, an auditory working memory deficit, and a disrupted sensory acoustic discrimination (2–5).

To better understand the auditory processing in neurodevelopmental disorders, mismatch negativity (MMN) has been widely investigated by basic researches on neurocognitive processes and central auditory and attentional mechanisms (4, 6–9). Specifically, MMN is a negative wave deflection localized in the fronto-central region (10), resulting from the brain's response to infrequent auditory stimuli (deviants) in repetitive stimuli (standards) (6, 11). MMN originates in the auditory and frontal cortex by the central auditory system based on neuronal auditory memory (12) and reflects pre-attentive processes, involving executive functions such as set-shifting ability and working memory (13–15). Thus, researchers have proposed MMN deficit as a marker of auditory processing impairment and consequent disruption in higher cognitive domains

(e.g., attentional control and shifting, working memory) (7). Even in the ASD population, MMN has been used to identify auditory processing deficits, with conflicting results (16–18): a recent meta-analysis (17) on the topic shows that most of the available data report an MMN deficit in ASD individuals, suggesting an altered central ability in auditory discrimination within this population; specifically, Chen et al. (17) report shorter MMN latencies in autistic individuals compared to increased MMN latencies in subjects with Asperger syndrome (AS).

Abnormally decreased MMN has also been reported in other psychiatric disorders such as schizophrenia (19–24), especially in the early stages of the illness (7, 25–27). MMN has been widely investigated as a promising biomarker of conversion to psychosis (7, 26) and of remission (28) in individuals at a clinical high risk (CHR) and with attenuated psychosis syndrome (APS). To date, the majority of the available data reports a reduced amplitude of MMN in the at-risk adult population (29). In this context, Bodatsch et al. (30), evaluating the MMN paradigm in a young adult sample of 62 CHR subjects compared to 33 individuals with first-episode schizophrenia and 67 healthy controls (HC), concluded that MMN amplitude was significantly reduced in at-risk subjects who later converted to first-episode psychosis compared to non-converter individuals and to HC.

Despite distinct clinical and electrophysiological features, several studies have focused on the overlap between autistic symptoms and psychotic experiences in both adult and adolescent population (31–33). Longitudinal studies report that 20–50% of individuals with childhood-onset schizophrenia met the criteria for premorbid ASD (34–37). Moreover, a recent meta-analysis confirms that people affected with schizophrenia spectrum disorders (SSDs) show higher autistic symptoms compared to healthy controls (38). Similarly, in ASD individuals, the comorbid rates of SSDs ranging from 0 to 34.8% are reported, with higher rates of transition to SSDs in specific clinical subgroups such as AS and pervasive developmental disorder—not otherwise specified (PDD-NOS), categorized based on the Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition (DSM-IV) (32); this evidence could suggest a possible increased vulnerability in the autistic population (32).

Moreover, it is well-known that individuals with ASD and SSDs share some clinical features, such as social difficulties, language impairment, and common cognitive features (e.g., weak central coherence deficit and set-shifting difficulties) (33, 39, 40).

Thus, in the recent years, research aiming to detect possible cognitive and neurophysiological linkages between these disorders has grown considerably (33, 41–43).

However, despite the evidence of this strong association between ASD and SSDs, to our knowledge, no previous study using a clinical and neurophysiological approach has yet evaluated the co-occurrence of both conditions within a pediatric sample.

The present study aimed to characterize, from a clinical and neurophysiological point of view, a sample of ASD participants (age range: 9–18 years) with attenuated psychosis syndrome (ASD + APS) in comparison with ASD patients without APS (ASD) and with healthy control (HC) groups, pointing to better defining the ASD phenotype when associated with other psychiatric conditions such as APS.

MATERIALS AND METHODS

Participants

A total of 40 ASD individuals (age range: 9–18 years; age median: 13.67; eight females and 32 males), according to Diagnostic and Statistical Manual of Mental Disorders—Fifth Edition (DSM-5) criteria (1), were recruited from the Children Psychiatry Unit of the University Hospital Tor Vergata of Rome between January 2018 and July 2019.

A healthy control (HC) group of 20 individuals (age range: 9–18 years; age median: 13.04; eight females and 12 males), voluntarily recruited from a sport club, was also included.

The present study was approved by the Ethical Committee of our University Hospital, Fondazione Policlinico Tor Vergata (Register number 126/18), and informed consent was obtained from all legal holders of custody of both ASD and HC groups.

The adopted exclusion criteria were the presence of syndromic autism, intellectual quotient (IQ) equal or below 70, non-fluent speech, epilepsy, and other concurrent psychiatric or neurodevelopmental conditions (e.g., obsessive–compulsive disorder, attention deficit and hyperactivity disorder).

All participants underwent a clinical evaluation and electroencephalogram (EEG) to evaluate the MMN paradigm.

From the initial sample of 40 ASD individuals, three did not complete the clinical assessment and dropped out of the study. The final sample of 57 participants (37 ASD + 20 HC) was divided in three groups: ASD ($n = 21$), ASD + APS ($n = 16$), and HC ($n = 20$).

Clinical Assessment

All ASD individuals underwent a cognitive evalution to assess IQ. Depending on the age and on each individual's ability to cooperate, the Leiter International Performance Scale—Revised (Leiter-R) (44), the Wechsler Intelligence Scale for Children—Fourth Edition (WISC-IV) (45), or the Wechsler Adult Intelligence Scale—Revised (WAIS-R) (46) was performed.

ASD diagnosis was based on the DSM-5 criteria (1). All participants underwent the Autism Diagnostic Observation Schedule—Second Edition (ADOS-2) test (47), performed by a licensed clinician. The ADOS-2, a semi-structured observational assessment of autistic symptoms, includes five modules based on expressive language level and age. The ADOS-2 algorithm is organized in social affect (SA), restricted and repetitive behaviors (RRB), and the total score. Modules 1, 2, and 3 provide the calibrated severity score (CSS), ranging from 1 to 10, indicating a measure of autism severity level. By contrast, even if a recent revision of the algorithm for module 4 is now available (48), this has not been applied yet to the Italian population. Thus, based on age, language, and adaptive abilities, all ASD subjects were administered module 3, being in line with the ADOS-2 manual (47) which allows clinicians and researchers to choose module 3 even for adolescents over 16 years of age in order to permit a comparison between CSS scores in the ASD sample (47, 49).

Finally, to evaluate the presence of a concurrent APS condition, the Structured Interview for Psychosis-Risk Syndromes (SIPS) was administered to all ASD individuals (50–52). In this context, the proposed "Attenuated Psychosis Syndrome (APS)" DSM-5 diagnosis refers to a condition characterized by the recent onset of sub-threshold psychotic symptoms associated to a higher risk of conversion to psychotic disorder within the next year (53–55).

According to a previous study (56), the presence of an APS condition was confirmed when a score of 3 or 4 of 5 was obtained at the SIPS positive symptoms scale (SIPS-P) (51, 55) (see **Supplementary Figure 1** for SIPS-P score distributions in ASD and ASD + APS).

Moreover, the absence of a family history of schizophrenia was confirmed by the administration of a clinical interview.

Finally, the HC underwent a screening clinical evaluation of IQ [based on age, Raven Matrices colored (age < 11 years) or progressive (age > 11 years) (57)] and of behavioral problems (Child Behavior Checklist 6–18 years—CBCL 6–18 years) (58). Moreover, a clinical interview was performed by a child and adolescent psychiatrist in order to exclude the presence of autistic or psychotic symptoms in this population.

All the HC individuals presented normal cognitive function (IQ assessed with Raven Matrices above 25–50° centile for colored form and above 85 for the progressive form) and resulted negative for the presence of any behavioral problem or psychiatric condition.

Neurophysiological Evaluation

All subjects (ASD, ASD + APS, and HC) underwent a 64-channel EEG recorded while listening to a passive auditory paradigm and watching a silent video. The MMN waveforms to frequency-deviant tones (*f-MMN*) and duration-deviant tones (*d-MMN*) were obtained for the Fz channel. The MMN peak latency and peak amplitude were measured. MMN is, in fact, described by *latency*, which is the timing of the negative peak in different waveforms, and *amplitude*, which represents the average response on the negative peak, reflecting attentive cortical processes (4).

The EEG was recorded at 2,048 Hz with an EBNeuro 72-channel EEG system using sintered Ag/Ag-Cl electrodes in an electrode cap with 61 standard scalp sites and two single Ag/AgCl disk electrodes (1 mm in diameter) over the left and the right mastoids, with the reference electrode placed between AFz and Fz and the ground electrode between CPz and Pz; one polygraphic channel was also recorded to monitor vertical and horizontal eye movements, with the active electrode placed 1 cm lateral to the outer canthus of the right eye and the reference electrode placed on the lower eyelid. The electrode impedances were maintained below 5 kΩ.

Stimuli and Tasks

The auditory paradigm consisted of 2,000 standard tones (1,000 Hz, 50 ms), 200 frequency-deviant tones (1,200 Hz, 50-ms duration, 5-ms rise/fall), and 200 duration-deviant tones (1,000 Hz, 100 ms, 10-ms rise/fall), for a total of 2,400 tones. All tones were presented binaurally through Sennheiser HD25 SP II at 80 dB SPL with an interstimulus interval of 500 ms and in random order with the constraint that a deviant tone was preceded at minimum by three standard tones. During the auditory paradigm, the subjects were invited to watch a silent cartoon and to ignore the tones that they heard; at the end of the session, questions on the cartoon were asked to the participants in order to check the level of attention in watching the video.

MMN Analysis

The EEG data were processed offline using EEGLAB in MATLAB environment. The continuous EEG recordings were digitally filtered 1 to 20 Hz, re-referenced to the algebraic average of the left and the right mastoids, and segmented from −100 to 400 ms relative to the stimulus onset. Epochs with artifacts exceeding ±100 μV were excluded. Average ERPs were computed from the artifact-free epochs and baseline-corrected with a prestimulus baseline of −100 to 0 ms.

The frequency and duration MMNs were measured at Fz channel as an average amplitude under within 100 to 200 ms (frequency) and 150 to 250 ms (duration) post-stimulus onset in the different waveform (deviant–standard), respectively.

Statistical Analyses

Data were presented as means (SD) and frequencies (percentages). Differences in age and gender between HC, ASD, and ASD + APS were investigated, respectively, using one-way analysis of variance (ANOVA) and Pearson's chi-square test (χ^2). Comparisons between ASD and ASD + APS in ADOS and SIPS measures were performed with Student's *t*-test.

Explorative data analysis with the Kolmogorov–Smirnov test showed that the MMN indices had a normal distribution (consistently, $p > 0.20$). ANOVA models were used to measure the difference between HC, ASD, and ASD + APS in d-MMN and f-MMN latencies and amplitudes. *Post-hoc* tests were performed with Bonferroni confidence interval adjustment for multiple comparisons to define which variables contributed to the major effects.

Explorative correlation analysis was performed in order to investigate the relation between MMN and clinical (ADOS and SIPS) indices. Statistical significance was set at *p*-values < 0.05.

RESULTS

Demographic and Clinical Data

Age, sex, IQ, ADOS-2, and SIPS subscale scores are summarized in **Table 1**.

No significant differences emerged in terms of age [ASD vs. HC: 14.16 (3.05) vs. 14.20 (4.56); $t_{55} = -0.040$, $p = 0.969$] and sex ($\chi^2_1 = 2.172$, $p = 0.141$). Moreover, within the ASD sample, no differences in terms of IQ came out (see **Supplementary Figure 2**).

At the clinical level, the ASD + APS group exhibits a higher level of psychotic symptoms as assessed by the SIPS interview compared to the ASD (SIPS total, $p < 0.0001$). Specifically, compared to the ASD, in the ASD + APS group, we observe a higher value of positive (SIPS-P, $p = 0.001$), disorganized

TABLE 1 | Descriptive and univariate statistics of sociodemographic and clinical characteristics in healthy controls (HC) and autism spectrum disorder (ASD) and ASD + attenuated psychosis syndrome (ASD+APS) patients.

	HC ($N = 20$)	ASD ($N = 21$)	ASD + APS ($N = 16$)	Statistics
Gender (F/M)	8/12	4/17	4/12	$p = 0.312$
Age	14.20 (4.56)	14.28 (2.92)	14.00 (3.31)	$F_{2,54} = 0.028$, $p = 0.973$
IQ		105.14 (17.77)	96.50 (19.49)	$t_{35} = -1.406$, $p = 0.169$
ADOS-2 SA	–	7.86 (2.52)	9.25 (3.13)	$t_{35} = -1.501$, $p = 0.142$
ADOS-2 RRB	–	1.67 (1.49)	2.50 (2.03)	$t_{35} = -1.439$, $p = 0.159$
ADOS-2 CSS	–	5.81 (1.54)	6.88 (2.09)	$t_{35} = -1.787$, $p = 0.083$
SIPS-P	–	2.38 (3.07)	6.44 (3.60)	$t_{35} = -3.696$, $p = 0.0008$
SIPS-N	–	3.29 (2.53)	3.81 (1.83)	$t_{35} = -0.703$, $p = 0.487$
SIPS-D	–	1.43 (1.50)	2.81 (0.91)	$t_{35} = -3.252$, $p = 0.003$
SIPS-G	–	1.38 (1.12)	2.19 (1.05)	$t_{35} = -2.235$, $p = 0.032$
SIPS total	–	8.48 (5.02)	15.25 (3.53)	$t_{35} = -4.597$, $p < 0.0001$

Values are frequencies and means (and SDs).
IQ, intelligence quotient; ADOS-2: Autism Diagnostic Observation Schedule—Second Edition; ADOS-2 SA, social affect domain; ADOS-2 RRB, restricted and repetitive behaviors; ADOS-2 CSS, calibrated severity score; SIPS: Structured Interview for Psychosis-Risk Syndromes; SIPS-P, positive symptoms domain; SIPS-N, negative symptoms domain; SIPS-D, disorganization symptoms domain; SIPS-G, general symptoms domain.

TABLE 2 | Descriptive and univariate statistics of dMMN and fMMN latency and amplitude in healthy controls (HC) and autism spectrum disorder (ASD) and ASD + attenuated psychosis syndrome (ASD+APS) patients.

	HC ($N = 20$)	ASD ($N = 21$)	ASD + APS ($N = 16$)	ANOVAs			
				Main effect	Bonferroni *post-hoc*		
					HC vs. ASD	HC vs. ASD + APS	ASD vs. ASD + APS
d-MMN							
Latency (ms)	182.70 (15.00)	184.62 (21.70)	189.25 (30.43)	$F_{2,54} = 0.386$, $p = 0.682$	$p = 1.000$	$p = 1.000$	$p = 1.000$
Amplitude (μV)	−6.72 (1.70)	−4.53 (2.00)	−4.22 (2.10)	$F_{2,54} = 9.471$, $p = 0.0003$	$p = 0.002$	$p = 0.0009$	$p = 1.000$
f-MMN							
Latency (ms)	153.80 (13.13)	172.62 (26.13)	175.25 (34.27)	$F_{2,54} = 4.090$, $p = 0.022$	$p = 0.062$	$p = 0.043$	$p = 1.000$
Amplitude (μV)	−4.80 (1.33)	−3.57 (1.83)	−3.24 (1.98)	$F_{2,54} = 4.317$, $p = 0.018$	$p = 0.076$	$p = 0.027$	$p = 1.000$

d-MMN, duration-deviant tones mismatch negativity; f-MMN, frequency-deviant tones mismatch negativity.

(SIPS-D, $p = 0.002$), and general psychotic symptoms (SIPS-G, $p = 0.031$).

However, no relevant differences emerged between the two groups in terms of negative symptoms (SIPS-N, $p = 0.468$) and autistic features measured by the ADOS-2 test (ADOS-2 CSS, $p = 0.098$).

MMN Component Characteristics

Compared to HC, the whole ASD group showed significantly less negative values of d-MMN amplitude [−4.40 (2.02) vs. −6.72 (1.70); $t_{55} = 4.355$, $p < 0.0001$] as well as longer f-MMN latency [173.76 (29.50) vs. 153.80 (13.13); $t_{55} = 2.867$, $p = 0.006$] and less negative values of f-MMN amplitude [−3.43 (1.88) vs. −4.80 (1.33); $t_{55} = 2.900$, $p = 0.005$] (**Table 2**; **Figure 1**).

No difference between ASD and HC in d-MMN latency [186.62 (25.55) vs. 182.70 (15.00); $t_{55} = 0.629$, $p = 0.532$] came out.

The ANOVA models showed that the three groups were different in d-MMN amplitudes and f-MMN latencies and amplitudes. Specifically, the *post-hoc* analysis showed that ASD and ASD + APS had higher values in latencies and lower values in amplitudes with respect to HC. However, in terms of MMN indexes, no significant differences came out between the ASD and the ASD + APS groups (**Table 2**). Moreover, including the IQ as

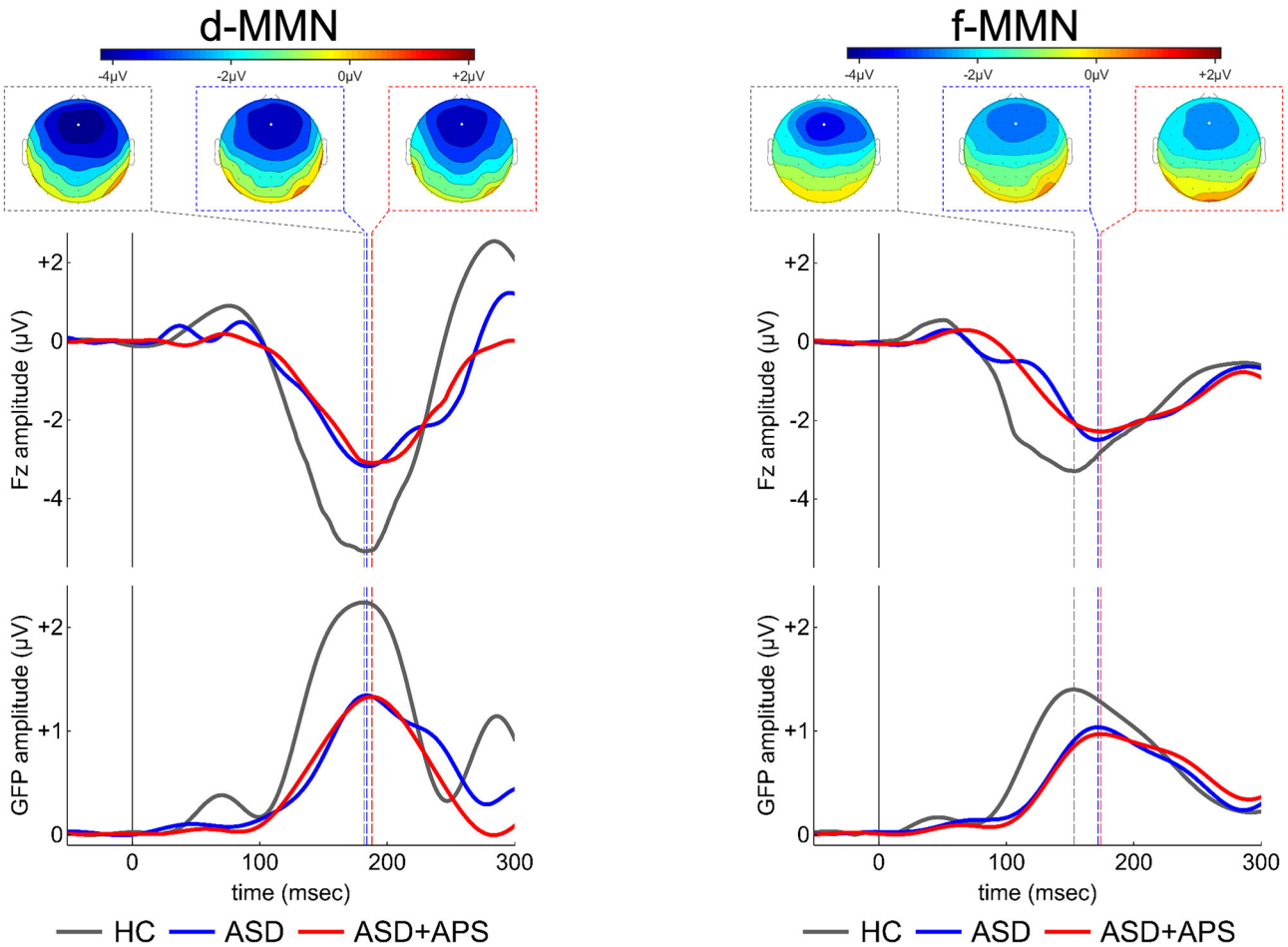

FIGURE 1 | Electrical scalp map topographies (for each group, at the MMN grandaverage peak; upper panels portion), grandaverage waveforms at Fz channel **(middle panels portion)** and Global Field Power (GFP, a global measure of electrical field strength; **middle panels portion**) in the three groups (ASD, ASD+APS, and HC) for each condition, d-MMN **(left panel)** and f-MMN **(right panel)**. As expected, MMN has a fronto-central distribution over the scalp midline, with strongest electrical field responses around Fz channel (indicated as a white circle in the scalp map images). ASD: Autism Spectrum disorder; ASD+APS: Autism Spectrum Disorder + Attenuated Psychosis Syndrome; HC: Healthy Controls.

a covariate, no significant differences emerged between the two groups (see **Supplementary Tables 1, 2**).

Correlation Between MMN Component Characteristics and Clinical Data

Correlation coefficients, with Bonferroni-adjusted *P*-values (*p*-value threshold / number of comparisons = 0.05/36 = 0.0013889 = 0.0014), were computed between d-MMN and f-MMN amplitude and latency indices and ADOS-2 and SIPS subscale scores separately in the ASD and the ASD + APS groups (**Table 3**).

Specifically, in the ASD group (**Table 3**), we found a negative correlation between d-MMN latency and ADOS-2 CSS score ($r = -0.457$; $p = 0.037$) and a positive correlation between f-MMN and ADOS-2 RRB ($r = 0.478$; $p = 0.028$).

In the ASD + APS group (**Table 3**), applying Bonferroni correction (*p*-value threshold / number of comparisons = 0.05/36 = 0.0013889 = 0.0014), a strong negative correlation emerged between f-MMN latency and ADOS-2 CSS ($r = -0.811$; $p < 0.0001$), RRB ($r = -0.535$; $p = 0.033$), and SA ($r = -0.616$; $p = 0.011$) and between d-MMN latency and ADOS-2 CSS ($r = -0.650$; $p = 0.006$) and ADOS-2 SA ($r = -0.575$; $p = 0.020$), demonstrating that a higher level of autistic symptoms was linked to reduced MMN latencies (**Figure 2**).

No significant correlation emerged between MMN amplitude and latency parameters to SIPS scores in both groups (ASD and ASD + APS).

DISCUSSION

MMN has been well-established as a good reliable marker for pre-attentional mechanism. However, during the past years, MMN has been separately studied in the autistic (16, 17) and in the at-risk psychotic population (20, 21, 59), and findings of the concurrent presence of both ASD and APS have not been reported so far. Thus, in the present study, we aimed

TABLE 3 | Results of correlation analysis between mismatch negativity indices and clinical phenotype in autism spectrum disorder (ASD) and ASD + attenuated psychosis syndrome (ASD+APS) groups are reported.

	SA	ADOS-2 RRB	ADOS-2 CSS	SIPS-P	SIPS-N	SIPS-D	SIPS-G	SIPS-tot
ASD								
dMMN_Fz_latency	$r = -0.197$	$r = -0.400$	*$r = -0.457$*	$r = 0.155$	$r = 0.150$	$r = 0.028$	$r = 0.400$	$r = 0.268$
	$p = 0.392$	$p = 0.072$	*$p = 0.037$*	$p = 0.502$	$p = 0.518$	$p = 0.903$	$p = 0.072$	$p = 0.240$
dMMN Fz amplitude	$r = -0.061$	$r = 0.132$	$r = 0.051$	$r = -0.148$	$r = -0.358$	$r = -0.219$	$r = -0.294$	$r = -0.403$
	$p = 0.792$	$p = 0.568$	$p = 0.826$	$p = 0.522$	$p = 0.111$	$p = 0.341$	$p = 0.195$	$p = 0.070$
fMMN Fz latency	$r = -0.101$	$r = 0.478$	$r = 0.185$	$r = 0.152$	$r = 0.015$	$r = 0.131$	$r = 0.134$	$r = 0.169$
	$p = 0.665$	$p = 0.028$	$p = 0.422$	$p = 0.511$	$p = 0.950$	$p = 0.573$	$p = 0.563$	$p = 0.463$
fMMN Fz amplitude	$r = 0.316$	$r = 0.043$	$r = 0.371$	$r = -0.227$	$r = -0.071$	$r = -0.151$	$r = -0.148$	$r = -0.254$
	$p = 0.163$	$p = 0.852$	$p = 0.098$	$p = 0.322$	$p = 0.759$	$p = 0.512$	$p = 0.521$	$p = 0.268$
ASD + APS								
dMMN Fz latency	*$r = -0.575$*	$r = -0.426$	*$r = -0.650$*	$r = 0.076$	$r = 0.094$	$r = -0.010$	$r = -0.029$	$r = 0.115$
	$p = 0.020$	$p = 0.100$	*$p = 0.006$*	$p = 0.780$	$p = 0.729$	$p = 0.970$	$p = 0.916$	$p = 0.672$
dMMN Fz amplitude	$r = -0.420$	$r = -0.108$	$r = -0.232$	$r = -0.193$	$r = -0.059$	$r = 0.139$	$r = 0.400$	$r = -0.073$
	$p = 0.106$	$p = 0.690$	$p = 0.387$	$p = 0.473$	$p = 0.830$	$p = 0.611$	$p = 0.124$	$p = 0.788$
fMMN Fz latency	*$r = -0.616$*	*$r = -0.535$*	*$r = -0.811$*	$r = -0.090$	$r = 0.024$	$r = -0.122$	$r = -0.282$	$r = -0.195$
	$p = 0.011$	*$p = 0.033$*	*$p = 0.000$*	$p = 0.740$	$p = 0.929$	$p = 0.652$	$p = 0.290$	$p = 0.470$
fMMN Fz amplitude	$r = -0.309$	$r = 0.097$	$r = -0.125$	$r = 0.095$	$r = 0.196$	$r = 0.108$	$r = 0.300$	$r = 0.315$
	$p = 0.244$	$p = 0.722$	$p = 0.645$	$p = 0.727$	$p = 0.467$	$p = 0.690$	$p = 0.259$	$p = 0.235$

Significant results are shown in italics.

ADOS-2: Autism Diagnostic Observation Schedule—Second Edition; ADOS-2 SA, social affect domain; ADOS-2 RRB, restricted and repetitive behaviors; ADOS-2 CSS, calibrated severity score; SIPS-tot, SIPS total score; SIPS: Structured Interview for Psychosis-Risk Syndromes; SIPS-P, positive symptoms domain; SIPS-N, negative symptoms domain; SIPS-D, disorganization symptoms domain; SIPS-G, general symptoms domain; p, Bonferroni adjusted p-values (statistical significance at p-values < 0.05).

to investigate differences in MMN features concerning both frequency and duration deviants in a pediatric sample of ASD participants with or without co-occurrent APS compared to a healthy control group.

Being in line with a recent meta-analysis on the topic by Chen et al. (17), showing a reduced amplitude in response to non-speech sound deviants in the ASD population, our results support the evidence that young ASD individuals present a different pattern of pre-attentional processes measured as MMN amplitude indexes compared to HC. By contrast, our data demonstrate a prolonged MMN latency in response to tone–frequency deviants in the whole ASD group, as reported in AS individuals. As is known, previous research also suggests a key role of the brain temporal regions in either processing language and social cognition abilities (60–62) or auditory memory processes in ASD individuals (63). Taking these results that refer to available studies together, our findings yield the knowledge that ASD individuals present a significant impairment in pre-attentive temporal auditory processing (64), showing a slower response in the sound duration identification task (65).

Additionally, we have evaluated the MMN paradigm not only in ASD participants but also in individuals with co-occurrent APS in order to investigate whether the presence of concurrent attenuated psychotic symptoms could influence the pre-attentive pattern in this "at-risk population." Our results show that, when an APS condition is associated to ASD, no significant differences emerged in terms of MMN indexes, leading to the hypothesis that, in autistic individuals, the presence of a concurrent APS condition does not significantly impair the pre-attentive temporal auditory process measured at MMN.

Furthermore, to better investigate the differences between the two groups (ASD and ASD + APS) and the impact of the clinical phenotype, we analyzed the correlations between MMN indexes to both autistic and psychotic symptoms. Our results demonstrate a significant correlation between electrophysiological indexes, referred to MMN latencies, and autistic symptoms level. Specifically, in the ASD group, we found a negative correlation between d-MMN latency and ADOS-2 CSS score, with reduced latency in response to duration deviants linked to a higher autistic symptom level. In the ASD + APS group, we noticed an even stronger negative correlation between ADOS-2 CSS score and both d-MMN and f-MMN latency indexes, with reduced MMN latency associated with a higher level of autistic symptoms. No significant correlations to attenuated psychotic symptoms measured by the SIPS interview came out. Interestingly, it is known that a shorter MMN latency, generated by both frequency and duration tone deviants, is described in individuals affected with schizophrenia (66–68) and in those considered at risk for psychosis (59), without a significant correlation to the severity of the psychotic symptoms (68). Thus, from a neurobiological perspective, if the earlier peak of MMN could reflect temporal responsiveness in the auditory cortex, both in ASD and ASD + APS populations (69), from a clinical point of view, the presence of a strong negative

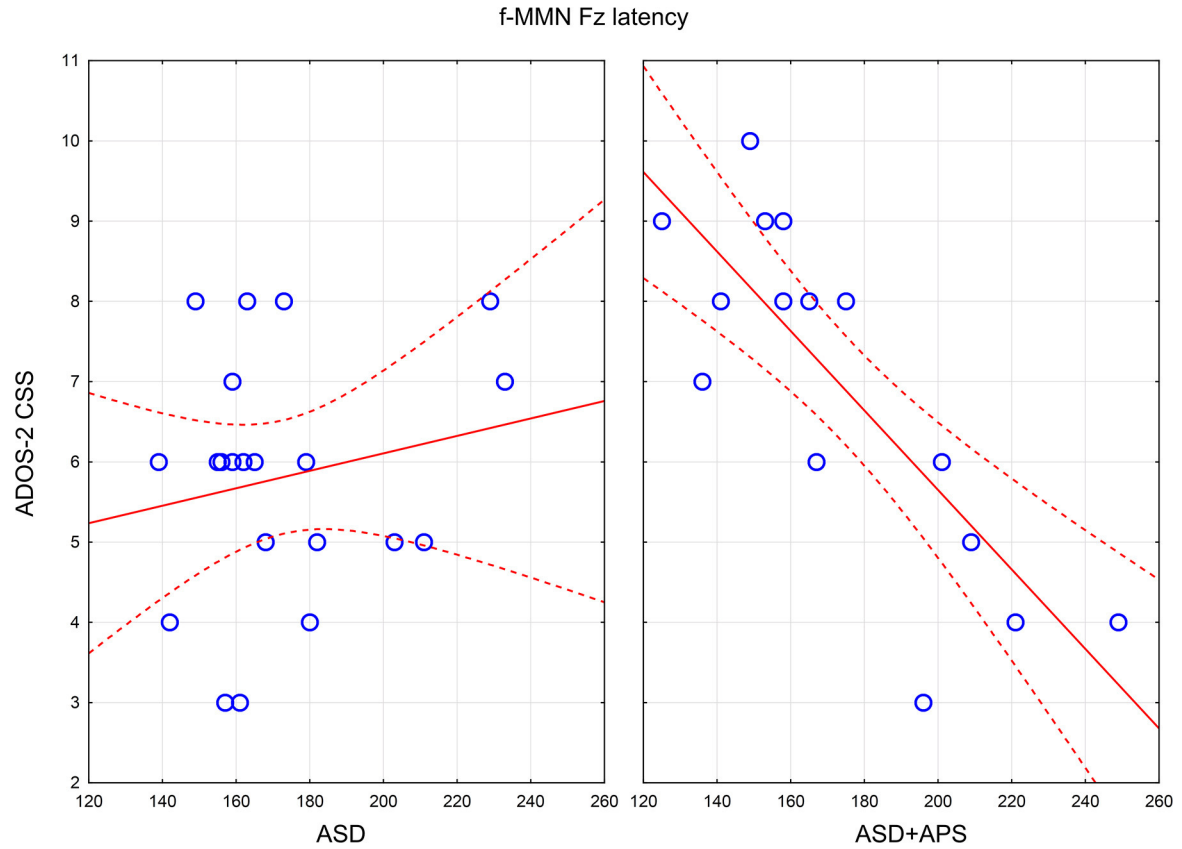

FIGURE 2 | Scatterplots of relations between f-MMN latency and ADOS-2 CSS in ASD **(left panel)** and ASD+APS **(right panel)**. In the panels, the continuous lines are the linear regression lines, the dashed lines indicate the 95% Confidence Intervals for mean, and the empty circles represent the value for each autistic subject. ADOS-2 CSS: Autism Diagnostic Observation Schedule—Second Edition, calibrated severity score; ASD: Autism Spectrum disorder; ASD+APS: Autism Spectrum Disorder + Attenuated Psychosis Syndrome; f-MMN: frequency-deviant tones mismatch negativity.

correlation between the latency indexes in both deviants (d-MMN and f-MMN) to the severity of autistic symptoms in the ASD + APS group could describe a greater clinical impairment in this population, especially referring to autistic symptoms. Moreover, given that other studies (21, 70–72) reported that different MMN latency features, in both d-MMN and f-MMN, could be a possible biomarker in different stages of psychotic symptoms, it is crucial to further investigate whether the duration of the illness could impact on the correlation between MMN features and clinical phenotype. Thus, the next step of this research study will be the differentiation, in terms of MMN latency parameters, between ASD + APS subjects who would convert to psychosis and those who would not.

Although in ASD individuals it is still challenging to translate neurophysiological indexes into clinically prognostic features, understanding the role of MMN as a possible biomarker of psychotic symptom progression could help clinicians to better describe ASD individuals at risk for psychosis. In this context, our findings start to provide a more informative characterization of the ASD sub-phenotype by a dimensional approach and a better evaluation of illness progression within individuals considered "at-risk" for developing psychotic disorders. This knowledge might consequently lead to an optimal management of the therapeutic intervention in terms of choice, timing, and duration.

Thus, despite some strengths such as the clinically well-described ASD sample and the inclusion of young individuals, our study presents some limitations that should be taken into account when interpreting our data. Firstly, the sample size. Even if our study is in line with the majority of available studies aimed to assess MMN in ASD individuals (17), the sample size is relatively small if compared to other clinical studies [see Foss-Feig et al. (73)]. Secondly, the age range (9–18 years). Indeed even if including young individuals in the sample is a strength of the study, allowing to assess the presence of psychosis risk at a very early prodromal phase (74), the exclusion of individuals aged over 18 years old does not permit to explore the possible onset of psychotic symptoms in the ASD group at that point. Moreover, the evaluation of psychotic symptoms in young autistic individuals with cognitive borderline functioning could be challenging, even for trained clinicians. Besides, the lack of information about the age onset of psychotic symptoms in ASD individuals before our assessment is a limitation. Furthermore, the lack of an APS control group without ASD, in order to better evaluate the significance of our results in the ASD +

APS group, is another limiting factor. Finally, it is important to highlight a possible recruitment bias in the fact that we included all participants with well-established compliance. This strongly highlights the need for further investigations, especially through longitudinal studies, in order to better evaluate the possible relevance and the prognostic meaning of the MMN preattentive patterns deficit in ASD individuals at risk for psychosis.

DATA AVAILABILITY STATEMENT

The data that support the finding of this study are available on request from the corresponding authors, GDL and LM.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethical Committee of our University Hospital, Fondazione Policlinico Tor Vergata, Rome (Register number 126/18). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LM, GDL, and MR conceived and designed the present study. AR and MS evaluated autism spectrum disorder and assessed the symptom severity. MR evaluated the psychotic symptoms. GDL performed the electrophysiological recordings and analyzed the data. GDL, AR, and MS wrote the manuscript, and LM and PC substantially revised the manuscript. All the authors contributed to the writing of the manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fpsyt.2020.555340/full#supplementary-material

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Personality Traits and Disorders in Adolescents at Clinical High Risk for Psychosis: Toward a Clinically Meaningful Diagnosis

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Aims: Recent meta-analytic data show that approximately 40% of individuals at clinical high risk for psychosis (CHR) receive at least one personality disorder (PD) diagnosis. Personality pathology could significantly influence CHR patients' prognosis and response to treatment. We aimed at exploring the PD traits of CHR adolescents, in order to outline a prototypic description of their most frequently observed personality characteristics.

Methods: One hundred and twenty-three psychiatrists and psychologists used a Q-sort procedure [i.e., the Shedler–Westen Assessment Procedure-200 for Adolescents (SWAP-200-A)] to assess personality traits and disorders in 58 (30 male; mean age = 16 years, range = 13–19 years) CHR adolescents and two gender- and age-matched samples, respectively, with (n = 60) and without PDs (n = 59).

Results: Differences between the CHR, PD, and clinical groups showed that CHR adolescents had pervasive and more clinically relevant schizoid, schizotypal, borderline, and avoidant traits, as well as poorer adaptive functioning. Moreover, by collecting the highest mean SWAP-200-A items, we empirically outlined a prototypic description of CHR youths, comprised of avoidance of social relationships; suspiciousness; obsessional thoughts; lack of psychological insight; dysphoric and overwhelming feelings of anxiety and depression; odd and anomalous reasoning processes or perceptual experiences; symptoms of depersonalization and derealization; and negative symptoms of avolition, abulia, blunted affects, and impaired role functioning.

Conclusions: The results suggest that avoidant interpersonal strategies, impaired mentalization, and difficulties in emotional regulation could become important targets for psychosocial interventions with CHR adolescent populations.

Keywords: clinical high risk (CHR) for psychosis, personality, adolescence, early detection & prevention, personality traits

INTRODUCTION

Over the last two decades, two complementary sets of operational criteria have been developed to identify young people putatively considered at imminent risk for developing a psychosis spectrum disorder (1). First, the ultra-high risk (UHR) criteria refer to attenuated psychotic symptoms (APS), brief limited intermittent psychotic symptoms (BLIPS), and genetic vulnerability associated with a marked decline in psychosocial functioning [genetic risk and deterioration syndrome (GRD)] (2). Second, the basic symptoms (BS) criteria describe subjectively experienced subclinical disturbances in perception, thought processing, language, and attention; such symptoms are phenomenologically distinct from those of full-blown psychosis, as the patient's insight and reality testing are preserved (3, 4). Longitudinal research has suggested that individuals at clinical high risk for psychosis (CHR; i.e., individuals meeting UHR and/or BS criteria) are up to 20 times more likely to develop psychosis, compared to the general population (5).

Evidence has revealed that the CHR population may display heterogeneous clinical presentations and a high prevalence of psychiatric syndromes—particularly depressive and anxiety disorders—which may influence the psychopathological frame and treatment outcome (6–8). Moreover, reports from the largest studies in the field—such as the Prevention through Risk Identification, Management, and Education [PRIME (9)] and the Recognition and Prevention [RAP (10)] programs, as well as the North American Prodrome Longitudinal Study [NAPLS (11)]—have shown that certain personality disorders (PDs) are prevalent among CHR adolescents and young adults. Indeed, a recent and comprehensive meta-analysis (12) of 17 empirical investigations ($n = 1{,}868$) showed a 39.4% prevalence rate of PDs (at least one PD diagnosis) within this population. In particular, 13.4 and 11.9% of the CHR patients suffered from schizotypal and borderline PDs, respectively. These rates are four times larger than those of the general population (13) and roughly equivalent to those reported in previous meta-analyses concerning other clinical psychiatric diagnoses [e.g., 41% for depressive disorders and 34.4% for anxiety disorders (2, 4, 5)].

Despite the high prevalence and variability of PDs among CHR individuals (12), studies on the psychosis-predictive value of PDs have generated mixed results, highlighting a potential impact of schizoid and borderline PDs only (12, 14)[1]. However, PD diagnoses might contribute to explaining the severe distress and disability of CHR patients, difficulties in their provision of care, and differences in their responses to treatment (12, 16).

[1]It would seem that the presence of a PD does not affect clinical outcomes, irrespective of a transition to full-blown psychotic disorder. For example, a recent investigation by Polari et al. (15) demonstrated that an additional diagnosis of borderline personality disorder was not associated with poorer outcomes, in terms of the recurrence, relapse, and remission of APS, as well as general functioning. However, further research is needed, and these results should also be replicated for outcomes other than APS.

Overall, we propose that studies of personality features in CHR research have suffered from at least one major limitation, linked to their assessment procedures. In fact, the great majority of studies in this field (16–19) have used self-report measures or structured interviews to assess personality pathology in CHR patients [e.g., the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders 4th ed.* [SCID (20)]; the Millon Multiaxial Inventory, Version III [MCMI-III (21)]]. Such instruments may suffer from several weaknesses. For example, many personality features cannot be measured via direct questioning, due to the implicit nature of their underlying cognitive and affective processes and/or respondents' lack of self-awareness or defensive biases (e.g., respondents may provide misleading information when describing socially undesirable symptoms or traits) (22, 23).

Such limitations may be especially pronounced in research involving patients with a schizophrenia-spectrum disorder. Boberg et al. (24) showed that outcomes from the Structured Clinical Interview for *Diagnostic and Statistical Manual of Mental Disorders 5th ed.* (SCID-5) (25) were only marginally correlated with the diagnoses of expert clinicians. In particular, when considered alone (i.e., without clinician assessments), the interview misdiagnosed a high proportion of schizophrenia-spectrum disorders as PDs (in particular, borderline PDs) and tended to overlook schizotypal PDs. Clinician-report methods for assessing personality rely on the observations of experienced raters and their longitudinal knowledge of patients. For this reason, such measures can overcome the abovementioned biases, ensuring greater validity (26).

Starting from these premises, the present study aimed at deepening our understanding of personality traits and disorders in the CHR adolescent population. An accurate assessment of patients' features could have relevant clinical implications, particularly in promoting patient-tailored interventions to enhance treatment effectiveness (26). In the study, we asked a sample of experienced clinicians to describe their patients (with a positive or negative CHR status) by rating 200 descriptors (items) on a Q-sort assessment tool (i.e., the Shedler–Westen Assessment Procedure for Adolescents [SWAP-200-A (27, 28)]) pertaining to a wide range of personality and clinical characteristics. The SWAP-200 (see also "Measures" section) was designed to provide a comprehensive assessment of patients' personality and psychological functioning by quantifying clinical observations. The use of this assessment procedure enabled us to address the relevant methodological shortcomings of previous studies in the field.

In more detail, we investigated personality traits and personality pathology in a group of CHR individuals, in comparison with two adolescent clinical groups of non-CHR subjects, respectively, with and without a PD diagnosis. Second, we aimed at producing an empirically derived prototypic description of personality characteristics in the CHR population, in terms of affective states and emotional regulation strategies; interpersonal functioning; cognitive styles; mental representations of self, others, and the interaction between self and others; and overall psychological functioning.

METHOD

Participant Sampling

Three clinical populations of outpatients were recruited from Italian National Health System centers and public associations providing psychotherapeutic treatment to adolescent and young adult patients with a CHR condition or different psychopathological presentation. Specifically, data were collected from: (a) a sample of CHR patients enrolled at the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Pediatric Hospital in Rome and (b) two distinct samples of patients, respectively, with or without a PD, who were enrolled in psychotherapy associations in Genoa, Milan, Rome, and Turin.

Inclusion criteria for all participants were: (a) aged 13–19 years; (b) no psychotic psychiatric disorder based on the *DSM-5* (25) classification system; (c) no traumatic brain injury, neurological disorder, or clinically significant cognitive impairment; (d) fluency in Italian; and (e) IQ > 70.

Clinicians from the Bambino Gesù Pediatric Hospital were asked to select patients who satisfied at least one UHR criterion (29), such as APS, brief intermittent psychotic syndrome (BIPS), and/or GRD, with no full-blown psychotic disorder and/or a Presence of Psychotic Symptoms (POPS) state according to the Structured Interview for Prodromal Syndromes (SIPS) (see "Measures" section). Conversely, clinicians from other recruitment sites were asked to select non-CHR patients, in accordance with the following exclusion criteria: (a) no clinical presentations referable to the psychosis spectrum, including the *DSM-5* attenuated psychosis syndrome (25), which has recently been shown to have significant concurrent and prognostic validity (30); (b) no predominantly psychotic disorders (especially, no condition related to the prodromal phase of schizophrenia), according to the Psychodiagnostic Chart [PDC-A; (31)]; and (c) no high scores (>3) on subscales relevant to psychosis (i.e., Paranoid Ideation, Psychoticism) on the Symptom-Checklist 90–Revised (SCL-90-R) (32). All participants were drug-naïve patients at the time of the first clinical interview.

Research data on the patients who met the abovementioned criteria were provided by a wide group of clinicians (clinical psychologists and psychiatrists), who were asked to conduct a comprehensive diagnostic assessment of their patients' personality and psychological functioning.

The study obtained approval from the Ethics Committee of the Bambino Gesù Pediatric Hospital and the Ethics Committee of the Department of Dynamic and Clinical Psychology, Sapienza University of Rome (n°44/2017). All clinicians furnished written informed consent and were instructed to withhold any identifying information about their patients. They received no remuneration for their participation. Adolescent patients were not directly involved in this study.

Practitioners

The sample consisted of 123 clinicians: 76 female (62%) and 47 male (38%). The mean age of all practitioners was 45.15 years (*SD* = 7.82, range = 27–61). Twenty-five (20%) were psychiatrists, and 98 (80%) were clinical psychologists. The average length of their clinical experience was approximately 12 years (*SD* = 7.53, range = 2–31). All clinicians received the same formal training for the SWAP-200-A (see "Measures" section)—provided by two authors of the present paper—and obtained an IRR in the range of 0.69–0.75 when assessing video-recorded therapy sessions with different patients. All SWAP-200-A assessments were performed after patients had participated in at least five psychotherapy sessions, to ensure that clinicians had deep and longitudinal knowledge of their patients. Specifically, the mean number of psychotherapy sessions provided by clinicians to each patient before the SWAP-200-A assessment was 8.63 (SD = 1.2; range = 5–12).

Patients

The population examined in the present study consisted of 177 individuals, subdivided into the following samples.

Clinical High Risk (CHR) for Psychosis Group

This group consisted of 58 help-seeking inpatients (30 female, 28 male) who had been consecutively admitted to the Child and Adolescent Neuropsychiatry Unit of the Bambino Gesù Pediatric Hospital in Rome between January 2017 and October 2019. Their mean age was approximately 16 years (*SD* = 1.6; range = 13–19). All patients who met the eligibility criteria were approached, and the majority agreed to participate (response rate, 78%). Most patients (62%) presented at least one comorbid clinical diagnosis. In particular, 14 were diagnosed with a generalized anxiety disorder, 10 with a panic disorder, 6 with a persistent depressive disorder (dysthymia), and 6 with a major depressive disorder. Notably, many patients had been referred to the Bambino Gesù Pediatric Hospital by other psychiatric clinicians, on the suspicion that they were at risk for developing psychosis. This resulted in a "pre-assessment enrichment," which conferred great validity of the UHR criteria (33, 34).

Personality Disorder (PD) Group

This group consisted of 60 patients (30 female, 30 male) who had been diagnosed with a PD according to the *DSM-5* classification system. Their mean age was approximately 16 years (*SD* = 1.6; range = 13–18). Nine had a Cluster A diagnosis, 28 had a Cluster B diagnosis, and 23 had a Cluster C diagnosis.

Clinical Group

This group consisted of 59 patients (38 female, 21 male) who had been diagnosed with various clinical syndromes (without PD comorbidity), according to the psychopathological categories of the *DSM-5* classification system. Their mean age was 16 years (SD = 1.4; range = 13–18). The majority of these adolescents presented different syndromes, including anxiety, depressive, and feeding and eating disorders. In particular, 14 were diagnosed with a generalized anxiety disorder, 11 with a feeding and eating disorder, 10 with a panic disorder, 7 with a persistent depressive disorder (dysthymia), 6 with a major depressive disorder, 6 with an attention-deficit/hyperactivity disorder, and 5 with an oppositional defiant disorder.

Measures

Clinical Questionnaire

We used a clinician-report questionnaire (35) to collect comparable general information about the different patient populations. Clinicians provided basic demographic data for patients, as well as patients' *DSM-5* diagnoses at intake. Moreover, the questionnaire gathered information on all clinicians (with respect to, sex, age, years of experience, and profession).

Shedler–Westen Assessment Procedure-200 for Adolescents [SWAP-200-A (27, 28)]

The SWAP-200-A is a clinician-report instrument for assessing personality pathology and psychological functioning in adolescent patients; it is used for both clinical and research purposes (36, 37). The measure was adapted from the SWAP-200 for adults (38, 39), and it comprises 200 statements written in jargon-free language, describing pathological and healthy features of adolescent personality. To describe a young patient using the SWAP-200-A Q-sort, an experienced clinician scores each of the 200 items on a scale ranging from 0 (*irrelevant or not descriptive*) to 7 (*highly descriptive*), according to a fixed distribution. A computer program then provides dimensional and categorical diagnoses for: (a) 10 PD prototypes (Paranoid, Schizoid, Schizotypal, Antisocial, Borderline, Histrionic, Narcissistic, Avoidant, Dependent, and Obsessive-Compulsive *PD scales*) and (b) 6 personality styles/disorders (Antisocial-Psychopathic, Emotional-Dysregulated, Histrionic, Narcissistic, Avoidant-Constricted, and Inhibited Self-Critical *Q-factors*). Final scores are presented as T-points, with scores in the range of 55–60 considered indicative of sub-threshold or mild pathology or PD and scores > 60 considered indicative of severe pathology or PD. These results enable a taxonomy of adolescent personality to be drawn (36). Moreover, the SWAP-200-A also considers high-functioning personality characteristics and includes an index of healthy personality functioning to detect clinically relevant strengths and resources. In this study, we used only the SWAP-200-A PDs and High-Functioning scales. The overall measure has been shown to have excellent psychometric properties (36).

Structured Interview for Prodromal Syndromes (SIPS)

The SIPS (40, 41) is a structured diagnostic interview comprised of four measures: (1) the Scale of Prodromal Symptoms (SOPS), (2) the *DSM-IV* Schizotypal Personality Disorder Checklist, (3) a questionnaire pertaining to family history of mental illness, and (4) the Global Assessment of Functioning scale. The SOPS assesses 19 symptom constructs across four subscales: Positive Symptoms (five items), Negative Symptoms (six items), Disorganization Symptoms (four items), and General Symptoms (four items). For each of these subscales, symptoms are rated on a seven-point Likert scale ranging from 0 (*never*) to 6 (*severe*). Scores of 3, 4, or 5 on at least one of the positive items are sufficient to meet the classification criteria for the CHR condition. Conversely, a score of 6 indicates the presence of a full-blown psychotic syndrome (POPS criteria). At the end of the evaluation procedure, the SIPS provides diagnostic criteria for three psychosis-risk syndromes: (1) BIPS; (2) attenuated positive symptom syndrome (APSS); and (3) GRD, characterized by schizotypal PD and/or first-degree familiarity with schizophrenia-spectrum disorders and a significant decline in global functioning over the past 12 months. The SIPS has been found to have excellent inter-rater reliability and predictive validity (41).

Statistical Analysis

Statistical analyses were carried out using SPSS 20 for Windows (IBM, Armonk, NY). A χ^2 analysis and an analysis of variance (ANOVA) were conducted to compare CHR, PD, and clinical adolescent groups on some demographic variables (sex and age). Group differences in patients' PDs and psychological functioning (evaluated using the SWAP-200-A) were analyzed using a multivariate analysis of variance (MANOVA) with Bonferroni *post hoc* analyses ($p < 0.05$). The MANOVA was conducted to examine the data at the individual disorder level, considering all SWAP-200-A PD scales. Finally, we composed an empirically derived prototype of CHR personality to identify the specific psychological features that characterize this adolescent population. For this purpose, SWAP-200-A items across CHR patients were standardized (z-scored), and item scores were averaged to create a composite personality profile.

RESULTS

Sample Characteristics

The total sample was comprised of 177 participants: 98 female (55.37%) and 79 male (44.63%). The mean age of the sample was 16 years ($SD = 1.52$; range = 13–19). The three subsamples of CHR, PD, and clinical adolescents were compared on demographic variables (sex and age). The χ^2 analysis did not reveal any significant difference between groups in terms of sex, $\chi^2 = 2.96$, $p = 0.23$. Similarly, no significant difference was found by the ANOVA in terms of age, $F_{(2,174)} = 0.13$, $p = 0.88$, $\eta^2 = 0.01$.

Group Differences in Personality Pathology and Psychological Functioning

The first aim of the present study was to compare the CHR, PD, and clinical adolescent groups on PDs and global psychological functioning (assessed by the SWAP-200-A PD and High-Functioning scales). A MANOVA was conducted, using groups as the independent variable and all SWAP-200-A PD scales as dependent variables. The findings showed significant main effects for the groups on the SWAP-200-A PD and High-Functioning scales, Wilks's $\lambda = 0.22$, $F_{(22,328)} = 17.18$, $p < 0.001$, $\eta^2 = 0.54$ (**Table 1**).

The *post hoc* analyses using Bonferroni's correction showed significant differences between the CHR, PD, and clinical adolescent groups on all SWAP-200-A PD scales, except for the Paranoid scale (**Figure 1**). The CHR adolescent

TABLE 1 | Differences between CHR, PD, and clinical adolescent groups on SWAP-200-A PDs and global psychological functioning ($N = 177$).

SWAP-200-A PD scale	CHR group ($n = 58$)		PD group ($n = 60$)		Clinical group ($n = 59$)			
	M	*SD*	*M*	*SD*	*M*	*SD*	$F_{(2,174)}$	η^2
Paranoid	43.42	0.46	43.60	0.45	42.20	0.45	2.83	0.03
Schizoid	51.55^a	0.95	48.19^b	0.93	46.39^c	0.94	7.71***	0.08
Schizotypal	55.20^a	0.91	49.14^b	0.90	44.65^c	0.90	34.11***	0.28
Antisocial	45.35^a	0.92	51.17^b	0.91	44.87^a	0.92	14.86***	0.15
Borderline	46.66^a	1.02	49.13^a	1.00	43.08^b	1.01	9.15***	0.10
Histrionic	46.81^a	0.98	51.40^b	0.96	46.61^a	0.97	7.86***	0.08
Narcissistic	43.72^a	1.05	49.84^b	1.03	43.37^a	0.1.04	8.69***	0.09
Avoidant	47.77^a	0.87	48.64^a	0.86	43.94^b	0.86	8.40***	0.09
Dependent	45.80^a	0.88	49.47^b	0.87	45.70^a	0.88	6.09**	0.07
Obsessive	42.94^a	0.65	45.34^b	0.64	41.93^a	0.64	7.54***	0.08
High-functioning	47.71^a	0.74	48.61^a	0.73	55.20^b	0.73	31.17***	0.26

*CHR group, clinical high-risk group; PD group, personality disorder group; SWAP-200-A, Shedler–Westen Assessment Procedure-200 for Adolescents; η^2, measure of effect size in analysis of covariance. Alphabetical superscripts indicate significant differences in the post hoc analyses. Means with different alphabetic superscripts (a, b, and c) were statistically significant, while means with identical alphabetic superscripts were not significantly different. **$p < 0.01$. ***$p < 0.001$.*

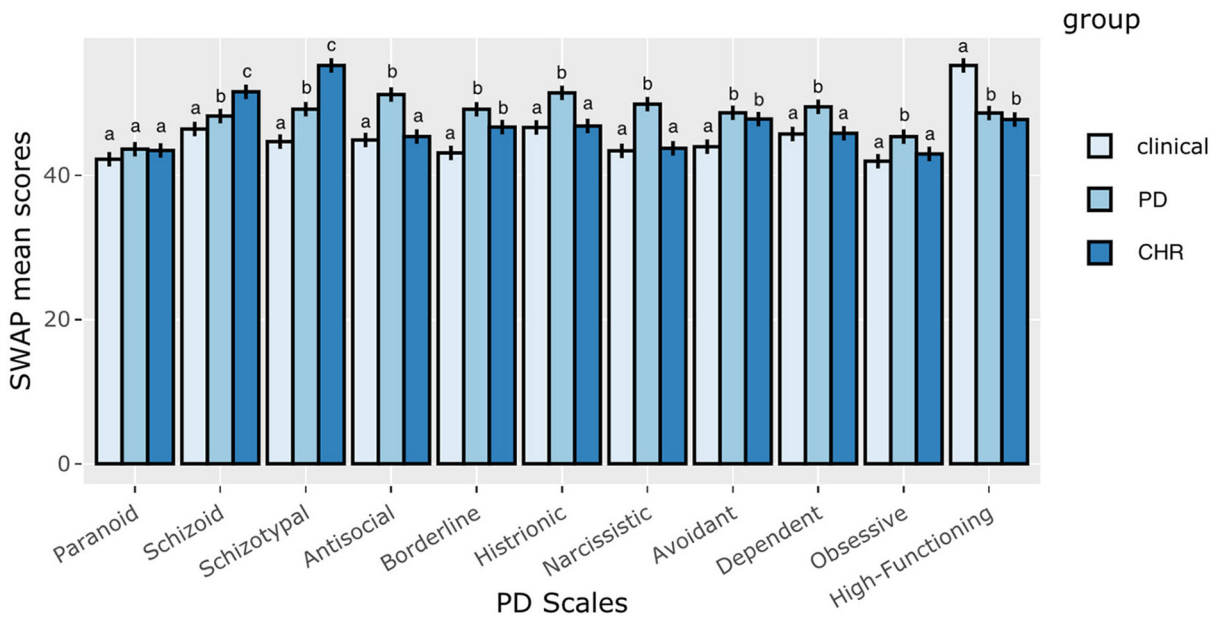

FIGURE 1 | CHR group, clinical high-risk group; PD group, personality disorder group; SWAP-200-A, Shedler–Westen Assessment Procedure-200 for Adolescents. Alphabetical superscripts indicate significant differences in the *post hoc* analyses. Means with different alphabetic superscripts (a, b, and c) were statistically significant, while means with identical alphabetic superscripts were not significantly different.

group had significantly higher mean scores in the SWAP-200-A Schizoid and Schizotypal PD scales than the PD and clinical groups. Moreover, the CHR and PD groups had significantly higher mean scores in the SWAP-200-A Borderline and Avoidant PD scales and lower mean scores in the SWAP-200-A High-Functioning scale than the clinical group. For the remaining SWAP-200-A PD scales (Antisocial, Histrionic, Narcissistic, Dependent, and Obsessive-Compulsive), the PD patient group had significantly higher mean scores than the CHR and clinical groups.

Empirically Derived Prototype of CHR Personality

The second aim of this study was to provide an empirically derived prototype of the CHR personality, creating a composite description of the specific psychological traits that characterize these patients. **Table 2** shows the SWAP-200-A items that

TABLE 2 | SWAP-200-A items most descriptive of the personality and psychological functioning of CHR adolescent patients ($N = 58$).

Empirically derived prototype **20 most descriptive items of the SWAP-200-A**	**Mean**
35. Tends to feel anxious.	1.42
44. When distressed, perception of reality can become grossly impaired (e.g., thinking may seem delusional).	1.41
60. Tends to be shy or self-conscious in social situations.	1.18
189. Tends to feel unhappy, depressed, or despondent.	1.12
124. Tends to avoid, or try to avoid, social situations because of fear of embarrassment or humiliation.	1.11
188. Her/his psychological problems interfere with an adequate academic performance (or with an adequate working capacity, if s/he no longer goes to school).	1.08
130. Reasoning processes or perceptual experiences seem odd and idiosyncratic (e.g., may make seemingly arbitrary inferences; may see hidden messages or special meanings in ordinary events).	1.06
12. Emotions tend to spiral out of control, leading to extremes of anxiety, sadness, rage, etc.	1.02
138. Tends to enter altered, dissociated states when distressed (e.g., the self or world feels strange, unreal, or unfamiliar).	0.95
6. Is troubled by recurrent obsessional thoughts that s/he experiences as senseless and intrusive.	0.90
30. Tends to feel listless, fatigued or lacking in energy.	0.89
29. Has difficulty making sense of other people's behavior; often misunderstands, misinterprets, or is confused by others' actions and reactions.	0.84
54. Tends to feel s/he is inadequate, inferior, or a failure.	0.84
87. Is quick to assume that others wish to harm or take advantage of her/him; tends to perceive malevolent intentions in others' words and actions.	0.83
105. Is suspicious; tends to assume others will harm, deceive, conspire against, or betray her/him.	0.82
117. Is unable to soothe or comfort her/himself without the help of another person (i.e., has difficulty regulating own emotions).	0.78
148. Has little psychological insight into own motives, behavior, etc.	0.76
86. Tends to feel ashamed or embarrassed.	0.75
98. Tends to fear s/he will be rejected or abandoned by those who are emotionally significant.	0.71
119. Tends to be inhibited or constricted; has difficulty allowing self to acknowledge or express wishes and impulses.	0.69

obtained the highest mean scores and were most descriptive of personalities in the CHR sample. A multifaceted portrait was obtained, indicating a pattern of avoidance of interpersonal relationships (item 124), associated with feelings of shame, shyness, embarrassment, and fear of rejection (items 60, 98, 54); a tendency to express suspicion toward others (items 105, 87); obsessional thoughts (item 6); severely impaired mentalization, in both self-oriented (item 148) and other-oriented dimensions (item 29); emotional dysregulation (items 12, 117), with dysphoric feelings of anxiety (item 35) and depression (item 189); odd and anomalous reasoning or perceptual experiences (items 44, 130), especially when under stress; dissociative symptoms of depersonalization and derealization (item 138); and negative symptoms of avolition (item 30), abulia and blunted affects (item 119), and impaired role and academic/occupational functioning (item 188).

DISCUSSION

The first aim of the present study was to examine differences between CHR, PD, and clinical groups pertaining to personality disorder traits. In line with previous studies (12), the results revealed that CHR patients had a higher prevalence of schizoid and schizotypal traits, compared to the other groups. Schizoid PDs have been rarely considered in CHR research, with the exception of a study by Shultze-Lutter et al. (16), which found schizoid—rather than schizotypal—personality traits to be prevalent in a CHR sample, as well as predictive of a transition to psychosis; this psychosis-predictive affect was mainly attributed to deficits in social interaction, rather than indifference and emotional coldness. In our sample, the higher prevalence of schizotypal traits is not surprising, since schizotypal PD is linked with psychotic disorder, both phenomenologically (i.e., both disorders involve positive and negative psychotic-like features) and physiologically (i.e., both disorders are associated with similar genetic and neurobiological factors) (42, 43). Moreover, in line with previous studies and meta-analyses (12, 16, 18), CHR adolescents in our study showed pervasive and more clinically relevant borderline and avoidant traits, as well as poorer adaptive functioning, relative to adolescent clinical groups. These findings suggest that the emotional dysregulation, dissociative experiences, transient paranoid ideation, and psychosis-like symptoms that are included in borderline personality pathology, as well as the avoidant personality traits of increased sensitivity to interpersonal relationships and high levels of anxiety, could partially explain the CHR clinical morbidity.

Of note, the co-occurrence of the CHR state and schizotypal and borderline PDs is questionable from a diagnostic and conceptual standpoint, as it is complicated by a phenomenological overlap. In the first half of the 20th century, schizotypal and borderline PD criteria were

developed to provide more reliable descriptors of the so-called "borderline" or "latent schizophrenia" states—meant to indicate characteristics, traits, and symptoms indicative of schizophrenia liability [(44, 45); for a review, see also (43, 46)]. These historical vicissitudes regarding the diagnostic boundaries between certain PDs and psychosis spectrum disorders has led to "conceptual circularity," impacting research on the relationship between personality traits, PDs, and CHR status. The empirically derived prototypic description of CHR personality characteristics outlined in the present study could overcome this limitation, as it extends beyond the current nosology of PDs, simply describing the observations of clinicians in daily practice.

The multifaceted and complex portrait obtained in the present study provides valuable information on broad aspects of the psychological functioning of CHR individuals. Looking at this picture as a Gestalt, it seems to tap into different dimensions of the schizotypy construct (47). The schizotypy construct refers to the continuum of positive, negative, and disorganized psychotic-like signs and symptoms, ranging from healthy to pathological, that has been theoretically considered—and empirically demonstrated—to predict schizophrenia-spectrum disorders (48–50). In particular, odd thinking and behaviors, unusual perceptual experiences, and suspiciousness could refer to positive symptoms of schizotypy, which are included in the UHR criteria. In fact, the UHR criteria[2] mainly pertain to sub-threshold psychotic-like experiences, as defined by Chapman and Chapman (51), as well as positive features of schizotypy (50, 52). On the other hand, symptoms of avolition, abulia, blunted affect, and impaired role and academic/occupational functioning account for the negative dimensions of schizotypy. It is important to note that the present study produced no findings for the negative symptom of asociality, which refers to reduced social initiative due to decreased interest in establishing close relationships with others (53–55). In the SWAP-A, asociality is assessed by the item "Appears to have little need for human company or contact; is genuinely indifferent to the presence of others" and, in purely behavioral terms, by the item "Lacks close friendships and relationships." Interestingly, neither of the abovementioned items was included in our prototypic description of the CHR personality. On the contrary, this description included a relatively high number of SWAP items referring to interpersonal relationships characterized by social anxiety, avoidance of social interaction, and fear of rejection (e.g., item 60, "Tends to be shy or self-conscious in social situations"; item 124, "Tends to avoid, or try to avoid, social situations because of fear of embarrassment or humiliation"; item 86, "Tends to feel ashamed or embarrassed"; item 98, "Tends to fear s/he will be rejected or abandoned by those who are emotionally significant"). Therefore, our results unexpectedly point to avoidant interpersonal strategies, rather than asociality, in the CHR population. It appears that CHR individuals preserve the motivation for social contact but avoid social situations due to feelings of shame or embarrassment, or fear of embarrassment, humiliation, and rejection. Avoidance of social interactions could also be explained by an incapacity to properly cope with the salience of both social and physical stimuli (56, 57), which might be perceived as overwhelming. Such an experience might lead to a general inhibition that diminishes expression in interpersonal contexts (57). Deficits in social functioning in CHR individuals represent a relatively underresearched area, partly due to the high variety of research constructs involved. For example, the construct of interpersonal sensitivity describes a personality trait characterized by "an undue and excessive awareness of, and sensitivity to, the behavior and feelings of others... particularly to perceived or actual situations of criticism or rejection..." [p. 342 (58)]; it has been found to be heightened in CHR individuals, compared to those who have screened negative to psychosis risk (59, 60). Interpersonal sensitivity has also been shown to be associated with difficulties in mentalization (61), represented by a diminished capacity to understand one's own and others' behavior and intentions, thereby hindering proper interpersonal communication and leading to interpersonal withdrawal (62).

Our results also point to significant indicators of impaired social cognition in the CHR sample (i.e., "Has difficulty making sense of other people's behavior; often misunderstands, misinterprets, or is confused by others' actions and reactions"; "Has little psychological insight into own motives, behavior") (63). To date, mentalizing difficulties in CHR individuals have been primarily investigated in terms of neurocognition, using theory of mind (ToM; i.e., the ability to infer the mental states of others) tasks to demonstrate significant moderate deficits in affect recognition and discrimination of faces, voices, and verbal ToM (64). Moreover, recent findings have also shown that impaired mentalization [as assessed by the Reflective Functioning Scale (RFS) (65)—a quantified index of mentalization ability that is applied to clinical interview transcripts] is more severe in CHR individuals compared to help-seeking clinical controls, strongly associated with APS (SIPS scales), and a significant predictor of the transition to psychosis (66).

Major impairments in social functioning and mentalization could also be attributed to the (less considered) disorganized dimensions of schizotypy (67). These dimensions refer to both cognitive and emotional dysregulation (67, 68), including symptoms such as odd speech and behavior, as well as unusual thought processes and intense emotional experiences that are difficult to mentalize (49, 67). The current study found specific indicators of difficulties in emotional regulation (i.e., "Emotions tend to spiral out of control, leading to extremes of anxiety, sadness, rage, etc."; "Is unable to soothe or comfort him/herself without the help of another person [i.e., has difficulty regulating own emotions]"), in line with phenomenological accounts of the role of emotional dysregulation prior to the onset of psychosis (69). Our group comparisons also revealed that the CHR sample showed higher borderline personality

[2]However, it is important to note that the schizotypy and UHR criteria refer to complementary but different aspects of vulnerability to psychosis: the former refer to *trait* indicators of vulnerability (i.e., lifelong temporal stability), whereas the latter mainly focus on *state* signs of an imminent transition to full-blown psychotic disorder (48, 50).

traits (marked by emotional dysregulation that severely affects global functioning and interpersonal relationships) than the clinical group without PDs. Such findings speculatively link the positive and disorganized dimensions of schizotypy through cognitive dysfunction in the ability to properly deal with stress (68).

Symptoms of emotional instability or borderline personality traits may also be signified in terms of a Bleulerian *ambivalence* (70). Considering the lack of self-insight and self-consciousness that is frequently presented by CHR adolescents (71–73), it is reasonable to suppose that CHR youths may perceive several emotions simultaneously and that this could be a chaotic and overwhelming experience that they are unable to elaborate through higher-order cognition. In this perspective, the constellation of psychological symptoms in the empirical prototype presented here (i.e., avoidant interpersonal strategies, impaired mentalization, difficulties in emotional regulation) could be understood as the result of a lack of integration between emotions and cognitions—also derived from the atypical brain development observed in CHR individuals and those on the schizophrenia-spectrum (74).

Overall, the CHR personality prototype derived in the present study can reveal important targets for psychosocial interventions. For example, mentalization-based treatments (75, 76) have been shown to be effective in reducing social anxiety and promoting more adaptive emotional strategies (77), as well as in enhancing mentalizing (78). In a similar vein, the new group of therapies referred to as the "third wave" (79) of behavioral and cognitive therapies [e.g., dialectical behavior therapy (80), functional analytic therapy (81), integrative behavioral couples therapy (82), acceptance and commitment therapy (83), and mindfulness-based cognitive therapy (84)] might meet the clinical needs of CHR youths (85) by focusing on contextual and experiential change strategies, including acceptance, cognitive defusion, mindfulness, relationships, values, emotional deepening, contact with the present moment, and related ideas (86).

Some limitations of the present study should be noted and discussed. First, the cross-sectional nature of the research did not allow us to examine the role of personality in clinical outcomes over the long term. In particular, future studies should seek to establish whether specific personality traits and/or disorders may adversely affect or moderate the outcomes of preventive treatments in the CHR population[3]. Second, the SWAP-200-A data were produced by different clinical centers, and raters were not equally distributed across the three groups of patients. Consequently, effects reflecting rater assessment differences (i.e., rater bias) cannot be completely excluded. However, we assume that any rater bias, if present, would be trivial, since all participating clinicians were trained to administer the SWAP-200-A assessment and obtained an IRR in the range of 0.69–0.75. Third, the SIPS was not administered to the control groups to rule out CHR status in these individuals; this may have affected the validity of the grouping variable. Nevertheless, as specified, in all recruitment sites for non-CHR patients, specific exclusion criteria were applied to overcome this limitation (see "Methods" section). Moreover, the validity of the UHR criteria strongly depends on the specific population to which they are applied. Specifically, there is compelling evidence that the UHR criteria lack validity when the criteria are applied to so-called "unselected psychiatric samples" (i.e., individuals who have not been referred to a clinical service specializing in the early detection and treatment of psychosis), especially in the younger population (33, 34, 88)–as was the case in the present study. Finally, although the SWAP-200-A assessment provides a broad and deep evaluation of psychological functioning, the literature on psychosis predominantly includes diagnostic approaches emphasizing the distress that is subjectively experienced by patients [e.g., basic symptoms (89) and minimal self-disturbances (90)], rather than signs and symptoms that are detectable by external observers. This leads to a paradox in which the same assessment method can reliably measure some key phenomenological elements of psychotic-spectrum disorders but fail to reliably assess other clinical aspects that might be crucial for treatment planning (e.g., personality).

[3]A variability ratio meta-analysis (87) found no evidence for differences in individual responses to preventive treatments in CHR individuals; nevertheless, no outcomes other than APS were explored, and it was impossible to exclude the possibility that *subsets* of CHR individuals may have systematically responded differently to preventive treatments.

DATA AVAILABILITY STATEMENT

The data of this study are not available due to ethical concerns. We must protect patient privacy and security and follow the ethical rules of our institutions and their restrictions on data sharing.

ETHICS STATEMENT

The study obtained the approvals of Ethics Committee of the Bambino Gesù Clinical and Research Hospital and the Ethics Committee of the Department of Dynamic and Clinical Psychology of Sapienza University of Rome (n°44/2017). All clinicians furnished written informed consent and were instructed to withhold any identifying information about their patients. They received no remuneration for their participation. Adolescent patients were not directly involved in this study.

AUTHOR CONTRIBUTIONS

TB conceived the research study and wrote the first draft of the manuscript. AT conceived the research study and contributed to data analysis/interpretation and the writing of the manuscript. GDC contributed to the writing of the manuscript. MT and IG collected data. SS, SV, and VL contributed to the interpretation of the results and critically reviewed the final draft of the manuscript. MP assisted with data collection and contributed to the study design. All authors contributed to the article and approved the submitted version.

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Local, Early, and Precise: Designing a Clinical Decision Support System for Child and Adolescent Mental Health Services

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Mental health disorders often develop during childhood and adolescence, causing long term and debilitating impacts at individual and societal levels. Local, early, and precise assessment and evidence-based treatment are key to achieve positive mental health outcomes and to avoid long-term care. Technological advancements, such as computerized Clinical Decision Support Systems (CDSSs), can support practitioners in providing evidence-based care. While previous studies have found CDSS implementation helps to improve aspects of medical care, evidence is limited on its use for child and adolescent mental health care. This paper presents challenges and opportunities for adapting CDSS design and implementation to child and adolescent mental health services (CAMHS). To highlight the complexity of incorporating CDSSs within local CAMHS, we have structured the paper around four components to consider before designing and implementing the CDSS: supporting collaboration among multiple stakeholders involved in care; optimally using health data; accounting for comorbidities; and addressing the temporality of patient care. The proposed perspective is presented within the context of the child and adolescent mental health services in Norway and an ongoing Norwegian innovative research project, the Individualized Digital DEcision Assist System (IDDEAS), for child and adolescent mental health disorders. Attention deficit hyperactivity disorder (ADHD) among children and adolescents serves as the case example. The integration of IDDEAS in Norway intends to yield significantly improved outcomes for children and adolescents with enduring mental health disorders, and ultimately serve as an educational opportunity for future international approaches to such CDSS design and implementation.

Keywords: child and adolescent mental health, clinical decision support system (CDSS), clinical decision support (CDS), innovation & technology strategy, child and adolescent psychiatry (CAP), child and adolescent mental health services (CAMHS)

INTRODUCTION

Nearly one half of mental health problems develop prior to the age 15 (1) and 75% of all psychiatric disorders have their onset prior to the age of 25 (2–4). In Norway, one out of five children has a mental disorder at any point in time (5, 6) and nearly five percent of all children and adolescents receive treatment in child and adolescent mental health services (CAMHS) (7, 8).

Modern electronic health records (EHRs) provide detailed documentation of a patient's health, but the complexity of psychiatric and neurodevelopmental disorders in childhood and adolescence requires clinical decision-making support beyond the EHRs' scope (9, 10). EHRs rarely provide adequate insight into the complex situations of psychiatric care, including recently updated biological frameworks for disorders and emerging methods for identifying syndromes (11–13). The incorporation of telepsychiatry and other computer supported health approaches can efficiently utilize existing resources to improve evidence-based early intervention and preventative CAMHS (13–15).

Clinical Decision Support Systems

A clinical decision support system (CDSS) aims to provide clinicians with real-time, step-by-step guidance through their clinical decision-making process (16–18). A CDSS intends to provide recommendations and guidance, not to replace the clinical judgment of practitioners. In general, a CDSS can be designed to rely solely on clinical practice guidelines to provide the evidence-based support, and/or incorporate previous patient cases by including healthcare datasets (18). The construction of guidelines for a CDSS is typically done with guideline development tools and computer-interpretable guideline (CIG) modeling languages, such as PROforma and SAGE (19). However, depending on the specific purpose of the CDSS, relying on modeled guidelines alone could be a suboptimal approach (20, 21). Traditional CDSS design and implementation aspects critical to successful CDSS adoption have included: (1) integration and adaptation to workflow; (2) construction of the information system structure and components; (3) knowledge management, interoperability, and sharing; (4) cognitive tasks and reasoning processes to be supported; (5) health system priorities and CDSS adoption paradigms; (6) quality improvement impacts, and (7) evaluation of effectiveness of decision support intervention (21, 22).

Child and Adolescent Mental Health Services in Norway

Norway is one of many Western nations that use an integrated approach for CAMHS. A family member, a teacher, or school counselor usually serves as the initial contact for children experiencing mental health problems, and refers them to a care provider. For example, if a teacher notices a child is challenged academically, they will involve the Educational and Psychological Counseling Service (PPT), which assesses the problem and determines whether special education assistance is an appropriate intervention, or if involvement of different local, regional, or national services is most appropriate for the child (23).

Typically children are first referred to their local primary care provider (PCP) for further assessment. If the mental health problem is more complex in nature, a PCP needs to involve additional services from professionals who are trained to address such problems. For example, if there are child safety and well-being concerns, child protection services are involved, and if a child requires assessment and/or interventions by a child and adolescent psychiatrist, a referral to CAMHS is made (23, 24).

In addition to Norway's standardized, integral approach to patient assessment and treatment, the Norwegian Directorate of Health has also established national clinical guidelines and care pathways (i.e., Pakkeforløp in Norwegian) for several mental health disorders, similar to the United States' American Academy of Child and Adolescent Psychiatry (AACAP), formation of clinical updates and practice guidelines (25, 26). The national guidelines and standardized pathways help to improve the predictability and safety of care and facilitate collaboration between the different services involved (23, 27, 28).

CDSS DESIGN IN THE CAMHS CONTEXT

While CDSS implementation for general medicine has been well researched, the use of CDSS in CAMHS has been limited, with only a handful of studies focusing specifically on CAMHS, and many reporting shortcomings (11, 12, 18). CDSS design for CAMHS requires careful consideration of the complexity of the care process. The design and implementation should therefore take into consideration not only the previously documented challenges but also the structure and needs of local CAMHS (10–12).

To structure our discussion of the care context that a CAMHS CDSS must support, we have identified four key design considerations, representing (1) the collaborative aspect of mental health care, (2) the many and distributed sources of information, (3) the complexity introduced by multiple stakeholders and comorbidities, and (4) the long-term perspective of the care process.

A CDSS for Collaborative Care

Traditionally, standardized clinical guidelines and care pathways are designed for healthcare professionals directly involved in clinical care. But, providing quality care needs to involve all stakeholders, including teachers, community mentors (i.e., youth groups), coaches, as well as the patients and their families. Similar to clinical guidelines, traditionally CDSSs focus on the clinical provider and assists one individual through clinical decision-making (i.e., a psychologist or PCP) (22). There are several practical reasons for this, including legacy EHR systems' minimal interoperability, yet such approaches limit the scope of CDSS functionality, especially in CAMHS.

To maximize the value, usefulness, and impact of a CDSS, the correct information must reach all relevant stakeholders, whether directly or indirectly engaged (29). As the patient is the most important stakeholder in his or her own care, their active participation helps them to better understand the treatment,

and ultimately improves disease self-management (30, 31). In Norway, the Patients' Rights Act stipulates that all Norwegian citizens have the legal right to participate in their own care (32). Children and adolescents can provide consent and have a parent serve as a proxy (32, 33). Previous CDSS studies have shown CDSS system design should consider involvement of a parent as a proxy, as it increased patients' adherence to CDSS recommendations (17).

A CDSS for Application of Health Data

In a typical clinical scenario, decision-making is based on the patient's EHR, data from an associated patient database, and single-user data entry. The EHR should provide a holistic, comprehensive overview of the patient's health to maintain a consensus among all stakeholders involved in the patient's care. Assessment tools help identify the extent of a patient's problems and which stakeholders to involve in the patient's care. Self-reporting of symptoms has also become more common with the increased use and popularity of digital and web-based tools, especially among children and adolescents (34, 35). These methods of collecting information from multiple stakeholders involved, contributes to establishing a clearer picture of a patient's health. Clear communication and efficient sharing of the patient's health information is needed to provide the best quality care for each patient, as challenges with poor information flow and transparency directly affect the quality of care (36). A collaborative CDSS design, where multiple stakeholders participate in data collection and data entry, would increase the CDSS's utility as well as improve information flow among stakeholders (10).

Design of CDSS guidance based on analysis of health datasets has been found to provide greater improvement of clinical decision-making than guideline based CDSS suggestions alone (37). The data-driven approach to CDSS design can, not only provide decision-making support beyond the capacity of clinical guidelines, but also provide clinical learning opportunities (38). Reported secondary benefits of data-driven CDSS have included enhancing education, expanding research knowledge, improving guideline adherence, and clarifying training needs (39). Extending the role of a CDSS in this way can yield positive outcomes for patients with the most complex psychiatric needs.

A CDSS to Address Stakeholder Perspectives & Comorbidities

Applying a CDSS in clinical CAMHS also faces a challenge related to "cognitive collaboration" (40). "Cognitive collaboration" involves distributed cognitive processes from all stakeholders contributing to care, whose expertise covers a variety of professions (40, 41). Despite their common goal of helping the patient, the stakeholders' criteria for success, and their approaches to achieve that goal, may differ. For example, a school counselor's perspective on aspects of the clinical process may differ from that of a psychiatrist. A CDSS designed for one aspect of treatment might optimally address that particular focus, but this design approach could be less relevant to the overall clinical profess if it neglects the "cognitive collaboration" involved in care (42).

In addition to multiple cognitive perspectives, the CDSS design also needs to account for comorbidities. Approximately 40% of all children and adolescents who meet the criteria for one disorder (i.e., anxiety, behavior, mood, or substance-use disorders) also meet the criteria for another disorder (43). Without considering abnormal symptomatic display or symptom overlap, comorbidity patterns can be concealed and mislead the practitioner to provide an invalid diagnosis (44). However, most CDSS models do not account for comorbidities, and research is scare on how to apply multiple CIGs, in order to do so (11, 12, 45). A CDSS for CAMHS needs to be able to account for commonly occurring comorbidities, as well as the collaborative nature of clinical care (46).

A CDSS for Temporality of Care

In Norway, the Patients' Rights Act guarantees every individual the right to immediate, appropriate care (32). For example, if a patient is referred to a psychologist or psychiatrist, they have the right to be seen within ten working days, and even sooner if the illness is deemed life-threatening (23, 32). Despite such policies, the patient's care progress and overall improvement of health can be delayed. Misdiagnosis, for example, can arise with child and adolescent mental health disorders due to the large variations in frequency, severity, and types of symptoms displayed, such as with ADHD (10).

Reaching a clinical diagnosis is only the first step in a complex and collaborative care process. A 2009 study on medical treatment for children with ADHD, found that only about half of the cohort managed to adhere to the ADHD medication plan (47). For a CDSS to be relevant to all components of the care process, potential complications that could arise in treatment management and follow-up also need to be taken into account. For example, a CDSS could be designed to consider any developments between appointments, or to register any irregularities prescribed medications and automatically alert the practitioner (48). To date, CDSS implementation and evaluations have predominantly focused on short-term outcomes rather than long-term care for the patient (42). While CDSS design has not yet optimally addressed the longitudinal and collaborative nature of patient care, many CIG modeling languages that can be used for a CDSS (i.e., EON, GASTON, etc.) do (49). In addition to utilizing a CIG language with longitudinal context, it is essential to assess how the different components of temporality of clinical care, and the specific timing of each intervention step, can impact the use of a CDSS (42).

A COMPLEX PROPOSITION TO MEET COMPLEX NEEDS: THE IDDEAS PROJECT

The complexities of a CDSS for CAMHS have all come under consideration in the development of the Individualized Digital DEcision Assist System (IDDEAS) project. IDDEAS, an innovation and research project in Norway, aims to design and implement a CDSS that can support the diagnoses and treatment of mental health disorders in children and adolescents, starting with ADHD as the first model clinical paradigm (50, 51). With

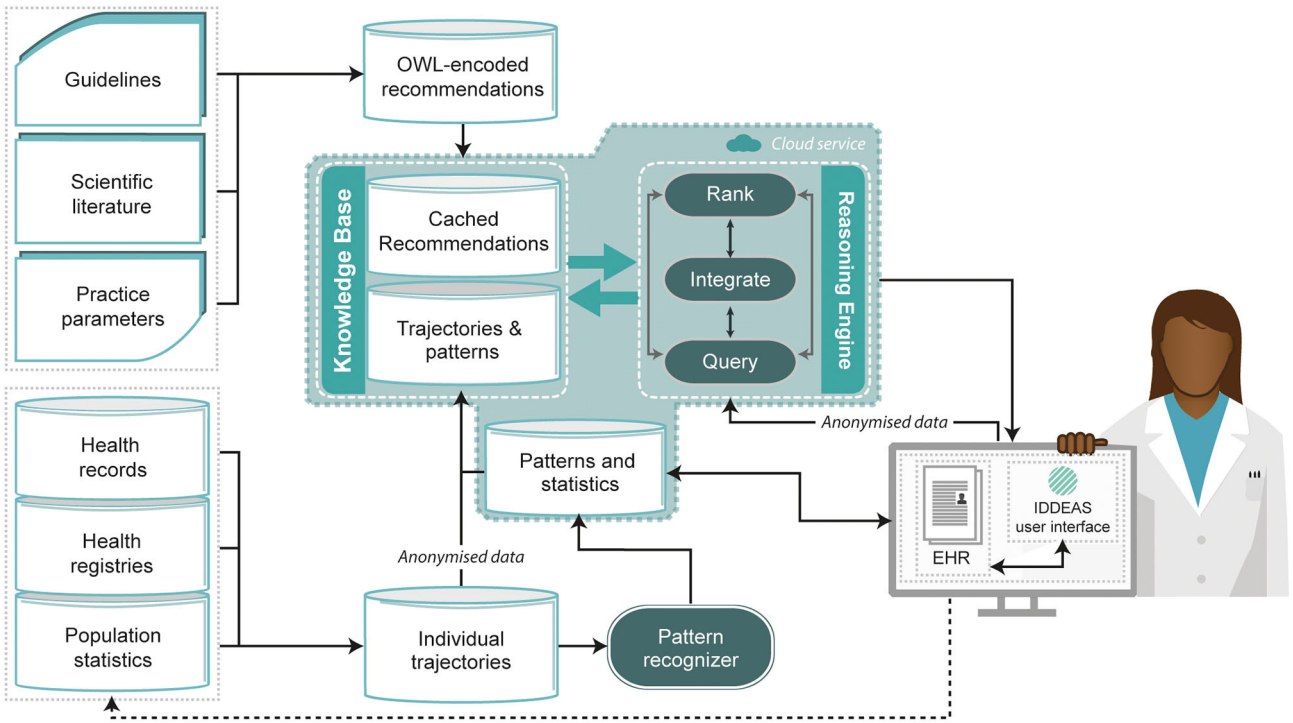

FIGURE 1 | The IDDEAS clinical decision support system model. This figure is adapted from (50) which was published under the CC BY 4.0 license (https://creativecommons.org/licenses/by/4.0/). It has been slightly revised to reflect architecture development.

nearly 4% of all 12 year olds in Norway having ADHD at any point in time (7), the disorder will serve as the first case example for IDDEAS. IDDEAS brings innovation to patient care to allow earlier and more precise clinical decision-making.

The main goal of IDDEAS is to develop a CDSS that will improve mental health outcomes for children and adolescents by supporting the practitioner through clinical decision-making. IDDEAS specifically seeks to improve care by providing clinicians data-driven and evidence-based guidance in real time, to ensure earlier and more precise decision-making, avoid misdiagnosis and inefficient care practices, and improve individualized treatment management. In addition to the Norwegian CAMHS guidelines and clinical care pathways, IDDEAS will also use Norway's unique and existing resources—CAMHS datasets and other health datasets—to provide data-driven support.

The central and most important innovation in IDDEAS is the *L*ocal *E*arly and *P*recise (LEaP) model, which allows for the application of IDDEAS *locally* in community settings, *early* in the clinical process, to add *precision* to patient care. The LEaP model is designed to provide real-time decision support for busy practitioners. IDDEAS integrates existing heterogeneous, geographically distinct, current and historical datasets, to generate new information and models to provide clinical decision support at the individual patient level (**Figure 1**). Data representing multiple episodes of care for different patients are structured into domains of inter-related concepts and hierarchical clinical patterns. They are then ranked within the system, matched with the current patient and ultimately provided within the system's interface to support the practitioner through clinical decision making (50, 51). In addition, guidelines and other clinical recommendations are compiled and encoded before being combined with the data-driven trajectories and patterns to provide ranked suggestions in response to any practitioner queries (50, 51). By designing a CDSS that utilizes both guidelines and big data, the system has the potential to be curated based on evolving scientific evidence, and with the use of each individual patient's own EHR data to also build upon the available evidence base within the system (51).

The IDDEAS CDSS will be designed and evaluated in iterations. As this approach to CDSS design for CAMHS is relatively novel, to ensure IDDEAS is usable and appropriate for clinicians and patients, all iterations will be conducted collaboratively among the technical and clinical experts of the IDDEAS Consortium (50). With IDDEAS being an innovation project, each stage will build upon the previous one, with first identifying the needs of practitioners and assessing the perceived usability of the prototype system before going on to investigate the utility and efficacy of the system to care for real patients (50).

Preserving patient confidentiality is a fundamental project requirement. To mitigate the risk of re-identification we will seek to model patient trajectories in a way that reduces the patient representation to a set of care events (e.g., physiological

findings and health care system interactions). These will then be clustered so that we operate with representations of similar patient trajectories rather than unique trajectories tied to single individuals.

In developing the project, it was important first to consider the previously encountered challenges of successful CDSS implementations and then evaluate them within the context of the Norwegian local approach to CAMHS. A contribution of this paper is a framework to discuss which considerations a CDSS for local CAMHS must consider both for design and implementation: the involved stakeholders, how they share information, the explicit and implicit "cognitive collaboration" involved and how to address the longitudinal component of patient care. We recognize that some of these challenges, e.g., the handling of comorbidities or supporting multiple distributed stakeholders, are many-faceted and complex and do not often have straightforward solutions. In the IDDEAS project we seek to use this framework as a foundation for a structured engagement with our clinician partners and ultimately better understand the context and processes of CAMHS. We believe this will help us to understand the design and implementation trade-offs we must make but also where a CDSS can realistically have a positive impact on care delivery.

IDDEAS involves multiple stakeholders, including clinicians, researchers, computer engineers, service-user organization representatives, among others, and aims to facilitate "cognitive collaboration" throughout the project. While designated responsibilities lead to differing extents of active involvement from these stakeholders, the IDDEAS Consortium holds regular collaborative meetings for all stakeholders to consistently include multidisciplinary perspectives through development, evaluation and implementation. In addition to multidisciplinary cooperation, IDDEAS is nationally funded by the Norwegian Research Council (i.e., Norges Forskingsrådet) and involves collaboration on a national level (i.e., between different regional CAMH clinics), as well as on an international level, with Consortium members representing Norway, the United States, and several countries of the European Union (50, 51).

Overall, IDDEAS proposes an approach to CDSS design and implementation that not only utilizes the local available resources but also builds off of previously-established challenges and limitations of CDSS uptake and use in other settings, to try to avoid past shortcomings while adapting the approach to meet the local CAMHS.

DISCUSSION

CDSS implementation in CAMHS has the potential to improve the quality of care and clinical outcomes for patients. The complexity of child and adolescent mental health requires a CDSS design that approaches treatment as a long-term, highly complex process. The optimal approach will encourage collaboration among stakeholders, involving their perspectives and knowledge as part of the foundation for the decision-making processes, while ensuring the patient receives appropriate, individualized care. The proposed IDDEAS in Norway offers helpful means to use innovative technology to improve CAMHS. While IDDEAS is first proposed for Norway, the project intends to test the CDSS within Scandinavia and Europe. A CDSS for child and adolescent mental health, designed and implemented based on established evidence, and using the LEaP approach, can result in improving the quality of services and the health of patients.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are included in the article/supplementary material, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

TR was responsible for establishing the direction and writing the manuscript. CC also contributed substantially to the planning, writing, revising, and finalizing of the manuscript. TR, ØN, and KK contributed to the development of content on computer decision support systems and computer engineering. NS, BL, RK, LF, OW, and VB all contributed to the development of content related to clinical components. NS provided extensive feedback throughout the entirety of the manuscript's development process. All authors contributed to the article and approved the submitted version.

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Pluripotential Risk and Clinical Staging: Theoretical Considerations and Preliminary Data From a Transdiagnostic Risk Identification Approach

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Most psychiatric disorders develop during adolescence and young adulthood and are preceded by a phase during which attenuated or episodic symptoms and functional decline are apparent. The introduction of the ultra-high risk (UHR) criteria two decades ago created a new framework for identification of risk and for pre-emptive psychiatry, focusing on first episode psychosis as an outcome. Research in this paradigm demonstrated the comorbid, diffuse nature of emerging psychopathology and a high degree of developmental heterotopy, suggesting the need to adopt a broader, more agnostic approach to risk identification. Guided by the principles of clinical staging, we introduce the concept of a pluripotent at-risk mental state. The clinical high at risk mental state (CHARMS) approach broadens identification of risk beyond psychosis, encompassing multiple exit syndromes such as mania, severe depression, and personality disorder. It does not diagnostically differentiate the early stages of psychopathology, but adopts a "pluripotent" approach, allowing for overlapping and heterotypic trajectories and enabling the identification of both transdiagnostic and specific risk factors. As CHARMS is developed within the framework of clinical staging, clinical utility is maximized by acknowledging the dimensional nature of clinical phenotypes, while retaining thresholds for introducing specific interventions. Preliminary data from our ongoing CHARMS cohort study ($N = 114$) show that 34% of young people who completed the 12-month follow-up assessment ($N = 78$) transitioned from Stage 1b (attenuated syndrome) to Stage 2 (full disorder). While not without limitations, this broader risk identification approach might ultimately allow reliable, transdiagnostic identification of young people in the early stages of severe mental illness, presenting further opportunities for targeted early intervention and prevention strategies.

Keywords: at-risk (youth), transdiagnostic, pluripotency, clinical staging model, at risk mental state

INTRODUCTION

Over the past decade, we have observed increased public awareness of the prevalence and debilitating consequences of severe mental illness. A substantial contributor to the burden of severe mental illness can be the long, progressive illness trajectories that typically become established early in a person's life, generally during adolescence, or late childhood (1, 2). Consequently, there has been a move toward early identification and intervention frameworks, with the aim of reducing the burden by halting the progression of illness or preventing the onset of disorder altogether (3–5).

However, a successful move toward earlier identification and intervention requires a different operationalisation of psychopathology than its current, increasingly criticized, form. Current diagnostic and research systems are less appropriate for these early approaches, as they are based on cross-sectional features observed in entrenched or chronic mental illness, thus embodying the "end-state" of illness trajectories only, failing to represent the progressive and dynamic nature of (emerging) psychopathology (6, 7). Analogically speaking, this corresponds to relying on descriptions of cancer based on final stages of the disease only, ignoring any earlier cell anomalies and their progressive dynamics which might have been present for years. Furthermore, the staggering extent of co-morbidity (8, 9) and phenomena present across disease entities, such as psychomotor slowing, agitation, anhedonia, or delusions, especially early in illness trajectories (10–14), do not support the status quo of separate diagnostic classes. Similarly, a rapidly emerging body of research investigating interacting symptom networks demonstrates widespread and significant interconnections between different diagnostic entities (15–17).

Despite the barriers caused by the current operationalization of mental illness, researchers in Australia initiated a significant move toward pre-emptive psychiatry and early intervention by developing the ultra-high risk (UHR) criteria two decades ago (18). The clinical criteria, identifying young people at risk of developing first episode psychosis (FEP) by a combination of attenuated/short-lived psychotic symptoms and/or trait vulnerability[1], did not rely on thresholds provided by current diagnostic systems. The UHR paradigm was developed based on the long-standing understanding that psychotic disorders do not emerge "out of the blue," but typically have a forerunner phase characterized by milder symptomatology and functional decline (18, 20, 21). This paved the way for a clinical staging model as further outlined below. Three decades later, a multitude of studies have shown that these criteria have a valence for psychosis, *as well as for other disorders* (mainly anxiety and depression) (22–24), further challenging the siloed approach to diagnostic systems. Similarly, only a small proportion of young people in FEP programs linked to UHR programs go through UHR clinics first (25), implying that there might be alternative early symptom trajectories leading to psychosis, which might be missed by services focusing exclusively on (attenuated) psychotic symptoms (21). These observations, and the modest proportion of UHR young people transitioning to psychosis in research trials [∼20% over 2 years (26)] causing statistical challenges for the design of intervention studies (27), highlight the need for the development of a broader, transdiagnostic at-risk approach.

The great challenge lies in developing these wider, transdiagnostic frameworks for early risk identification while maximizing *clinical utility*. Guided by the principles of the clinical staging framework, we will introduce the concept of a pluripotent at-risk mental state. First, we will provide a theoretical overview of the underpinnings of clinical staging and pluripotency; second, we will present the Clinical High At Risk Mental State (CHARMS) approach and some preliminary data of this ongoing cohort study.

CLINICAL STAGING

"Sub-threshold" versions of mental disorders (i.e., conditions that fall below the threshold of "caseness" as defined by psychiatric diagnostic systems), frequently precede later full syndrome disorders (28), aligning with the increasingly prevailing notion that there is no clear-cut demarcation between absence and presence of mental disorder (29, 30). Dimensional models of mental disorder conceptualize psychopathology on a continuum of severity, ranging from mild liability or expression at one end of the spectrum to fully-fledged, chronic and treatment-resistant disease at the other (31–34). While the view of a continuum of illness and illness progression has gained traction, it poses a challenge for the process of clinical decision making and clinical communication, which inherently requires thresholds (35, 36). Clinical staging, a framework adapted from other areas of medicine, adopts the dimensional approach to mental illness while offering step-wise anchors for phase-specific treatment selection (6, 37, 38). In other words, a person's clinical presentation is mapped onto the spectrum of mental illness, informing intervention plans, and offering a prognosis of potential trajectories of progression and remission (5). In clinical practice, this translates into less aggressive, safer, and more targeted treatment approaches. Rather, a staged care approach recognizes the need for interventions that are tailored according to symptom severity, allowing clinicians to provide low-intensity interventions for patients with milder presentations along the spectrum of illness, prior to reaching a full-threshold disorder.

Stages are defined using symptom severity, specificity, persistence and disability. An early stage is typified by mild symptom severity, a lack of specificity, mild functional impairment; an advanced stage is associated with severe symptom burden, clearer syndromal specificity and stability, significant functional impairment and persistent/recurrent

[1]The UHR criteria are assessed using the Comprehensive Assessment of At-Risk Mental States (CAARMS, (19)). Young people at UHR are identified by one or more of the following characteristics: (1) Attenuated Psychotic Symptoms (APS)—young people who have experienced subthreshold, attenuated forms of positive psychotic symptoms during the past year, (2) Brief Limited Intermittent Psychotic Symptoms (BLIPS)—young people who have experienced episodes of frank psychotic symptoms that have not lasted longer than a week and have spontaneously abated, and (3) Trait and State Risk Factor (Trait)—individuals who have a first-degree relative with a psychotic disorder or who have a schizotypal personality disorder in addition to a significant decrease in functioning, or chronic low functioning, during the previous year.

patterns (39, 40). The original clinical staging model spans from stage 0 to stage 4, starting with an at-risk but asymptomatic state (Stage 0) and increases in severity to help seeking, nonspecific symptoms (Stage 1a), attenuated syndrome (stage 1b), full-threshold disorder (Stage 2), recurrence and persistence of illness (Stage 3), and lastly severe and chronic mental health disorders (Stage 4). A revised version of the clinical staging model, currently only focused on psychosis, has been formulated (41). This model further segregates Stage 1 ("high-risk") into three sub-stages with increasing symptomatic specificity, moving from negative/cognitive symptoms (1a) and attenuated symptoms (1b) to short lived remitting episodes (1c). Stage 3 ("late/incomplete recovery") is also further subdivided into three stages, moving from single relapse (3a) over multiple relapses (3b) to incomplete recovery from first episode (3c).

A key assumption of the clinical staging framework is that a return to previous stages is not possible. For example, a client in Stage 3a can fully remit, i.e., a "Stage 3 in full remission"; however, they cannot return to a "Stage 0" nor to "Stage 1." In fact, remission and recovery is an integral part of the staging process. Stage 2 is associated with symptomatic and functional early full recovery (remission). Stage 3 is associated with late/incomplete recovery in any symptomatic or functional domain while Stage 4 is severe, persistent, or unremitted illness (41). Recent research has shown that 20% of individuals identified to be at Stage 1b progressed to a more severe stage within 12 months (42). Interrater reliability for the clinical staging model has been found to be adequate, with 90% concordance between independent raters ($k = 0.72$) (39). Cross et al. (43) identified a range of variables in transdiagnostic samples with attenuated symptoms (Stage 1b) which were associated with progression to a full-threshold disorder (Stage 2) such as not being in education, being unemployed and greater negative symptom severity (43).

The aim is to further develop clinical staging into a clinicopathological framework, linking clinical features with objective pathophysiological measures, improving precision of intervention and prognosis (6). Most importantly, it is a diagnostic framework that increases clinical utility.

A PLURIPOTENTIAL AT RISK MENTAL STATE: CHARMS

The shortcomings of current diagnostic classification systems, new findings regarding the dynamic and overlapping nature of psychopathology and its heterotypic trajectories, including lessons learned from the UHR paradigm regarding specificity and predictive values, all indicate that we need a new, less siloed, and early risk identification approach. This led to the development of the CHARMS (Clinical High At Risk Mental State) identification strategy, a pluripotential at-risk mental state which broadens both inputs and outputs beyond psychosis and maximizes clinical utility by building on the clinical staging framework (5, 21, 44–47). Currently, we are in the process of conducting a pilot study validating and further refining the "CHARMS criteria." The CHARMS criteria are a set of clinical criteria that define a pluripotential at risk mental stage as described above and capture risk for a *range* of different outcomes (see below). Operationally, the CHARMS criteria are a broadening of the existing UHR criteria, extending it from UHR (capturing subthreshold versions/genetic vulnerability for psychotic disorder) to capturing subthreshold versions/genetic vulnerability for affective (unipolar and bipolar depression) and borderline personality disorder (BPD). The decision to also include BPD was informed by evidence that young people with emerging BPD features show non-specific and evolving mixtures of signs and symptoms that substantially overlap with precursors of bipolar and psychotic disorder, recognizing that the early stages of these disorders cannot yet be disentangled adequately to support disorder-specific identification frameworks and preventative interventions (48–50).

CHARMS is an extension of the UHR state and represents the clinical operationalisation of the first stage requiring significant clinical attention in the clinical staging model, that is, Stage 1b. Therefore, recruitment into the CHARMS cohort study is based on *presentation to services* (i.e., headspace centers in metropolitan Melbourne, Orygen Specialist Clinical Services) rather than based on presence of specific diagnoses.

The Term Pluripotency

The idea of a "pluripotential at risk mental state," introduced for the first time by Johannessen and McGorry (51) has attracted criticism and misconceptions based on the term used. First, there has been a perception in the literature that the term "pluripotent risk" refers to the existing UHR operationalisation, i.e., the *UHR for psychosis state* itself is considered pluripotent in that it predicts the onset of disorders other than psychosis (52–55). While UHR is indeed part of CHARMS, the idea of a pluripotential at-risk mental state was always to broaden both input and output points, thus moving beyond UHR for psychosis and considering other mental disorders (44). Second, the term "pluripotential" should be interpreted in light of the clinical staging framework, rather than through the lens of cell biology or oncology as some critics have done (56). Literally, "pluri" refers to *several*, "potential" refers to *capable or possible*: It reflects the potential for the picture to evolve into several syndromes or outcomes (51), akin to heterotypy. In other words, we remain agnostic about the future trajectory of the disorder, and simply maintain that a broad range of outcomes are possible. This is not to say that all mental illness is a manifestation of the exact same origin, and the specific trajectory is a result of environmental influences (57). As an example, we do not assert that *every* young person meeting CHARMS criteria, regardless of clinical presentation and genetic make-up, placed in a certain environment, is capable of developing a particular syndrome. Rather, the CHARMS criteria aim to identify young people who are presenting with unspecified, sub-threshold levels symptoms consistent with stage 1b of the clinical staging model, and therefore considered to be a population with a high risk of transition to a range of full threshold disorders.

Specificity Might Increase Over Time

Among the core principles of CHARMS is the assumption that psychopathology in its earliest stages is protean and non-specific, with greater specificity for certain disorders gained in later stages (58). This is not too dissimilar from the view of a general "liability" psychopathology factor crystallizing into more specific conditions with increasing age ("p-differentiation") (59–61). While the empirical evidence for p-differentiation has been mixed, these studies have investigated differentiation as a function of age rather than illness severity as suggested by the clinical staging framework.

Another source of support for later, more stable symptom patterns stems from studies investigating the network structure of psychopathology. These studies show that there is increasing connectivity in symptom networks with increasing levels of severity (62–65), pointing toward increasing stability in psychopathology. While a recent study failed to demonstrate increase in global network structure with increasing severity (66), network findings are generally in line with large epidemiological studies. These epidemiological studies have shown how non-specific states in children and adolescents, usually characterized by anxiety and depressive symptoms, develop into more stable adult-type major mood (depression, bipolar) or psychotic disorders (11, 67–69). For this reason, CHARMS proposes a transdiagnostic "lumping" approach (i.e., not differentiating between diagnostic entities as defined by international diagnostic symptoms), representing the most useful approach for providing healthcare to young people with undifferentiated clinical representations. By doing so, it also provides a sampling frame for prospectively researching the evolution of early stages of severe mental disorder, which has been hampered to date by the "diagnostic silo" approach to risk identification. Furthermore, it aligns with studies demonstrating the shared genetic and neurobiological basis of mental illness, as well as the number of shared environmental risk factors (70–73), as further outlined below.

Transdiagnostic

The *transdiagnostic approach* "involves trying to understand the shared, overarching processes that cut across the classification system" [(74), p. 360]. Although suggested otherwise by some authors (75, 76), the clinical staging framework adopts a transdiagnostic approach. This is in line with the "Research Domain Criteria" (RDoC) introduced by the National Institute of Mental Health (NIMH) (77–79) and the Hierarchical Taxonomy of Psychopathology (HiTOP) (80, 81).

RDoC aims to "implement, for research purposes, a classification system based upon dimensions of observable behavior and neurobiological measures" (78). In other words, the biopsychological basis of fundamental psychological constructs (e.g., reward seeking, memory, and fear) are explored and linked to clinical phenotypes (79). RDoC has primarily been developed as a research tool, not as an aid for practical clinical decision making. It aims to find (biological) explanations for clinical problems and to *inform* clinical schemes, such as the clinical staging framework. It also does not incorporate the temporal or dynamic aspect and does not facilitate early identification purposes. Thus, RDoC represents a framework *complementing* CHARMS and clinical staging, rather than representing a competing framework.

Similar to RDoC, HiTOP represents a hierarchical, dimensional approach to psychopathology, with lower-level syndromes based on empirical covariation of signs and symptoms which form higher-level spectra based on covariation of syndromes (80–82). This idea is related to the concept of micro-and macro phenotypes first articulated by van Os (83). In the context of HiTOP, the p-factor can be seen as very broad "super-spectrum," representing features shared across all mental disorders (81). As stated above, the p-factor and CHARMS approach have the same underlying idea of an underlying vulnerability for psychopathology that is not differentiated by disorder. However, the p-factor describes a transdiagnostic *structure* (i.e., a factor which is present across disorders). In contrast, the term "transdiagnostic" in CHARMS does not necessarily refer to a common shared factor, but rather to *not differentiating* or *not separating into diagnostic silos* according to clinical presentation.

Similar to HiTOP, aiming to integrate the traditionally separate domains of personality and psychopathology (84, 85), the CHARMS approach also aims to bridge the traditional separation between personality and psychopathology. The CHARMS criteria include borderline personality pathology, as this represents a general severity factor in personality pathology (86) and because subthreshold borderline pathology is clinically significant in young people (87).

The transdiagnostic approach in CHARMS has been criticized for pooling together potentially different phenotypes and illness trajectories, thereby interfering with individual risk prediction and specific treatment development (88). However, the CHARMS approach does not prohibit the identification of specific illness trajectories or risk factors for specific phenotypes (see below).

Homotypic vs. Heterotypic Continuity of Psychopathology

There is evidence that young people at UHR for psychosis also have incident or persistent disorders other than psychosis (22–24). Similarly, there is evidence that young people at risk for non-psychotic disorders (such as depression) might develop psychotic disorders (54). Both these trajectories are examples of heterotypic development, i.e., one condition predicting another condition at a later time point (89) There is increasing evidence for heterotypic continuity in children and adolescents (14, 90, 91). For example, a recent study in the ALSPAC cohort (N = 4,815, ages 7.5–14 years) demonstrated widespread heterotypic continuity, even when controlling for homotypic continuities (92). However, heterotypic continuity is also observed in "established" disorder (9, 93). A recent Danish registry study (N = 5,940,778) showed that any given index mental illness is associated with an increased risk of developing any other mental illness, even across diagnostic class (94). Similarly, the Dunedin Study birth cohort (N = 1,037) demonstrated that mental disorder life history traverse across internalizing, externalizing, and thought disorders and all disorders are associated with an

increased risk for all other disorders (95). These studies support the idea that mental disorder categories are not a static. Rather, they are highly dynamic process that ought to be considered from a developmental perspective. It also provides support for the idea of pluripotentiality, i.e., it might be useful to not specify the "terminus" of an illness trajectory. The clinical staging/CHARMS approach allows for both (capturing of) homotypic progression (e.g., young person with depressive symptoms without significant comorbidities goes on to develop recurrent depression) and heterotypic progression (e.g., young person with depressive and attenuated psychotic symptoms goes on to develop first episode mania). This will allow one to investigate and specify stable (homotypic, transdiagnostic) continuity, as well as heterotypic, disorder specific continuity (96).

The Power Problem and Prevention Paradox

By widening the outcome target and including high-prevalence disorders such as depression, we not only allow for heterotypic development on a conceptual level, but also allow for greater statistical power at a methodological level. As originally noted by Cuijpers (27), prevention trials rarely investigate whether they are, in fact, able to reduce the incidence of the disorder in question, as the number of participants needed for this is high, especially if the incidence of the target syndrome is low. This is partly explained by the relative non-specificity of known risk factors, as discussed above. By increasing the incidence rate of the target outcome in the population, we drastically reduce the number of participants needed to achieve adequate statistical power. The CHARMS approach increases the incidence rate of new disorders by following all three recommendations by Cuijpers (27): (1) focusing on indicated prevention (symptoms are present without reaching "full threshold"), (2) focusing on high-risk groups with multiple risk factors, and (3) focusing on target groups with multiple disorders. This approach also addresses the "prevention paradox" and "relative blindness" raised in traditional UHR research (45, 97, 98).

The CHARMS Study: Study Details and Preliminary Findings

As mentioned, we are in the process of conducting a pilot study validating and further refining the "CHARMS criteria." The CHARMS criteria can be sub-divided into four at-risk mental states: high risk for psychosis (UHR), high risk for severe depression (HRD), high risk for mania (HRM), and high risk for borderline personality disorder (HRB), although this division is not the focus of the study. Guided by the UHR criteria, the CHARMS criteria are based on subthreshold symptoms (comprising attenuated psychotic, moderate depressive, subthreshold manic symptoms, and BPD features), trait vulnerability and functional decline. For a detailed description of the criteria, see Hartmann et al. (46). As the focus of this study is on the (broad) early clinical phase of illness, all clients of our clinical services are eligible for the study regardless their presentation, unless full-threshold for illness (the main outcome of the study) has already been reached. That is, inclusion comprises one criterion: Help-seeking at our clinical services. Exclusion criterion comprises $\geq$ Stage 2 of illness. Important for recruitment, and key to the underlying CHARMS risk identification approach, are our *headspace* enhanced primary care services. *headspace* represents a transdiagnostic early intervention service for young people aged 12–25 with a range of subthreshold and threshold presentations and is the main recruitment source for the CHARMS study. Recruitment also takes place at Orygen Specialist programs (a secondary mental health service), however given our exclusion criterion of $\geq$Stage 2 and the more severe clinical presentation at the specialist programs compared to headspace, this is a minor source.

Consenting participants meeting the CHARMS criteria at baseline are allocated to *CHARMS+* (i.e., Stage 1b). Those falling below threshold are allocated to *CHARMS–* (i.e., Stage 1a, the control group). Participants meeting criteria for Stage 2 (for example, first episode psychosis or mania) are excluded. Participants are re-assessed after 6 and 12 months.

Our preliminary results (sample $N = 114$, ongoing recruitment) support the CHARMS concept. Sixty-eight percent of participants (68%) met CHARMS criteria at baseline and were allocated to the CHARMS+ group with the remainder allocated to the CHARMS– control group (please see **Table 1** for an overview of clinical and demographic variables). Of the CHARMS+ group, almost half (46%) satisfied the criteria for more than one at-risk group. **Figure 1** demonstrates the extensive overlap between the four different at-risk mental states. Of those who have completed the month 12 assessment in the CHARMS+ group thus far ($N = 78$), 34% have transitioned

TABLE 1 | Preliminary baseline characteristics.

	Total	CHARMS+	CHARMS–	*P*-value*
N	114	68	46	
Age (SD)	19.62 (3.49)	19.75 (2.89)	19.43 (4.29)	n.s.
Female (%)	71 (62%)	41 (60%)	30 (65%)	n.s.
In full or part-time education (%)	76 (67%)	40 (59%)	36 (78%)	0.03
Full- or part-time employed (%)	46 (40%)	26 (38%)	20 (43%)	n.s.
SOFAS (SD)	63.95 (13.49)	60.90 (13.29)	68.72 (12.51)	0.002
QIDS (SD)	7.17 (4.38)	8.75 (4.33)	4.68 (3.16)	<0.001

*SD, standard deviation; SOFAS, social and occupational functioning assessment scale; QIDS, quick inventory of depressive symptomatology. *t-test or chi-square.*

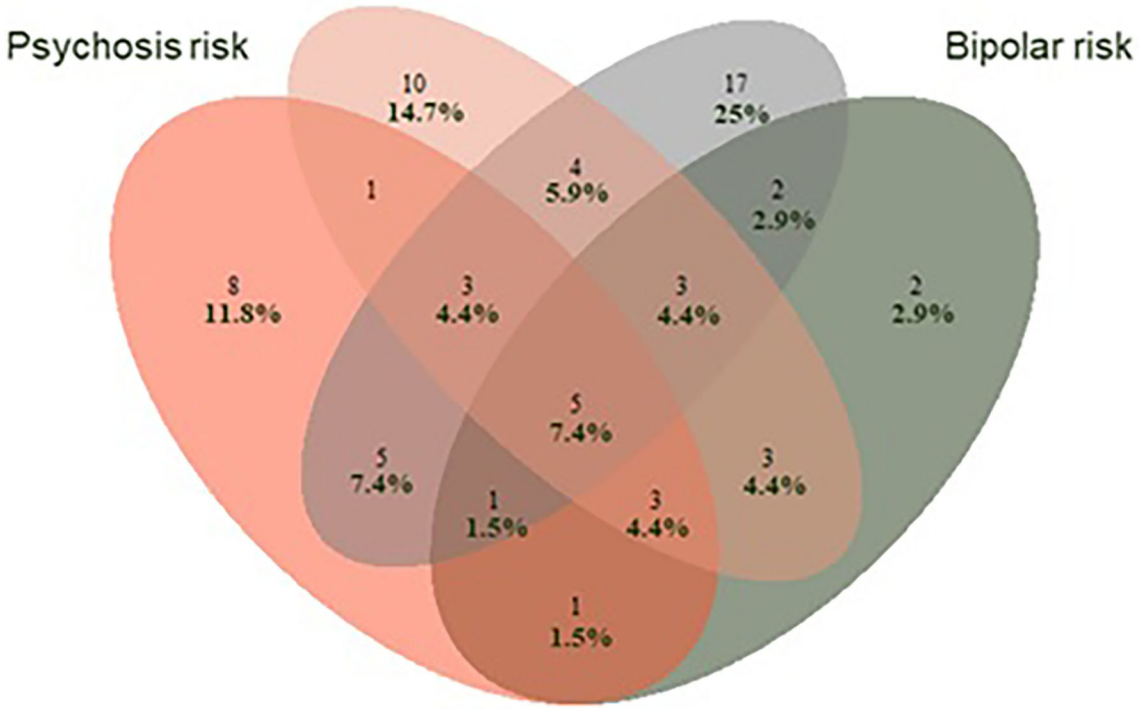

FIGURE 1 | Venn Diagram showing the extent of overlap of the four at-risk groups at baseline for those that meet CHARMS criteria ($N = 68$) at baseline.

to a Stage 2 disorder (mostly severe depression), compared with 3% in the CHARMS- group. Survival analysis (Kaplan Meier) on these preliminary data show a significant difference in these transition rates between the two groups ($p = 0.004$). Interestingly, the risk for transition (by 12 months) to Stage 2 in the CHARMS+ group increases to 40% if three or more at risk states are met. When we investigate the patterns of transition, we see homotypic (e.g., a young person meeting high-risk for psychosis transitions to first-episode psychosis) as well as heterotypic development [e.g., a young person meeting high-risk for psychosis transitions to severe depression (**Figure 2**)], further supporting the CHARMS approach.

LIMITATIONS AND FUTURE DIRECTIONS

The CHARMS can be criticized for still relying on existing categories, criteria sets and diagnostic outcomes, even if in a "merged" form. However, in the absence of any valid alternatives, the CHARMS approach provides a workable solution, and is directly implementable in clinical practice. A future thought to entertain is the possibility that findings born out of HiTOP and RDoC frameworks might help to re-define the CHARMS criteria completely independent of DSM criteria sets and cut-offs.

Furthermore, the CHARMS pilot study has three assessment points only, which contrasts with the discussion earlier regarding the dynamic, fluctuating nature of emerging psychopathology, for which more frequent assessment points would be required in the future. However, studies are underway implementing more dynamic approaches in this cohort, including a combination of intensive longitudinal Ecological Momentary Assessment (EMA) for the duration of 4 months, paired with passive monitoring of sleep-wake cycles, and physical activity. These data-rich, fine-grained time series in this unique CHARMS-cohort will allow for the dynamic modeling of the onset of mental illness (see below).

Dynamic Systems Approach and Joint Modeling

One approach we are taking is to conceptualize mental health as a complex dynamic system (99): A system composed of many elements which interact with each other over time. Other examples of complex systems comprise financial markets, the ecosystem of a lake, or the climate. While these systems are very diverse, they share underlying common (mathematical) principles which are universal to complex systems and describe their behavior. For example, the resilience of a system can be inferred by studying its stability, i.e., how far is a system from a phase transition or "tipping point" (100–102). In our CHARMS identification framework or clinical staging, a tipping point might represent the transition from subthreshold to threshold psychopathology, i.e., from at-risk mental state to full disorder

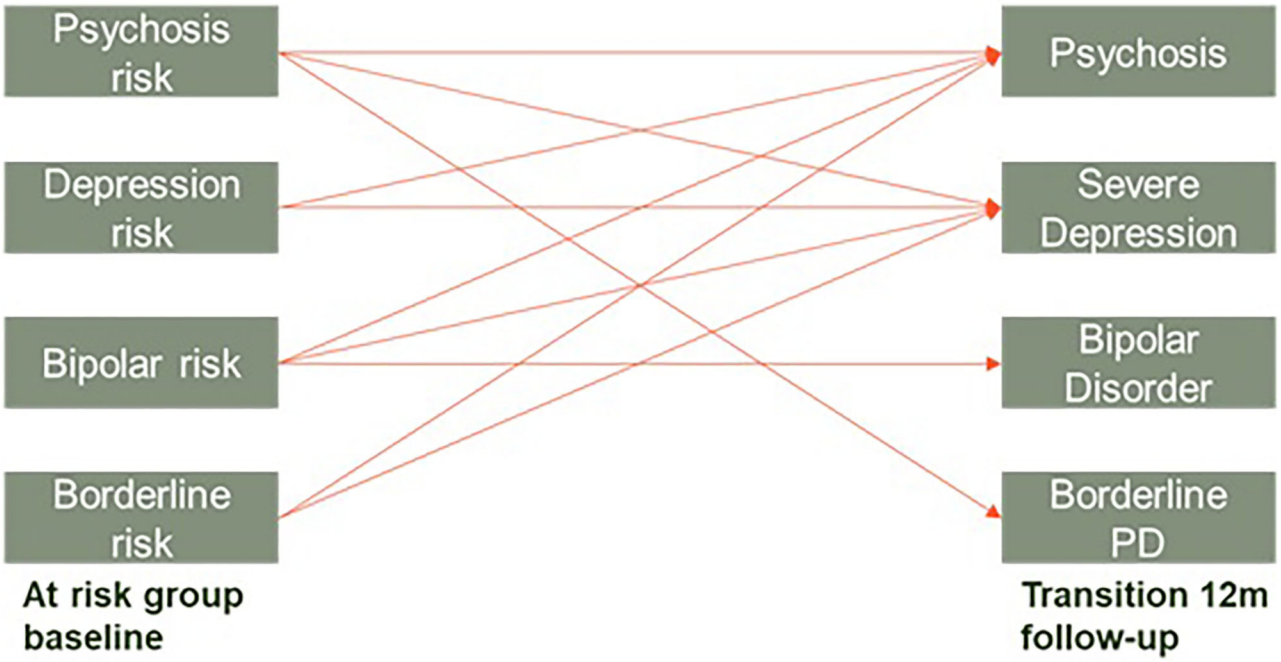

FIGURE 2 | Observed homotypic and heterotypic continuity from baseline to 12-months follow-up in those meeting CHARMS criteria. Young people can meet for multiple at risk groups.

(103, 104). The proximity of such phase transitions can be studied by resilience indicators or "early warning signs" identified in time series (e.g., time series of symptoms obtained using EMA) (105, 106).

Of relevance in the "dynamic" context is also our group's advancement of *joint modeling* in the mental health field. Joint modeling is a statistical technique that examines the dynamic association between variables assessed repeatedly over time ("longitudinal data") and time-dependent outcomes (e.g., death, transition to psychosis). It represents a *joint* approach of combining multilevel models with random effects and a survival model. Our group has investigated the performance of joint modeling and dynamic prediction in the context of transition to psychosis in UHR individuals (107–109). We have shown that, compared to with traditional prediction models that rely exclusively on baseline data, joint modeling offers a superior approach in predicting psychosis in UHR individuals (107–109). Therefore, the joint modeling approach will also be explored in the context of dynamic prediction in our CHARMS cohort.

A further limitation of the CHARMS framework at this stage is the focus on four specific outcomes/at risk groups. Based on the outcomes of our (pilot) CHARMS cohort study, we will investigate the expansion of the framework to encompass other syndromes as well, such as obsessive compulsive disorders and eating disorders. These syndromes are captured and may in the future be incorporated as input and outcomes of interest.

A final criticism that the CHARMS framework faces is its reliance on clinical interview data only at this stage. Incorporating other (neurocognitive, bio-physiological) modalities will be an important next step, as there is a clear demand to identify markers of illness which directly map onto pathophysiology (110). Clinical staging enables the identification and evaluation of pathophysiology and biomarkers at each stage of illness (110). If we investigate the association between (bio)marker and symptoms in relation to stages in the CHARMS approach, we might be able to identify and differentiate between transdiagnostic markers as well as syndrome-specific markers. Future expansions of the study will include the incorporation of a neurocognitive test battery, blood-based biomarkers, and digital phenotyping.

CONCLUSION

Emerging mental disorders develop in complex interacting trajectories over time with non-specific symptoms that overlap, intensify and recede, defying diagnostic borders. A new diagnostic approach and case identification framework is needed, with an emphasis on clinical utility. The clinical staging and the transdiagnostic CHARMS risk identification framework is guided by the principle that diagnostic terms or labels only need as much specificity to guide treatment selection (111). One key implication of the pluripotential CHARMS at-risk approach is that if identification and intervention can occur early, progression to later stages might be prevented. The instruments for such preventive treatment approaches, focusing on novel, broader target treatments such as psychosocial and neuroprotective approaches, will be trialed in this broad at-risk population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Melbourne Health Ethics Committee. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

JH and BN developed the first draft. LD wrote sections of the manuscript. PM, GA, AC, CD, RG, AP, AR, and HY provided significant input to all sections of the manuscript. All authors approved the final manuscript.

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BRIEF RESEARCH REPORT
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Familiarity for Serious Mental Illness in Help-Seeking Adolescents at Clinical High Risk of Psychosis

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Aim: Ultrahigh-risk (UHR) individuals have an increased vulnerability to psychosis because of accumulating environmental and/or genetic risk factors. Although original research examined established risk factors for psychosis in the UHR state, these findings are scarce and often contradictory. The aims of this study were (a) to investigate the prevalence of severe mental illness (SMI) in family members of distinct subgroups of adolescents identified through the UHR criteria [i.e., non-UHR vs. UHR vs. first-episode psychosis (FEP)] and (b) to examine any relevant associations of family vulnerability and genetic risk and functioning deterioration (GRFD) syndrome with clinical and psychopathological characteristics in the UHR group.

Methods: Adolescents (n = 147) completed an *ad hoc* sociodemographic/clinical schedule and the Comprehensive Assessment of At-Risk Mental States to investigate the clinical status.

Results: More than 60% UHR patients had a family history of SMI, and approximately a third of them had at least a first-degree relative with psychosis or other SMI. A GRFD syndrome was detected in ∼35% of UHR adolescents. GRFD adolescents showed baseline high levels of positive symptoms (especially non-bizarre ideas) and emotional disturbances (specifically, observed inappropriate affect).

Conclusions: Our results confirm the importance of genetic and/or within-family risk factors in UHR adolescents, suggesting the crucial need of their early detection, also within the network of general practitioners, general hospitals, and the other community agencies (e.g., social services and school).

Keywords: vulnerability, familiarity, early psychosis, early intervention, early detection, ultra-high risk (UHR) of psychosis, clinical high risk (CHR), adolescence

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INTRODUCTION

In the last three decades, the early intervention in psychosis (EIP) paradigm has achieved increased consideration attention in the scientific community, generating focused programs of care within the mental health care network of different countries (1). Indeed, leaving patients with early psychosis untreated may have severe consequences in terms of quality of life, functioning, and

health (e.g., treatment dropout, inpatient care, symptom severity), as well as in socioeconomic costs related to unemployment, long-term intervention, and poor outcomes of illness (2–4). However, to date, psychosis remains one of the most puzzling mental disorders, and our understanding of its etiopathological mechanisms is still far from being conclusive (5).

Vulnerability to Psychosis and the "Ultrahigh-Risk" Paradigm

The most validated model to explain the etiology of psychosis is based on environmental and genetic risk factors and their interaction (in various modalities and at various levels), likely involving epigenetic mechanisms (6, 7). The evidence that many subjects who are at ultrahigh risk (UHR) of psychosis actually do not develop a full-blown psychotic episode seems to confirm this hypothesis, suggesting a complex interplay among genetic, neurodevelopmental, neuropsychological, sociocultural, and environmental factors in psychoses (6).

The detection of risk factors correlated with early psychosis is crucial to advance early identification of vulnerable subjects and to propose tailored interventions for young help-seeking individuals (8). Indeed, the delivery of specialized, evidence-based treatments as early as possible has become one of the current priorities for professionals involved in mental health care service network (9, 10).

Since its conceptualization, the UHR paradigm quickly became increasingly influential in the field of psychiatry (7). The UHR mental state is currently defined on the basis of three main inclusion criteria, which have been internationally validated: brief and limited intermittent psychotic symptoms (BLIPSs), attenuated psychotic symptoms (APSs), and genetic risk and functioning deterioration syndrome (GRFD) [for details, see (11)]. Specifically, APSs are subthreshold positive psychotic symptoms within the past 12 months. In the BLIPS group, criteria for psychosis are met for <7 days at a time and ceasing spontaneously (i.e., without antipsychotic medications). The GRFD syndrome is a state/trait risk condition in which the patient has a family history of psychosis (i.e., in first-degree relatives) or manifests a schizotypal personality disorder, along with low functioning sustained for at least 1 month. Accumulating findings have confirmed that young help-seekers meeting well-defined UHR psychometric criteria show an increased risk of developing psychosis (mostly schizophrenia spectrum disorders) within a relatively short period of time (12). Indeed, the psychosis conversion in people at UHR is most likely to occur within the first 24 months after the first contact to clinical services, with a risk of transition accumulating to 29% at 2 years (13). After this period, the speed of psychosis progression tends to plateau from the third year, reaching ∼35% after 10 years (14). This risk is significantly greater than that reported in the general population: indeed, people at UHR have a 2-year relative risk of developing psychosis of 460, as compared to the general population (29%/0.063%) (7).

UHR subjects are likely to have an increased vulnerability to psychosis because of accumulating environmental and/or genetic risk factors (6). However, although several original research has explored the association of established risk factors for psychosis and the UHR state, the results are scarce and often contradictory, also with regard to the prevalence of severe mental illness (SMI) in family members of UHR individuals (15). As psychosocial dysfunction represents a common prodromal sign in UHR mental states, which exposes these young help-seeking individuals to social stigma and long-term interpersonal marginalization, reducing employment and economic opportunities (16), it is absolutely crucial to implement effective models of early detection of psychosis vulnerability as soon as possible within the mental health service network, especially because this "functional critical period" may be susceptible to change if effective interventions are provided (5).

Starting from this background, the first aim of the current study was to investigate the prevalence of SMI in family members of UHR adolescents compared to similar age group of help-seeking peers with first-episode psychosis (FEP) or not meeting both UHR and FEP criteria (11). Moreover, for better specifying the clinical profile of UHR adolescents with family prevalence of SMI (especially psychosis), we also examined any relevant associations of the presence of family members with SMI (and psychosis) with functioning and psychopathology in our UHR subgroup. Finally, for the same reasons, we also investigated any significant relationship of the presence of a GRFD syndrome (i.e., a specific clinical index of family history of psychosis in first-degree relatives of UHR subjects) with functioning, sociodemographic, clinical, and psychopathological characteristics in our UHR subsample. To the best of our knowledge, this is the first Italian study specifically developed to examine the prevalence of SMI in family members of UHR adolescent help-seekers recruiting within a specific EIP program, as well as the presence of a GRSD syndrome in adolescents with early psychosis.

MATERIALS AND METHODS

Subjects

Participants were help-seeking adolescents who entered the "Reggio Emilia at Risk Mental States" (ReARMS) program [for details, see also (1)] between September 2012 and December 2018. All participants ($n = 147$) and their parents gave an informed consent prior to their inclusion in the research. Relevant local ethical approvals were sought for the study. This research has been also performed according to the Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments including humans. The data that support the findings of this study are available on request from the authors. The data are not publicly available because of privacy or ethical restrictions.

Inclusion criteria of the present research were (a) age 13–18 years, (b) specialist help-seeking, (c) UHR criteria defined by the CAARMS (the "Comprehensive Assessment of At-Risk Mental States") (i.e., BLIPSs, APSs, and GRFD) [for details, see (11)], or (d) a duration of untreated psychosis (DUP: defined as the time interval between the beginning of psychotic features and

the first antipsychotic treatment) (17) <2 years if a CAARMS-defined FEP is identified at the initial assessment (11). According to the EIP paradigm (4), a DUP <2 years is a crucial limit to begin an EIP intervention, being a shorter DUP correlated with better FEP outcomes (18, 19). In the ReARMS program, early detection of UHR/FEP help-seeking adolescents was a 2-step procedure (1, 20). The first was a screening step using the "Screening Schedule" for Psychosis (21), administered by general service staff members. The second step consisted of the CAARMS interview (to explore the presence of an UHR mental state, a first-episode psychosis or neither), within a baseline multidimensional assessment process also including an *ad hoc* clinical/sociodemographic schedule [for details, see also (1)]. UHR– individuals were excluded from the ReARMS protocol, but received specific information for an appropriate treatment (2).

Exclusion criteria were (a) previous Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revised (DSM-IV-TR) affective and non-affective psychoses (22); (b) past exposure to antipsychotics; (c) known intellectual disability (IQ < 70); (d) neurological disease or any other medical illness with psychiatric features; and (e) current substance dependence, according to DSM-IV-TR criteria (22). Specifically, we considered past exposure to antipsychotics (i.e., before the ReARMS recruitment) as an equivalent of a previous psychotic episode, in accordance with CAARMS-defined FEP criteria, suggesting that the FEP threshold essentially corresponds to that at which antipsychotics would supposedly be started in the common clinical practice (11).

Instruments and Measures

In the present research, the following instruments were used:

- An "*ad hoc* schedule" collecting specific clinical and sociodemographic information: i.e., gender, age, level of education, ethic group, mother tongue, employment status, prevalence of SMI in family members, *DSM-IV-TR* diagnosis, duration of untreated illness (DUI, defined as the time interval between the beginning of a marked psychopathological symptom and the first psychological/pharmacological intervention) (23), past hospitalization, previous specialist contact, previous suicide attempts [defined as a potentially injurious, self-inflicted behavior without a fatal outcome for which there was (implicit or explicit) evidence of intent to die] (24, 25), current substance abuse at the ReARMS enrollment, 1-year "dropout" rate, 1-year "psychosis transition" rate, 1-year CAARMS-defined psychometric criteria, and the specific ReARMS interventions provided to the users.
- CAARMS: a semistructured interview exploring several characteristics of the attenuated and full-blown psychotic psychopathology (i.e., positive symptoms, negative symptoms, disorganization, cognitive change, emotional disturbances, and general psychopathology), as well as the socio-occupational functioning [using the SOFAS ("Social and Occupational Functioning Assessment Scale") module] [see (11), for details]. The CAARMS was administered by trained clinical psychologists and neuropsychiatrists [for details, see also (26)]. In the present research, we used the approved Italian version of the CAARMS (CAARMS-ITA) (27), which showed an excellent interrater reliability in Italian clinical samples of adolescents and young adults (26, 28).

In accordance with the DSM-IV-TR criteria (20), Axis I diagnoses were made using the Structured Clinical Interview for DSM-IV-TR Axis I Disorders (29). CAARMS UHR/FEP criteria (11) were used to separate the participants into the following three subsamples: (a) FEP sample; (b) UHR+ sample (i.e., BLIPSs, APSs, and GRFD), and (c) UHR– sample (i.e., those subjects who were below the CAARMS inclusion criteria). Finally, for better specifying the clinical profile of UHR adolescents with family history of SMI (especially psychosis), UHR+ participants were further dichotomized using the following criteria: (a) family history of SMI (i.e., considering all the degrees of family relationships), (b) presence of at least one first-degree relative with psychosis or other SMI, and (c) presence of a GRFD syndrome (i.e., alone or in comorbidity with APS or BLIPS condition). As suggested by Fulone et al. (30), for SMI, we expressly intended schizophrenia spectrum disorders or other related psychosis, bipolar disorder, and major depression.

Procedures and Statistical Analysis

In the present research all participants underwent ReARMS program, a baseline multidimensional assessment process including the *ad hoc* clinical/sociodemographic schedule and the CAARMS interview (to explore the presence of an UHR mental state, a first-episode psychosis or neither) [for details, see also (1)]. UHR– individuals were excluded from the ReARMS protocol, but received specific advises for an appropriate treatment (2).

Depending on the severity of their symptoms and functioning decline, UHR and FEP adolescents were provided with a 5-year intervention package composed by pharmacological therapy and a multielement psychosocial treatment [including individual cognitive-behavioral therapy (CBT), psychoeducational sessions for family members, and a case management for an early rehabilitation], in accordance with the modern guidelines (31–33). Specifically, antipsychotics were avoided unless the UHR+ participants (a) were rapidly deteriorating in daily functioning, (b) were overwhelmed by psychotic symptoms, and (c) had an imminent risk of suicide or serious violence (2, 19). Atypical antipsychotics in low dose were typically used. Benzodiazepines and selective serotonin reuptake inhibitors were also administered to treat anxiety, insomnia, and depressive symptoms.

Collected data were analyzed using the 15.0 version of the Statistical Package for Social Science for Windows (34). Significance threshold was fixed at $p = 0.05$ for all two-tailed tests. Descriptive variables were represented using mean values ± standard deviation (if continuous parameters) or frequencies and percentages (if categorical parameters). As all explorations were not normally distributed (Kolmogorov–Smirnov-test with Lilliefors correction: $p < 0.05$) (34), non-parametric statistics were used. Specifically, intergroup comparisons on characteristics involving continuous variables

were analyzed with the Kruskal–Wallis-test and the Mann–Whitney *U*-test (as appropriate). The χ^2-test or the Fisher exact test (i.e., when 20% of expected frequency was ≤5 or any expected frequency was <1) was performed for categorical parameters. The Mann–Whitney *U*-test was also used as *post-hoc* procedure in comparisons of continuous variables within more than two subgroups. Finally, the Holm-Bonferroni correction method (35) was performed to counteract the problem of multiple comparisons. Specifically, sociodemographic, clinical, and psychopathological features were compared in UHR+ participants subsequently dichotomized using the following categories: (a) family history of SMI (i.e., considering all the degrees of family relationships), (b) presence of at least one first-degree relative with psychosis or other SMI, (c) presence of GRFD syndrome (i.e., alone or in comorbidity with APS or BLIPS condition).

RESULTS

A total of 147 adolescents [80 females (54.4%); 127 white adolescents (86.4%); mean age = 15.84 ± 1.67 years] consecutively entered the ReARM protocol from September 2012 to December 2018; of them, 96 (65.3%) youths were treated in the ReARMS program. As previously described [for details on characterization of young people with early psychosis who entered the ReARMS protocol, see also (2)], 11 adolescents were excluded because of exclusion criteria.

In the UHR+ subgroup [$n = 51$ (34.7% of the total sample)], 48 adolescents (94.1%) met the APS criteria, 2 (3.9%) met the BLIPS criteria, and only 1 met the GRFD criteria alone. Among the APS and BLIPS participants, 17 (34%) also met the GRFD criteria. At baseline, the most common diagnoses were represented by major depression ($n = 23$; 45.1%), anxiety disorders ($n = 9$; 17.6%), schizotypal personality disorder ($n = 9$; 17.6%), and obsessive–compulsive disorder ($n = 4$; 7.8%).

The FEP subgroup [$n = 45$ (30.6% of the total sample)] was composed of patients with DSM-IV-TR schizophrenia ($n = 22$; 48.9%), psychotic disorder not otherwise specified ($n = 10$; 22.2%), affective (major depressive or bipolar) psychosis ($n = 9$; 20.0%), and schizophreniform disorder ($n = 4$; 8.9%).

The remaining 51 adolescents (34.7% of the total sample) were under the CAARMS-defined UHR/FEP threshold and composed the UHR– subgroup. The most common diagnoses were represented by DSM-IV-TR depressive disorders ($n = 22$; 43.1%), non-schizotypal personality disorder ($n = 18$; 35.3%) (i.e., borderline, narcissistic, and avoidance personality disorder), and anxiety disorders ($n = 11$; 21.6%).

No intergroup differences in terms of gender, age, ethnic group, mother tongue, and years of education were observed (**Table 1**). Compared to UHR+, FEP adolescents showed a longer DUI. No intergroup differences were also found in terms of family history of SMI, as well as in first-degree relatives with psychosis or other SMI.

Family History of SMI and UHR+ Individuals: Clinical Profile

Among 31 UHR+ adolescents with family history of SMI [i.e., UHR+/F+ (60.8% of the UHR+ total group)], 30 met the APS criteria, and 1 met the BLIPS criteria at the baseline assessment; of them, 11 (35.5% of the UHR+/F+ total subgroup) also met the GRFD criteria.

Compared to UHR+ individuals without a family history of SMI (i.e., UHR+/F–), UHR+/F+ subjects showed a significantly lower CAARMS "Alogia" item subscore (**Table 2**). No other between-group difference in terms of baseline functioning, sociodemographic, clinical, and psychopathological characteristics was found. Similarly, no intergroup differences were observed in terms of frequency of specific ReARMS interventions provided to the UHR+ participants (i.e., antipsychotic medication, CBT, psychoeducational sessions for family members and case management oriented to an early recovery and rehabilitation).

Among 15 UHR+ adolescents with at least a first-degree relative with psychosis or other SMI [i.e., UHR+/FDR+ (29.4%

TABLE 1 | Demographic and clinical characteristics of the total sample and the three subgroups.

Variable	Total sample ($n = 147$)	UHR– ($n = 51$)	UHR+ ($n = 51$)	FEP ($n = 45$)	Statistics (χ^2)	*Post-hoc*-test (Mann–Whitney *U*-test)
Gender (females)	80 (54.4%)	26 (51.0%)	31 (60.8%)	23 (51.1%)	1.27	—
Ethnic group (Caucasian)	127 (86.4%)	44 (86.3%)	46 (90.2%)	37 (82.2%)	1.29	—
Mother tongue (Italian)	139 (94.5%)	49 (96.1%)	50 (98.0%)	40 (88.9%)	1.57	—
Age at entry	15.84 ± 1.67	15.71 ± 1.72	15.57 ± 1.63	16.29 ± 1.60	5.51	—
Education (in years)	10.52 ± 1.68	10.67 ± 1.80	10.31 ± 1.57	10.60 ± 1.67	1.08	—
DUI (in weeks)	84.42 ± 57.08	81.00 ± 51.79	61.00 ± 40.57	113.77 ± 65.97	14.05*	FEP > UHR+†
Family history of SMI	89 (60.5%)	30 (58.8%)	31 (60.8%)	28 (62.2%)	0.12	—
First-degree relative with psychosis	21 (14.3%)	4 (7.8%)	8 (15.7%)	9 (20.0%)	3.01	—
First-degree relative with SMI	55 (37.4%)	21 (41.2%)	15 (29.4%)	19 (42.2%)	2.15	—

*DUI, duration of untreated illness; FEP, patients with first-episode psychosis; UHR, ultrahigh-risk; UHR+, individuals who met CAARMS-defined UHR criteria; UHR–, individuals who did not meet CAARMS-defined UHR/FEP criteria; CAARMS, Comprehensive Assessment of At-Risk Mental States; SMI, severe mental illness. Frequencies and percentages, mean ± standard deviation, Kruskal–Wallis-test (χ^2) and χ^2-values are reported. *$p < 0.001$; †Holm-Bonferroni corrected $p < 0.017$.*

TABLE 2 | Sociodemographic, psychopathological, and clinical characteristics between UHR+ participants with and without family history of SMI.

Variable	UHR+/F+ ($n = 31$)	UHR+/F– ($n = 20$)	Statistics (χ^2/z)
Gender (females)	19 (61.3%)	12 (60.0%)	0.01
Ethnic group (Caucasian)	29 (93.5%)	17 (85.0%)	1.00
Mother tongue (Italian)	30 (96.8%)	20 (100.0%)	0.66
Employment status (student)	27 (87.1%)	18 (90.0%)	0.65
Age at entry	15.61 ± 1.67	15.50 ± 1.61	−0.85
Education (in years)	10.35 ± 1.58	10.25 ± 1.58	−1.34
DUI (in weeks)	60.15 ± 39.27	62.83 ± 45.02	−0.60
Past hospitalization	2 (6.5%)	3 (15.0%)	1.00
Previous specialist contact	16 (51.6%)	10 (50.0%)	0.13
Previous suicide attempt	6 (19.4%)	2 (10.0%)	0.80
Current substance abuse	1 (3.2%)	3 (15.0%)	2.33
1-year "dropout" rate	1 (3.2%)	3 (15.0%)	2.33
1-year "psychosis transition" rate	1 (4.5%)	3 (17.6%)	1.79
T1 APS criteria	11 (35.4%)	4 (20.0%)	2.84
T1 BLIPS criteria	2 (6.4%)	0 (0.0%)	1.63
T1 UHR– criteria	17 (54.8%)	13 (65.0%)	1.04
CAARMS subscales			
SOFAS	47.61 ± 9.56	48.50 ± 6.92	−0.56
Positive symptoms	10.13 ± 3.08	10.70 ± 3.67	−0.47
Cognitive change	4.19 ± 2.35	5.40 ± 2.37	−1.71
Emotional disturbance	5.16 ± 3.94	4.95 ± 2.95	−0.22
Negative symptoms	7.55 ± 4.11	8.15 ± 3.88	−0.65
Behavioral change	10.97 ± 5.10	10.10 ± 3.37	−0.14
Motor/physical changes	2.68 ± 2.87	4.15 ± 3.90	−1.02
General psychopathology	15.74 ± 5.82	16.10 ± 6.66	−0.45
CAARMS items			
Unusual thought content	2.58 ± 1.50	3.30 ± 1.45	−1.99
Non-bizarre ideas	2.52 ± 1.48	2.60 ± 1.23	−0.78
Perceptual abnormalities	2.90 ± 1.27	2.65 ± 1.72	−0.12
Disorganized speech	2.13 ± 1.52	2.15 ± 1.42	−0.20
Subjective cognitive change	2.68 ± 1.42	3.45 ± 1.39	−1.90
Observed cognitive change	1.52 ± 1.61	1.95 ± 1.39	−1.20
Subjective emotional disturbance	2.06 ± 1.91	2.45 ± 1.64	−0.84
Observed blunted affect	2.23 ± 1.78	2.00 ± 1.62	−0.39
Observed inappropriate affect	0.87 ± 1.14	0.50 ± 1.28	−1.67
Alogia	1.45 ± 1.67	2.60 ± 1.57	−2.11*
Avolition/apathy	2.87 ± 1.69	2.80 ± 1.70	−0.24
Anhedonia	3.23 ± 1.56	2.75 ± 1.58	−1.20
Social isolation	3.61 ± 1.54	3.75 ± 1.62	−0.54
Impaired role functioning	3.19 ± 1.66	3.00 ± 1.65	−0.22
Disorganizing/odd/ stigmatizing behavior	1.71 ± 1.72	1.80 ± 1.85	−0.13
Aggressive/dangerous behavior	2.45 ± 1.96	1.55 ± 1.43	−1.80
Subjective impaired motor functioning	0.35 ± 0.98	0.80 ± 1.36	1.45
Objective impaired motor functioning	0.68 ± 1.42	0.25 ± 0.91	1.18
Subjective impaired bodily sensation	0.42 ± 1.25	1.40 ± 1.72	−1.99
Subjective impaired autonomic functioning	1.23 ± 1.50	1.70 ± 1.89	−0.99
Mania	0.29 ± 0.90	0.35 ± 0.99	−0.52
Depression	3.61 ± 1.38	3.15 ± 1.63	−0.80
Suicidality/self-harm	1.77 ± 2.06	1.55 ± 1.47	−0.01
Mood swings/lability	1.39 ± 1.41	2.10 ± 1.86	−1.42
Anxiety	3.42 ± 1.49	3.35 ± 1.78	−0.45
Obsessive–compulsive symptoms	1.26 ± 1.71	1.50 ± 2.11	−0.21
Dissociative symptoms	1.16 ± 1.53	1.55 ± 1.64	−0.81
Subjective impaired tolerance to normal stress	2.84 ± 1.71	2.55 ± 1.73	−0.44
T0 exposure to antipsychotics	12 (38.7%)	6 (30.0%)	0.40
CBT	13 (41.9%)	12 (60.0%)	0.55
Family psychoeducation	12 (38.7%)	7 (35.0%)	0.69
Case management	13 (41.9%)	12 (60.0%)	0.55

*DUI, duration of untreated illness; UHR, ultrahigh-risk; UHR+, individuals who met CAARMS-defined UHR criteria; UHR–, individuals who were below the CAARMS-defined UHR/FEP criteria; FEP, first-episode psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; SMI, severe mental illness; UHR+/F+, UHR participants with a family history of SMI; UHR+/F–, UHR participants without a family history of SMI; APS, attenuated psychotic symptoms; BLIPS, brief and limited intermittent psychotic symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; T0, baseline assessment; T1, 1-year assessment time; CBT, cognitive–behavioral therapy. Frequencies and percentages, mean ± standard deviation, Mann–Whitney U-test (z), and χ^2-values are reported. *Holm–Bonferroni corrected $p < 0.025$.*

of the UHR+ total group)], 14 met the APS criteria and 1 met the BLIPS criteria at the baseline assessment; of them, 7 (46.7% of the UHR+/FDR+ total subgroup) also met the GRFD criteria.

Compared to UHR+ individuals without a first-degree relative with psychosis or other SMI (i.e., UHR+/FDR–), UHR+/FDR+ subjects showed a significantly lower CAARMS "alogia" and "suicidality/self-harm" item subscores (**Table 3**). No other intergroup differences in terms of baseline functioning and sociodemographic, clinical, and psychopathological features were found. Similarly, no between-group difference was reported in

TABLE 3 | Sociodemographic, psychopathological, and clinical characteristics between UHR+ participants with and without first-degree relatives with psychosis or other SMI.

Variable	UHR+/FDR+ ($n = 15$)	UHR+/FDR– ($n = 36$)	Statistics (χ^2/z)
Gender (females)	6 (40.0%)	25 (69.4%)	3.85
Ethnic group (Caucasian)	13 (86.7%)	33 (91.7%)	0.30
Mother tongue (Italian)	14 (93.3%)	36 (100.0%)	2.45
Employment status (student)	12 (80.0%)	33 (91.7%)	2.83
Age at entry	15.82 ± 1.61	15.26 ± 1.63	−1.23
Education (in years)	10.54 ± 1.55	10.04 ± 1.58	−1.28
DUI (in weeks)	56.87 ± 39.73	67.33 ± 42.42	−0.73
Past hospitalization	0 (0.0%)	5 (13.9%)	2.31
Previous specialist contact	10 (66.7%)	16 (44.4%)	2.09
Previous suicide attempt	0 (0.0%)	8 (22.2%)	3.95
Current substance abuse	1 (6.7%)	3 (8.3%)	0.04
1-year "dropout" rate	1 (6.7%)	3 (8.3%)	2.33
1-year "psychosis transition" rate	1 (6.7%)	3 (8.3%)	1.79
T1 APS criteria	7 (46.6%)	8 (22.2%)	2.84
T1 BLIPS criteria	1 (6.7%)	1 (2.7%)	1.63
T1 UHR– criteria	6 (40.0%)	24 (66.7%)	2.04
CAARMS subscales			
SOFAS	47.43 ± 10.05	48.61 ± 6.44	−0.48
Positive symptoms	10.29 ± 3.21	10.43 ± 3.49	−0.02
Cognitive change	4.39 ± 2.30	5.00 ± 2.56	−0.96
Emotional disturbance	5.25 ± 3.90	4.87 ± 3.15	−0.41
Negative symptoms	7.57 ± 4.14	8.04 ± 3.89	−0.58
Behavioral change	11.32 ± 5.24	9.78 ± 3.26	−0.83
Motor/physical changes	2.75 ± 3.00	3.87 ± 3.71	−0.85
General psychopathology	15.89 ± 6.00	15.67 ± 6.35	−0.22
CAARMS items			
Unusual thought content	2.33 ± 1.34	3.08 ± 1.46	−1.80
Non-bizarre ideas	3.20 ± 0.94	2.64 ± 1.61	−1.42
Perceptual abnormalities	2.80 ± 1.52	2.44 ± 1.32	−1.06
Disorganized speech	2.07 ± 1.58	2.17 ± 1.44	−0.08
Subjective cognitive change	2.47 ± 1.60	3.19 ± 1.35	−1.53
Observed cognitive change	1.67 ± 1.45	1.69 ± 1.58	−0.06
Subjective emotional disturbance	1.60 ± 1.80	2.47 ± 1.76	−1.54
Observed blunted affect	2.20 ±1.78	2.11 ± 1.70	−0.25
Observed inappropriate affect	0.80 ± 1.08	0.69 ± 1.26	−0.62
Alogia	1.07 ± 1.39	2.25 ± 1.73	−2.21*
Avolition/apathy	2.93 ± 1.49	2.81 ± 1.69	−0.52
Anhedonia	3.33 ± 1.40	2.92 ± 1.64	−0.63
Social isolation	3.60 ± 1.45	3.69 ± 1.62	−0.53
Impaired role functioning	3.20 ± 1.37	3.08 ± 1.76	−0.21
Disorganizing/odd/ stigmatizing behavior	1.73 ± 1.98	1.75 ± 1.68	−0.25
Aggressive/dangerous behavior	2.40 ± 2.06	1.97 ± 1.71	−0.84
Subjective impaired motor functioning	0.47 ± 1.25	0.56 ± 1.13	−0.57
Objective impaired motor functioning	0.67 ± 1.59	0.44 ± 1.11	−0.36
Subjective impaired bodily sensation	0.13 ± 0.52	1.08 ± 1.71	−2.05
Subjective impaired autonomic functioning	0.87 ± 1.30	1.64 ± 1.76	−1.55
Mania	0.60 ± 1.24	0.19 ± 0.75	−1.22
Depression	3.33 ± 1.45	3.47 ± 1.52	−0.54
Suicidality/self-harm	0.87 ± 1.51	2.03 ± 1.87	−2.27*
Mood swings/lability	1.67 ± 1.34	1.67 ± 1.74	−0.18
Anxiety	2.93 ± 1.75	3.58 ± 1.50	−1.45
Obsessive–compulsive symptoms	1.40 ± 1.64	1.33 ± 1.97	−0.48
Dissociative symptoms	1.00 ± 1.60	1.44 ± 1.56	−0.95
Subjective impaired tolerance to normal stress	2.40 ± 1.80	2.86 ± 1.67	−1.70
T0 exposure to antipsychotics	6 (40.0%)	12 (33.3%)	0.21
CBT	8 (53.3%)	17 (47.2%)	0.46
Family psychoeducational	7 (46.6%)	12 (33.3%)	0.01
Case management	7 (46.6%)	18 (50.0%)	1.89

*DUI, duration of untreated illness; UHR, ultrahigh risk; UHR+, individuals who met CAARMS-defined UHR criteria; UHR–, individuals who were below the CAARMS-defined UHR/FEP criteria; FEP, first-episode psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; SMI, severe mental illness; UHR+/FDR+, UHR participants with at least a first-degree relative with psychosis or other SMI; UHR+/FDR–, UHR participants without first-degree relatives with psychosis or other SMI; APS, attenuated psychotic symptoms; BLIPS, Brief and Limited Psychotic Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; T0, baseline assessment; T1, 1-year assessment time; CBT, cognitive–behavioral therapy. Frequencies and percentages, mean ± standard deviation, Mann–Whitney U-test (z), and χ^2-values are reported. *Holm–Bonferroni corrected $p < 0.025$.*

terms of frequency of specific ReARMS interventions provided to the UHR+ adolescents.

GRFD Syndrome in UHR+ Individuals: Clinical Profile

Among 51 UHR+ participants, 18 (35.2% of the UHR+ total group) met the CAARMS-defined GRFD criteria (i.e., UHR+/GRFD+); of them, 17 individuals (94.4% of the total GRFD subgroup) showed a co-occurrence of GRFD syndrome with APS or BLIPS criteria.

TABLE 4 | Sociodemographic, psychopathological, and clinical characteristics between UHR+ participants meeting or not meeting CAARMS-defined GRFD criteria.

Variable	UHR+/GRFD+ ($n = 18$)	UHR+/GRFD– ($n = 33$)	Statistics (χ^2/z)
Gender (females)	11 (61.1%)	20 (60.6%)	0.01
Ethnic group (Caucasian)	15 (83.3%)	31 (93.3%)	1.48
Mother tongue (Italian)	17 (94.4%)	33 (100.0%)	1.87
Employment status (student)	15 (83.3%)	30 (90.9%)	1.96
Age at entry	16.06 ± 1.35	15.30 ± 1.72	−1.58
Education (in years)	10.67 ± 1.37	10.12 ± 1.65	−1.12
DUI (in weeks)	49.62 ± 32.71	66.92 ± 43.54	−1.20
Past hospitalization	2 (11.1%)	3 (9.1%)	0.05
Previous specialist contact	11 (61.1%)	15 (45.5%)	1.14
Previous suicide attempt	1 (5.6%)	7 (21.29%)	2.16
Current substance abuse	1 (5.6%)	3 (9.1%)	0.20
1-year "dropout" rate	1 (5.6%)	3 (9.1%)	0.20
1-year "psychosis transition" rate	2 (13.3%)	2 (8.3%)	0.25
T0 APS criteria	16 (88.9%)	32 (97.0%)	1.37
T0 BLIPS criteria	1 (5.6%)	1 (3.0%)	0.20
T1 APS criteria	4 (22.2%)	11 (35.4%)	1.43
T1 BLIPS criteria	1 (5.6%)	1 (3.0%)	0.12
T1 UHR– criteria	7 (38.9%)	20 (60.6%)	2.06
CAARMS subscales			
SOFAS	48.56 ± 5.19	47.64 ± 9.99	−0.29
Positive symptoms	11.94 ± 2.75	9.48 ± 3.29	−2.51*
Cognitive change	5.17 ± 2.18	4.39 ± 2.52	−1.26
Emotional disturbance	6.50 ± 3.03	4.30 ± 3.62	−2.21*
Negative symptoms	7.94 ± 3.37	7.70 ± 4.35	−0.09
Behavioral change	11.17 ± 5.06	10.33 ± 4.20	−0.31
Motor/physical changes	2.89 ± 3.56	3.45 ± 3.27	−0.89
General psychopathology	15.11 ± 6.50	16.30 ± 5.93	−0.62
CAARMS items			
Unusual thought content	3.22 ± 1.35	2.67 ± 1.57	−1.16
Non-bizarre ideas	3.44 ± 0.98	2.45 ± 1.56	−2.25*
Perceptual abnormalities	2.78 ± 1.55	2.42 ± 1.27	−0.95
Disorganized speech	2.50 ± 1.25	2.50 ± 1.25	−1.40
Subjective cognitive change	3.22 ± 1.31	2.85 ± 1.52	−0.65
Observed cognitive change	1.94 ± 1.39	1.55 ± 1.60	−0.98
Subjective emotional disturbance	2.50 ± 1.42	2.06 ± 1.98	−0.79
Observed blunted affect	2.72 ± 1.45	1.82 ± 1.78	−1.84
Observed inappropriate affect	1.28 ± 1.45	0.42 ± 0.90	−2.28*
Alogia	1.94 ± 1.63	1.88 ± 1.78	0.34
Avolition/apathy	3.06 ± 1.51	2.73 ± 1.68	−0.69
Anhedonia	2.94 ± 1.05	3.09 ± 1.81	−1.25
Social isolation	3.94 ± 1.26	3.52 ± 1.70	−0.55
Impaired role functioning	2.94 ± 1.80	3.21 ± 1.58	−0.37
Disorganizing/odd/stigmatizing behavior	2.00 ± 1.64	1.61 ± 1.82	−1.03
Aggressive/dangerous behavior	2.28 ± 2.14	2.00 ± 1.64	−0.59
Subjective impaired motor functioning	0.50 ± 0.98	0.55 ± 1.25	−0.21
Objective impaired motor functioning	0.33 ± 0.84	0.61 ± 1.43	−0.28
Subjective impaired bodily sensation	0.56 ± 1.38	0.94 ± 1.60	−1.00
Subjective impaired autonomic functioning	1.50 ± 2.00	1.36 ± 1.47	−0.01
Mania	0.22 ± 0.73	0.36 ± 1.02	−0.18
Depression	3.67 ± 1.49	3.30 ± 1.49	−0.88
Suicidality/self-harm	1.28 ± 1.53	1.91 ± 1.97	−1.03
Mood swings/lability	1.89 ± 1.71	1.55 ± 1.58	−0.76
Anxiety	3.28 ± 1.71	3.45 ± 1.54	−0.07
Obsessive–compulsive symptoms	1.11 ± 1.57	1.48 ± 2.02	−0.39
Dissociative symptoms	1.39 ± 1.65	1.27 ± 1.55	−0.18
Subjective impaired tolerance to normal stress	2.28 ± 1.71	2.97 ± 1.69	−1.42
T0 exposure to antipsychotics	7 (38.9%)	11 (33.3%)	0.16
CBT	10 (55.5%)	15 (45.5%)	0.07
Family psychoeducation	5 (27.7%)	14 (42.2%)	2.31
Case management	8 (44.4%)	17 (51.5%)	1.23

*DUI, duration of untreated illness; UHR, ultrahigh risk; UHR+, individuals who met CAARMS-defined UHR criteria; UHR–, individuals who were below the CAARMS-defined UHR/FEP criteria; FEP, first-episode psychosis; CAARMS, Comprehensive Assessment of At-Risk Mental States; GFRD, genetic risk and functioning deterioration syndrome; UHR+/GRFD+, UHR participants who met CAARMS-defined GRFD criteria; UHR+/GRFD–, UHR participants who did not meet CAARMS-defined GRFD criteria; APS, attenuated psychotic symptoms; BLIPS, Brief and Limited Intermittent Psychotic Symptoms; SOFAS, Social and Occupational Functioning Assessment Scale; T0, baseline assessment; T1, 1-year assessment time; CBT, cognitive–behavioral therapy. Frequencies and percentages, mean ± standard deviation, Mann–Whitney U-test (z), and χ^2-values are reported. *Holm–Bonferroni corrected $p < 0.025$.*

Compared to UHR+ subjects not meeting the GRFD criteria (i.e., UHR+/GRFD–), UHR+/GRFD+ individuals showed a significantly higher CAARMS "positive symptoms" and "emotional disturbance" subscale scores, as well as higher "non-bizarre ideas" and "observed inappropriate affect" item subscores (**Table 4**). No other intergroup differences in terms of baseline functioning and sociodemographic, clinical, and psychopathological characteristics were observed. Similarly, no between-group differences were found in terms of frequency of specific ReARMS interventions provided to the UHR+ participants.

DISCUSSION

The first aim of the present research was to examine the prevalence of SMI in family members of distinct help-seeking subsamples of adolescents identified through the UHR criteria (i.e., UHR+ vs. FEP vs. UHR–). Although no statistically significant intergroup-differences were found in terms of family

load for SMI, more than 60% of our UHR+ and FEP adolescents showed a general family history of SMI, and approximately a third of them (with percentages ranging from 29.4% in UHR+ subjects to 42.2% in FEP patients) had at least a first-degree relative with psychosis or other SMI. As expected, these findings confirm the epidemiological burden of a family history of SMI in the prodromal phase of psychosis and at the onset of illness, already in adolescence, consistently with the very few results reported in the current literature (15, 36–38).

However, our UHR+ adolescents with a family history of SMI (specifically those with a first-degree relative with psychosis or other SMI) showed lower levels of alogia, self-harm, and suicidality (i.e., suicidal thoughts and behaviors). These results seem to suggest that the experience of a family psychiatric suffering and the custom of living with people with an SMI could increase the personal ability to find words to express a request for specialist help and to describe their symptoms, as well as to support their hope and future projects. Moreover, this also confirms the absolute need for clinical attention for children and adolescents with family members with SMI (39) and the crucial importance of psychotherapeutic and psychoeducational interventions to support their coping skills, their resilience, and their quality of life (40).

In the present research, a GRFD syndrome was detected in ∼35% of UHR+ adolescents, mostly (i.e., almost in 95% of cases) in co-occurrence with APS or BLIPS criteria. This result is slightly higher than that reported in the current literature (6, 41) and confirms the very low incidence of a GRFD syndrome alone in adolescent help-seeking populations attending specialist mental health services offering dedicated EIP programs (2, 7). Hence, there is a specific need to diffusely spread the early identification of psychosis in all the community services (e.g., school and social agencies, general practitioners, general hospital, emergency room), going beyond the boundaries of mental health centers and emphasizing the crucial attention to be paid to children and adolescent with a family history of SMI (40, 41) or with schizotypal personality traits (42, 43), together with a socio-occupational functioning decline. From a psychopathological point of view, in the present study, GRFD adolescents showed baseline high levels of positive symptoms (especially, non-bizarre ideas) and emotional disturbances (specifically, observed inappropriate affect). These specific clinical features may be useful for an early characterization of adolescents with a genetic risk of psychosis and an incipient functioning deterioration, also in developing specific screening test.

Limitations

A first methodological limitation of the current research is the relatively small sample size. Therefore, further studies on larger populations of both UHR and FEP adolescents are needed.

Second, our sample was recruited within a specific EIP program. Thus, our results cannot be generalized outside UHR/FEP-enriched populations.

Third, future studies to better specify and deepen the clinical profile of UHR adolescents (e.g., non-bizarre ideas or emotional disturbances) meeting GRFD criteria are also recommended.

Conclusions

This is the first Italian study specifically developed to investigate the prevalence of SMI and in family members of adolescent help-seekers recruited within a specific EIP program, as well as the presence of a GRFD syndrome in Italian youths with early psychosis. Our results confirm the importance of family load and genetic risk factors in young people at UHR of psychosis (as well as in FEP adolescents), suggesting the need of their early detection, already within the network of general practitioners, general hospitals, and the other community agencies (e.g., social services and school). Moreover, this clinical attention becomes even more crucial because adolescents receiving treatment in CAMHS are at elevated risk of falling through the child-adult service gap as they cross the transition boundary between services (i.e., from child–adolescent mental health services to adult mental health services) (1). Bridging this gap might be achievable through a framework shift that incorporates the full continuum of service response within a prevention and promotion framework for youth mental health (44).

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by AVEN (Area Vasta Emilia Nord) Ethics Committee (protocol 36102/2019). Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR CONTRIBUTIONS

LP and AR designed the study and conducted the main data analysis. SA, FP, SG, IS, and LC collected data. LP and SP managed the literature. MP, LP, and AR drafted the manuscript. All authors read and approved the final version of the manuscript.

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SYSTEMATIC REVIEW
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Evaluation of a Family-Based Intervention Program for Children of Mentally Ill Parents: Study Protocol for a Randomized Controlled Multicenter Trial

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Background: Children of mentally ill parents have a three to seven times higher risk of developing mental disorders compared to the general population. For this high-risk group, specialized prevention and intervention programs have already been developed. However, there has been insufficient sytematic evaluation to date. Moreover, effectiveness and the cost-effectiveness data of the respective programs until today is very scarce and at the same time constitutes the pre-condition for the program's implementation into regular health care.

Methods: The study consists of a two-group randomized controlled multicenter trial conducted at seven study sites throughout Germany and Switzerland. Participants are families with mentally ill parents and their children aged from 3 to 19 years. The intervention comprises 6 to 8 semi-structured sessions over a period of about 6 months. Topics discussed in the intervention include parental mental illness, coping, family relations and social support. Families in the control condition will receive treatment as usual. The children's mental health, assessed using the K-SADS-PL by blinded external raters will constitute the primary efficacy outcome. Further outcomes will be assessed from the parents' as well as from the children's perspectives. Participants are investigated at baseline, 6, 12, and 18 months after baseline assessment. In addition to the assessment of various psychosocial outcomes, a comprehensive health-economic evaluation will be performed.

Discussion: This paper describes the evaluation of a family-based intervention program for children of mentally ill parents (CHIMPs) in the regular health care system in Germany and Switzerland. A methodically sophisticated study design has been developed to reflect the complexity of the actual health care situation. This trial will contribute to the regular health care for the high-risk group of children of mentally ill parents.

Clinical Trial Registration: www.ClinicalTrials.gov, identifier NCT02308462; German Clinical Trials Register: DRKS00006806.

Keywords: children of mentally ill parents, family intervention, randomized controlled trial, multicenter trial, evaluation

INTRODUCTION

Growing up with a parent who suffers from a mental disorder can be a major challenge for the affected children or adolescents. Around the world, 15–23% of all children are assumed to face this challenge (1). In Germany, about 3.6 million children are considered to have at least one parent with a mental illness (2). These children have a 3 to 7 times higher risk to develop a mental disorder compared to the general population. Moreover, the risk for a mental disorder of these children increases with the parental mental stress (3). The costs related to these children's use of mental healthcare services is up to five times higher compared to other children (4). This is why these children are an economically highly relevant target group for the health care system (5, 6).

Both, genetic and environmental factors were identified to account for the association between parents' and children's psychopathology (7–10). The children's mental health problems along with the risk and protective factors associated with the parental disorder can be described on multiple levels, including the child, parental, family, and social level (8).

Previous research has identified numerous risk factors for children's mental health. Risk factors on the parental level are e.g., the specific psychiatric diagnosis, the severity and chronicity of the disease, inappropriate coping strategies and poor emotional availability. On the family level, violence as well as a lack of communication and social isolation are examples of risk factors. The child's temperament and cognitive and social skills, as well as parentification are risk factors on the child level. Regarding the psychosocial level, insufficient social support and a lack of attachment figures outside the family represent risk factors for children's development. These risk factors do not simply add up, but have a multiplying effect (8, 11). Opposite these risk factors, specific protective factors have been identified. These are e.g., primarily positive relationships inside and outside the family, information about the parental disease which is adequate for the children's age and development, adequate individual and familial coping strategies, and supporting parental and family dynamics (12–14).

The tight association of parental mental disorders with the increased risk for mental health problems in children emphasizes the need for early treatment in order to prevent unfavorable development of these children (15–17). Correspondingly, a large number of programs that support families with mentally ill parents has been developed during the last decades. These programs are offered at different levels of the family system: at the child level (e.g., peer support groups, psychoeducational interventions), at the parent level (e.g., parent groups, couple therapy, parent skills groups) and at the family level (e.g., family counseling, family therapy, family assistance) (7, 18, 19).

In respect of intervention programs for children with mentally ill parents, Reupert and colleagues (20) described in their comprehensive review that psychoeducation regarding the parental mental disorder was the key element of the investigated programs. This review also showed that interventions for children of parents with affective or anxiety disorders were overrepresented compared to interventions for other parental diagnoses. Cognitive or behavioral and psychoeducational approaches were the most common therapeutic approaches. Main objects of these approaches are to increase parenting skills and children's knowledge about the parental disease, and to strengthen resilience factors (7). Regarding the programs' effectiveness, Siegenthaler et al. (7) reviewed thirteen randomized controlled trials of preventive interventions for children of mentally ill parents and reported that the risk of developing the same mental illness as the parent was decreased by 40%. Although the effectiveness of prevention and intervention programs was mostly evaluated in randomized controlled trials, the methodical quality of many studies was insufficient (7, 21). The use of cost-effectiveness analyses in the evaluation of these programs was also rare: only one study included an economic evaluation (22). The review by Thanhauser et al. (23) analyzed 50 independent samples from randomized controlled trials, quantifying effects of preventive interventions for children of mentally ill parents. They reported small but significant effects in reducing psychopathology and enhancing mother-infant interaction for different intervention programs. Interventions addressing parents and children jointly produced overall larger effects. The authors state that further studies of high quality are urgently needed. While many programs for the high-risk group of children of mentally ill parents have been developed and evaluated, the implementation of these programs into practice is not yet satisfactory. Even in regions with a high standard of mental health services, affected families do not benefit sufficiently from the respective programs. Assumed reasons are that these programs are not well-established, too expensive and that many parents are afraid of losing the custody for their children if they admit that they need support (24). Moreover, mental health problems are frequently associated with feelings

of shame and guilt with the result that often help-seeking is impaired (25).

The cited reviews emphasize the need for further studies with validated outcome measures, high methodic quality, rigorous evaluation designs, high quality cost data and sufficient sample size to implement feasible and acceptable interventions for this risk group (7, 20, 22). A family-based intervention program for children of mentally ill parents is currently implemented and evaluated in a randomized-controlled multicenter trial to address this demand.

The CHIMPs intervention (CHIMPs = Children of mentally ill parents) is based on 4 pillars.

1) The "Model of psychosocial development conditions for children of mentally ill parents" (26) describes the interaction of various risk and resilience factors for children of mentally ill parents.
2) The principles and interventional methods of psychoanalytic family therapy (27).
3) The findings of a needs assessment showed that family-based interventions are well-accepted by families with mentally ill parents, compared to other interventions like for example group interventions (28).
4) The psychoeducational behavior-oriented counseling program of Beardslee et al. (29, 30) is an internationally evaluated approach for families with parental affective disorders. The structure of the CHIMPs sessions is based on the program of Beardslee et al.

Based on these considerations, the CHIMPs intervention was developed in a previous pre- post-trial. The effectiveness of the intervention has been evaluated in a waiting-list control group trial (26). Results of this pilot trial showed that the CHIMPs intervention enhances children's mental health (31), quality of life and social support (32), the parents' coping strategies (33) and family relationships (34).

A crucial element of this study design is the comprehensive evaluation of the cost-effectiveness of the intervention. This trial intends to improve the mental health care situation for children and adolescents affected by a parental mental disorder; first in the participating centers, then nationwide.

METHODS

Aims and Hypotheses of the Study

The aims of the study are (1) to evaluate the long-term effectiveness of the intervention compared to a control group regarding the children's psychopathology and their health-related quality of life in seven participating sites, (2) to investigate the cost-effectiveness of the intervention in comparison to a control group under conditions of practice. The study for the cost-effectiveness of the intervention is described and published elsewhere (35).

In summary, we assume that the family-based intervention program for children of mentally ill parents will be associated with (1) an improvement of mental health and (2) an improvement of health-related quality of life in children and adolescents of the intervention group compared to the control group after treatment. We expect that these improvements remain stable during the follow-up period.

More specifically, the following hypotheses will be tested:

1) The whole group of children and adolescents (with and without mental health problems) of the intervention group exhibit on average less mental health problems (CBCL) and a higher health-related quality of life (KIDSCREEN) 18 months after baseline assessment compared to the control group.

Those children who have been evaluated having mental health problems at baseline (assessed by CBCL, cut-off T-score > 63) will be analyzed separately regarding the following hypotheses:

2) The proportion of children and adolescents with mental health problems in the intervention group (assessed by CBCL, cut-off T-score > 63) will be lower compared to the control group 18 months after baseline assessment.
3) Children and adolescents with mental health problems of the intervention group will show a better health-related quality of life (KIDSCREEN) 18 months after baseline assessment compared to the children and adolescents with mental health problems of the control group.

Those children who have been evaluated having psychiatric diagnosis at baseline (assessed by K-SADS-PL by an external rater which is blind for the group assignment of the family) will be analyzed separately. To evaluate the effectiveness of the intervention according to this stricter criterion the following primary hypothesis will be analyzed:

4) The proportion of children and adolescents with psychiatric diagnoses (assessed by K-SADS-PL) will be lower in the intervention group, compared to the control group 18 months after baseline assessment.

Additionally, the following secondary hypothesis will be evaluated:

5) Children and adolescents of the intervention group with psychiatric diagnoses will show a better health-related quality of life (KIDSCREEN) 18 months after baseline measurement compared to the children and adolescents with psychiatric diagnoses of the control group.

Study Design

The present study is a prospective, two-group randomized controlled multicenter trial. In a design with assessments at baseline as well as at 6, 12, and 18 months after baseline assessment, the family-based intervention program CHIMPs is evaluated against a control group. Families in the control group receive treatment as usual (TAU).

Outcomes will be assessed from the patient's, the partner's and the children's perspective (for children aged 10 years and older) as well as from the therapist's perspective. Moreover, the primary outcome of the study (children's mental health) will be externally assessed by rater which is blind for the family's group assignment (K-SADS-PL).

Study Centers

The following seven centers, which are located in Germany and Switzerland, are involved in the evaluation of the CHIMPs program: Hamburg (University Medical Center Hamburg-Eppendorf, Germany), Leipzig (University Medical Center Leipzig, Germany), Ulm-Günzburg (Ulm University, Department of Psychiatry and Psychotherapy II, Germany), Wiesbaden-Rheingau (Medical Center Vitos Clinic, Germany), Gütersloh-Paderborn (LWL Community Hospitals, Germany), Berlin (Charité – Universitätsmedizin Berlin, Germany) and Winterthur (Center of Social Pediatrics, Switzerland). All participating study sites will be involved in patient recruitment, diagnostics and in the implementation of the intervention. The study center in Hamburg will furthermore be responsible for the coordination of the study and for the data management. A steering committee at the coordinating site in Hamburg (SW-G, BF, KW) as well as an external scientific advisory board will regularly examine the study's progress. Yearly meetings of the scientific advisory board and monthly meetings of the steering committee will take place. In these meetings, the study progress, the recruitment, the protocol deviations, the loss-to-follow-up, serious adverse events (SAE) and all problems of the study conduct will be discussed.

Participants

Recruitment

Participants will be recruited from in- and outpatient departments of psychiatric clinics in the seven participating study centers. Recruitment will take place at both university and communal hospitals and at child and adolescent as well as adult psychiatric departments. These various access paths reflect the diversity of the population of mentally ill parents and their children.

A member of the research staff will approach the mentally ill parent at the end of his/her treatment period and inform him/her about the project. Moreover, therapists will be asked to inform their patients about the project and to encourage them to contact the study team. After all participating family members provided informed written consent, the study starts with the baseline questionnaires and interviews.

Eligibility Criteria

Families with at least 1 mentally ill parent and at least 1 child aged 3–19 years will be included. A parent is defined as mentally ill if he or she has a psychiatric disorder which is treated in an in- or outpatient department at the time of recruitment; in addition, parents currently not in treatment are eligible to participate if they had at least one episode of illness within the last 5 years.

If there is more than one child in the family, families are free to decide with which children they want to participate; however, all family members are encouraged to take part in the study. Couples as well as single parents can take part in the study. Participation is not limited to biological parents; adoptive parents, stepparents as well as foster parents may enter the study.

To compensate for their time conducting the interviews and filling in the questionnaires, each family will receive a staggered financial compensation.

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria[a]
- Family with at least one mentally ill parent and at least one child between the age of 3 and 19 years
- Parental diagnoses:
- Mental and behavioral disorders due to psychoactive substance use (F10–F19)
- Schizophrenia, schizotypal and delusional disorders (F20–F29)
- Mood (affective) disorders (F30–F39)
- Neurotic, stress-related and somatoform disorders (F40–F48)
- Disorders of adult personality and behavior (F60–F69)
- Regular contact between the mentally ill parent and the child/children
- Written informed consent with the study protocol
- Sufficient knowledge of the German language of parents and children
Exclusion criteria
- Severe psychiatric disorders and impairments with acute symptoms such as suicidal tendencies, massive self-injurious behavior, acute psychotic symptoms etc., with indication for inpatient treatment (these patients are placed in inpatient treatment)

[a] *The numbers in parentheses refer to the codes of the International Statistical Classification of Diseases and Related Health Problems (ICD-10).*

Complete inclusion and exclusion criteria are presented in **Table 1**.

Intervention: CHIMPs

Families in the intervention group will receive the manualized intervention program CHIMPs (26). The psychodynamic CHIMPs approach is based on a theoretical model that addresses coping strategies, family relationships as well as couple and family dynamics. All CHIMPs interventions are derived from these essential issues. Furthermore, the approach is based on key concepts of psychoanalytic family therapy. Moreover, the CHIMPs approach is inspired by Beardslee (29, 36) exclusively in the specific intervention setting of 8 interview sessions with parents, children and the whole family. However, the Beardslee approach is working mainly with cognitive-behavioral psychoeducation. In contrast, the CHIMPs intervention is working consequently with a psychotherapeutic process which is not structured in advance, using the psychodynamical (clarifying, confronting and interpreting) intervention techniques—with the result that the family plays a leading role in the planning of the session content. The psychodynamic approach is also expressed in the multi-generational work at all levels (parents, children, family) that is used for the management of present conflicts. For example, the parents will be asked to tell about how they grew up themselves and which experiences they remember from early childhood in their own family. The work continues with this material. The understanding of the individual psychodynamics of one of the family members will then be worked into the understanding of the psychodynamics of the whole family, and the re-enactment of the primary relationship experiences. Both the work with the parents and with the child is reflecting the respective development experiences. Furthermore, the family dynamic is the object of observation, in so far as it is the representation of earlier relationship experiences and unconscious family conflicts. The

relationship dynamics that are developing within the family-therapist-relationship is comprehensible against this background of the reported biographical experiences. Based on these results of the understanding of the dynamics on the different levels we address the focus issues disease coping, family relationships and social network looking at two directions: the reflection of the actual situation as well as entry points for a more positive, intentional, comprehended change process.

Over a period of ∼6 months, 8 semi-structured sessions (60–90 min) are conducted with the family. Central themes of the first session are procedure and topics of the CHIMPs program. In the next 2–3 sessions the parental mental illness, the communication and information about the disorder as well as the coping with the disorder within the family are discussed. At the same time, the couple's relationship, the children and the parent-child-relationship are examined; the parental families of origin, the contact with other family attachment figures and the family living conditions are also considered. This information serves as a starting point for the family-based intervention.

Children and adolescents are subsequently invited for one or two individual sessions per child. The main objective is to capture the family situation from the child's perspective with focus on the individual and familial coping as well as relationship structures inside and outside the family.

The core of the CHIMPs intervention is formed by the following three sessions for the whole family that complete the program. All family members together participate in these sessions. Main aim is to reflect the different perspectives that evolved from the single sessions. At the same time, openness, transparency and communication within the whole family are encouraged. The family's present and future handling of the disorder and support from inside and outside the family are reflected on and responded to. Depending on the family's needs and wishes, individual topics like current conflicts can also be discussed. If any family member or the whole family needs further treatment or support, this is initiated by the program staff.

All therapists are experienced in the field of adult or child and adolescent psychiatry or psychotherapy and received a comprehensive 2-day training based on the CHIMPs manual (26). To evaluate adherence to the intervention manual, therapists will complete a self-rate checklist asking for the main topics after each session. In addition, adherence will be evaluated by video or audio recording of sessions and subsequent analysis of the recordings. Furthermore, continuous supervision will enhance adherence to the manual intervention.

The goals of the CHIMPs program can be structured into the three levels family dynamics, coping and relationships. On the level of family dynamics, the main aims are to:

- Link the information on the parental illness to family-historical experiences considering family dynamics
- Promote the understanding of the disorder and the couple and family dynamics from a psychodynamic, multi-generational perspective

On the coping level, the main aims are to:

- Provide both parents with information about the disease (as needed)
- Provide the children with age-appropriate information about the parental mental disorder (as needed)
- Enhance communication about the mental disorder and the problems involved
- Reinforce the coping strategies for the handling of the disorder
- Inform about offers of assistance and encourage greater use of these offers
- Discuss important events maintaining conflicts inside the family, such as hospitalization, loss of employment or change of residence

On the relationship level, the main aims are to:

- Overcome social isolation caused by the parental mental disorder
- Strengthen intra-familial relationships
- Address the topic of extra-familial relationships with the focus on compensating relationships for the child
- Provide knowledge about both risk and protective factors for child development
- Talk about strengths and weaknesses of the child and support options

If participants agree, all sessions are video-recorded for quality control reasons (adherence).

Control Group

Families who have been randomly assigned to the control condition will receive treatment as usual (TAU). TAU comprises for example individual psychotherapy for children and/or parents, psychiatric treatment for parents and/or children and support at youth welfare services. Both the control and the intervention group are not prohibited from receiving additional treatment or additional interventions. In the context of the cost-effectiveness analysis, psychosocial and health care service use will be assessed in the intervention and in the control group (35).

Sample Size and Power Calculation

The primary analysis is based on the intention-to-treat population of all children and adolescents with initial psychiatric diagnosis (addressed in hypothesis 4). In a first step, we calculated the number of children and adolescents to demonstrate the assumed effect in this population. Since the intervention takes place at family level, we determined the total number of children and adolescents and their families to be recruited in a second step.

We assume that 18 months after the baseline assessment 76% of children and adolescents in the intervention group and 90% in the control group still have a psychiatric diagnosis according to K-SADS-PL. Further, we suppose that 25/55/15/5% of the families have 1/2/3/4 children, so that on average a family has 2 children and adolescents. With a power of 80%, a two-sided alpha of 5% and an intracluster correlation of 0.05, we need 116 children and adolescents per group (232 children and adolescents in total) with an initial psychiatric diagnosis in 58 families per group (116 families in total) to detect this difference. We

rounded up to 240 children and adolescents in 120 families. Additionally, we expect that 15% of children and adolescents show an initial psychiatric diagnosis according to K-SADS-PL. With this assumption, we have to recruit in total 800 families with 1,600 children and adolescents.

In this study, we have two additional populations. The first population consists of all children and adolescents (addressed in hypothesis 1) and the second population consists of all children and adolescents with initial mental health problems (addressed in hypothesis 2). For these two hypotheses, we calculated the power with which we can detect the assumed effects based on the sample size calculated for the primary analysis. This sample size enables us to demonstrate with a power of at least 80% the assumed between-groups difference of 0.25 standard deviations in the whole sample (continuous outcomes, hypothesis 1) 18 months after baseline assessment. Furthermore, for the population of hypothesis 2 we expect 400 children and adolescents in 200 families with initial mental health problems if the calculated sample size for the primary hypothesis will be included. In the population, we then can demonstrate a between-groups difference of 10% (80% of the children and adolescents in the intervention group still have mental health problems and 90% in the control group) with a power of 79%.

We used the modules "Tests for Two Proportions in a Cluster-Randomized Design" and "Tests for Two Means in a Cluster-Randomized Design" in PASS 15 (NCSS, LLC. Kaysville, Utah, USA) for these calculations.

Outcome Measures

Sociodemographic information including age, gender, number of children, educational and employment status, somatic and psychiatric diseases, history of treatment and current treatment are recorded with a specifically designed questionnaire at baseline.

Primary Outcome Measure

Schedule for Affective Disorders and Schizophrenia for School Aged Children, Lifetime Version (K-SADS-PL).

The primary outcome in this study is the children's psychopathology measured by the German version of the K-SADS-PL (37, 38). The K-SADS-PL (Schedule for Affective Disorders and Schizophrenia for School Aged Children, Lifetime Version) is a standardized semi-structured interview for an early diagnosis of mental disorders in children and adolescents according to DSM-III-R and DSM-IV criteria. A trained external rater (blind to the family's group assignment) performs the K-SADS-PL by interviewing one parent for each participating child and adolescent—and in addition all children and adolescents aged 10 years and older about current and past episodes of the children's psychopathology. Children and adolescents are classified as having a psychiatric diagnosis if the interview of either the parent or the child or both indicate a psychiatric diagnosis. The K-SADS-PL has been widely used in research due to its good reliability and validity (39). The K-SADS-PL interviews are audiotaped for quality control.

Secondary Outcome Measures

Child Behavior Checklist/Youth Self Report

The children's psychopathology will further be assessed by the German version of the Child Behavior Checklist (CBCL) (40) and the Youth Self Report (YSR) (41). Both questionnaires describe a variety of internalizing and externalizing behaviors in children between the ages of 4 and 18. The CBCL consists of 113 items on which the parents are asked to rate the frequency of their children's behavior; a 3-point Likert-scale (0 = does not apply; 2 = clearly/often) is used. In addition, children 10 years of age and older report on their own behavior with the YSR. Children and adolescents are classified as having mental health problems, if the CBCL assessed by a parent or the YSR assessed by the child or both indicate mental health problems (T-score > 63). Both instruments provide raw and T-scores for internalizing and externalizing behavior as well as a total problem score. Due to their satisfactory psychometric properties (42), the CBCL and YSR are among the most widely used questionnaires in research.

KIDSCREEN-27

The health-related quality of life of the children is assessed by the KIDSCREEN-27 questionnaire (43). The KIDSCREEN instruments are a set of self-assessment questionnaires used to assess subjective health and well-being of children and adolescents between the ages of 8 and 18; corresponding versions for the parents' assessment of their children's quality of life are available. The short version of the KIDSCREEN questionnaire includes 27 items and covers 5 health-related quality of life dimensions. The questionnaire assesses the child's quality of life in consideration of his or her physical, mental and social well-being. Health-related quality of life is assessed by one parent for each participating child and adolescent and in addition by all children and adolescents aged 10 years and older. A short version of the KIDSCREEN 27 questionnaire, the KIDSCREEN 10 questionnaire, will be used for the calculation of QALYs for children and adolescents (44, 45).

Children Global Assessment Scale

In addition, the children's global impairment will be assessed by the German Skala zur Gesamtbeurteilung von Kindern und Jugendlichen (SGKJ) (46), the German version of the Children Global Assessment Scale (CGAS) (47). This scale is the internationally most commonly used scale for the assessment of the severity of psychiatric disorders in children and adolescents. The severity of the disorder is rated on a scale from 1 (needs constant supervision) to 100 (superior functioning in all areas).

Brief Symptom Inventory and Patient Health Questionnaire

The parent's symptomatology will be assessed by the German version of the Brief Symptom Inventory (BSI) (48), a short version of the Symptom Checklist-90-Revised (SCL-90-R). This self-assessment questionnaire measures psychological symptoms during the last 7 days. Parents are asked to rate their individual psychological stress on a 5-point Likert-scale from 0 ("not at all") to 4 ("very strong"). In addition to the BSI, the German version of the Patient Health Questionnaire (PHQ-D) (49) is applied to screen for depressive, anxiety, somatoform, alcohol, and

eating disorders. The PHQ-D showed good agreement with the Structured Clinical Interview for DSM-IV (SCID-I) (49); good validity of the PHQ-D for the diagnostic of psychiatric disorders can therefore be assumed. Further aspects of the parental psychopathology will be assessed by the German versions of the Clinical Global Impressions Scale (CGI) (50) and of the Global Assessment of Functioning (GAF) (51). While the CGI is used to measure the severity of the disease, the GAF is used to rate the person's overall level of functioning.

European Quality of Life 5 Dimensions Scale

The parents' health-related quality of life is assessed by the German version of the European Quality of Life 5 Dimensions Scale (EQ-5D) (52–54). This health questionnaire expresses the patient's quality of life. The EQ-5D defines the participants' health states at 5 dimensions (mobility; ability to fend for oneself; daily activities; pain; anxiety); The EQ-5D is the most frequently used instrument worldwide for the assessment of health-related quality of life in adults and will be used for the health-economic analyses.

Freiburg Questionnaire of Coping With Illness (Freiburger Fragebogen zur Krankheitsverarbeitung)

The Freiburg Questionnaire of Coping with Illness (Freiburger Fragebogen zur Krankheitsverarbeitung, FKV) (55) is a self-report instrument that assesses the parents' coping with the disorder. The FKV assesses a broad spectrum of coping mechanisms on the levels of cognition, emotion and behavior. The short version includes 35 items on the 5-point Likert-scale from 1 (not at all) to 5 (very strong) and is particularly appropriate for follow-up measurements.

General Family Questionnaire (Allgemeiner Familienfragebogen)

Family relations and family functioning will be assessed by the German General Family Questionnaire (Allgemeiner Familienfragebogen, FB-A) (56). This self-report instrument focusses on the family system and includes the scales task fulfillment, role behavior, communication, emotionality, affective establishment of relationships, control, values and norms, social desirability, and defense. Forty items are answered on a 4-point Likert-scale ranging from "exact agreement" to "no agreement at all."

Global Assessment of Relational Functioning Scale

In Addition, the dysfunction and relational health of the family is rated based on the German version of the Global Assessment of Relational Functioning Scale (GARF) (51).

Oslo Social Support Questionnaire

The Oslo Social Support Questionnaire (OSSQ) (57) measures social support of parents and children. The original version of the OSSQ consists of three items regarding (1) the number of confidants, (2) the sense of interest from other people and (3) the relationship to neighbors. An extended version developed by our research group was used, covering prospective individuals providing social support.

Questionnaire for the Assessment of Therapy Outcome (Fragebogen zur Beurteilung der Behandlung)

The evaluation of the treatment will be assessed by the Questionnaire for the Assessment of Therapy Outcome (Fragebogen zur Beurteilung der Behandlung, FBB) (58), which offers the possibility to assess the subjective quality of care according to the two main aspects quality of results (treatment success) and process quality (treatment procedure).

Comparative Psychotherapy Process Scales (Vergleichende Psychotherapie Prozess Skalen)

The therapeutic process is also assessed by the Comparative Psychotherapy Process Scales (Vergleichende Psychotherapie Prozess Skalen, VPPS) as the German translation of the Comparative Psychotherapy Process Scale (CPPS) (59, 60). The VPPS was developed to measure therapeutic activity like the process and techniques that are used in the therapeutic setting. It was designed as a primarily descriptive measure (i.e., what was done), but not as an evaluative measure (i.e., how it was done). The aim of the VPPS is to describe the therapeutic session as accurately and objectively as possible.

Client Socioeconomic and Services Receipt Inventory

The assessment of psychosocial and health care service use (as a basis for the estimation of treatment costs for the parents) will be performed by the German version of the "Client Socioeconomic and Services Receipt Inventory" (CSSRI-DE) (61). The CSSRI-DE is an interview including five dimensions (sociodemographic data, living conditions, occupation and income, utilization of health services, and medication). The CSSRI-DE was developed for cost analysis of the psychiatric supply system and allows a comprehensive assessment of all substantial components for direct and indirect costs.

Children and Adolescent Mental Health Service Inventory

The German version of the "Children and Adolescent Mental Health Services Receipt Inventory" (CAMHSRI) (62) will be used to assess the health and psychosocial service use as a basis for the assessment of treatment costs for the children.

All interviews and questionnaires are administered at baseline as well as at 6, 12, and 18 months after baseline assessment. Although participants are aware of the group they have been assigned to, the external raters assessing the primary outcome and the health-economics, are not.

The measures to be administered at each time point are listed in **Table 2**.

Randomization Procedure

Computerized lists for familywise randomization with an allocation ratio of 1:1 stratified by centers with a variable block length will be prepared by the Department of Medical Biometry and Epidemiology of the University Medical Center Hamburg-Eppendorf. The subsequent central allocation procedure is managed by the coordinating study center in Hamburg to guarantee allocation concealment.

Randomization will take place once the standardized baseline diagnostics are complete. Thus, every randomized

TABLE 2 | Outcomes and measures.

Outcome		Instrument		Source					Time (months)			
		Questionnaire	Interview	Patient	Partner	Child (>10 year)	Therapist	External rater	pre	6	12	18
Demographics		*Ad hoc* items		x	x				x			
Diagnoses/Psychiatric symptomatology	Parents	Medical history						x	x			
		PHQ-D		x	x				x			
		BSI		x	x				x	x	x	x
		CGI						x	x	x	x	x
		GAF						x	x	x	x	x
	Children	CBCL	Kiddie-SADS-PL	x	x				x	x	x	x
		YSR				x			x	x	x	x
		SGKJ						x	x	x	x	x
Health-related quality of life	Parents	EQ-5D		x	x				x	x	x	x
	Children	Kidscreen-27/-10		x	x	x			x	x	x	x
Family relations and family functioning		FB-A		x	x	x			x	x	x	x
		GARF						x	x	x	x	x
		Ad hoc items		x	x	x			x	x	x	x
Coping with the disorder	Parents	FKV		x	x				x	x	x	x
Social support		OSSQ		x	x	x			x	x	x	x
Evaluation of treatment		FBB*		x	x	x	x			x	x	x
Health economic assessment of treatment costs	Parents		CSSRI-DE	x	x			x	x	x	x	x
	Children		CAMHSRI-DE	x	x			x	x	x	x	x
Formulation of goals		*Ad hoc* items*		x	x	x			x			
Achievement of goals, satisfaction		*Ad hoc* items*		x	x	x	x			x	x	x
Therapeutic process		VPPS*					x		x**			
		Ad hoc items*					x		x**			

**For intervention group only.*
***During the intervention.*

family, both in the intervention and in the control group, will receive comprehensive standardized diagnostics of every participating child.

Data Assessment and Data Management

At the beginning of the study (T1; see **Figure 1**), the mentally ill parent and—if there is one—the partner fill in the baseline questionnaires and participate in the K-SADS-PL interviews about their child/children. All children aged 10 years and older are also asked to complete this diagnostic process. As soon as all documents are completed, the family is randomized to either control or intervention group. The research staff subsequently informs the family about their group assignment and provides feedback on the results of the child's K-SADS-PL interview.

If the family has been referred to the intervention group, the therapist who carries out the CHIMPs program is informed and the start of the intervention is initiated. If the family has been referred to the control group, no further treatment is provided within the CHIMPs study.

At 6 (T2), 12 (T3), and 18 (T4) months after baseline assessment, the families will be contacted again by the research staff. The questionnaires and diagnostic interviews for all three follow-up assessments are the same as at the baseline assessment. Families receive a financial compensation (up to €50) if a follow-up assessment is completed, in order to further promote a complete follow-up.

All study-related information will be stored securely at the study site. All records that contain names or other personal identifiers, such as locator forms and informed consent forms, will be stored separately from study records identified by code number. The coordinating study site will oversee the intra-study data sharing process.

All study outcomes, especially the primary outcome papers, will be published in peer-reviewed journals and presented at

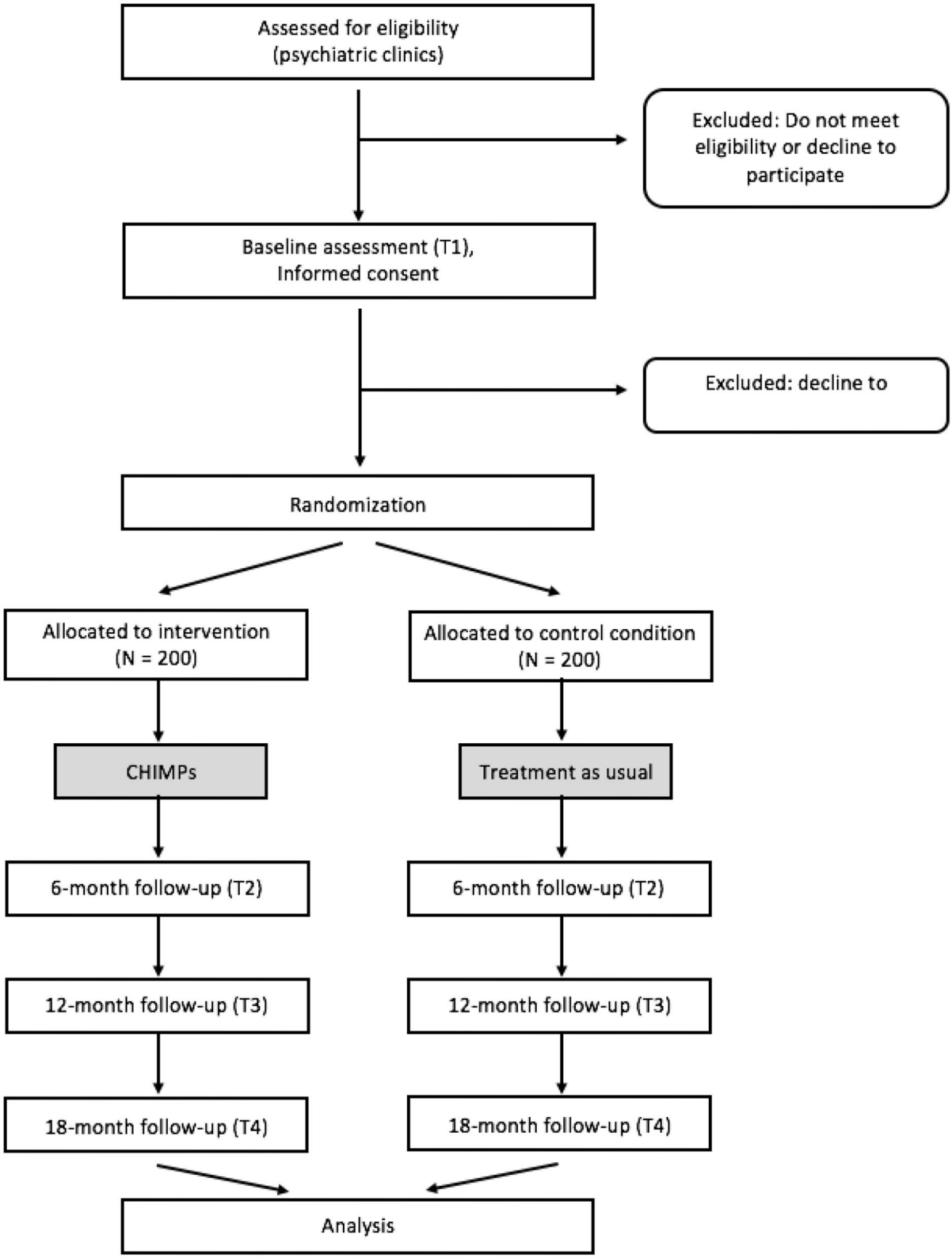

FIGURE 1 | Overview of the CHIMPs study design.

scientific conferences. All papers and abstracts must be approved by the coordinating site before submission.

Data Analysis

All data will be entered twice at the coordinating site. Original study forms will be sent to the coordinating site and a copy of them will be kept at the participating site. Participant files will be stored in a secure and accessible place for a period of 3 years after completion of the study.

Data will be analyzed and reported according to the CONSORT statement. Mean and standard deviation will be presented for the continuous variables and absolute and relative frequencies for the categorical variables for the whole sample and separated by treatment groups. Since the relatives of a family are subject to common influences, cluster effects are generally to be expected. Therefore, the inferential statistics will be conducted using mixed models with the family and the relatives as random effects. As further covariates, recruitment center, treatment group, time, and the interaction between the two, as well as baseline variables that are unbalanced between the treatment groups. As further possible covariate, the type of clinic (university clinic vs. supply clinic) will be examined. For this purpose, baseline comparisons will be performed. If significant differences are found, this variable will be included in the model as a further fixed effect. We will use the direct Maximum-Likelihood as the statistical estimation procedure in the intention-to-treat population (ITT), which results in unbiased estimations under the missing-at-random assumption. The ITT analysis will be based on the available clinical data from all randomized families. The primary outcome analysis is the treatment group contrast (CHIMPs vs. TAU) at 18 months after baseline assessment in the ITT population of the children with an initial psychiatric diagnosis according to K-SADS-PL in a mixed logistic regression with the above-mentioned specification. The primary outcome is a psychiatric diagnosis according to K-SADS-PL (yes/no). Only the result of this comparison will be interpreted in a confirmatory manner. Additionally, this analysis will be repeated in the per protocol population. Sensitivity analyses will be performed for the primary outcome analysis with different methods of missing value imputation such as multiple imputation and last observation carried forward (LOCF) to study the robustness of the findings. Odds ratios, their 95% confidence intervals and *p*-values will be reported. The type I error will be set at 5% (two-sided). The secondary outcomes will be examined with appropriate methods in the ITT population in an exploratory manner. As far as possible, these outcomes will be operationalised as difference to baseline. Interim analyses are not planned. Subgroup analysis will be conducted on study sites, children's and adolescents' age and children's and adolescents' gender. A detailed statistical analysis plan will be finalized based on an analysis of a blinded, pooled data set. Statistical analyses will be carried out with SPSS, version 24 or newer (IBM Corp, Armonk, NY, USA) R, version 3.6.3 or newer (R Foundation for Statistical Computing, Vienna, Austria) or SAS, version 9.4 or newer (SAS Institute, Cary, NC, USA).

Cost differences between both study groups will be analyzed by linear regression models (63–65). The adjustment of standard errors in case of deviations from the normal distribution will be performed by non-parametric bootstrapping (65, 66). The cost-effectiveness of the CHIMPs intervention compared to treatment as usual (TAU) will be computed by the net-monetary-benefit method (67–69). Quality adjusted life years (QALYs) will be computed by transforming KIDSCREEN-10 values into Child Health Utility (CHU9D) values (70) using the algorithm provided by Chen and colleagues (71). Incremental cost-effectiveness ratios (ICER) will be calculated to estimate the maximum willingness to pay necessary for the gain of one quality-adjusted life year (QALY) by implementing the CHIMPs intervention in comparison to standard care (69). ICER will be interpreted on the basis of the cost-effectiveness plane (67–69). Stochastic uncertainty of the ICER will be estimated by non-parametric bootstrapping and the cost-effectiveness acceptability curve (67–69).

DISCUSSION

The present study will implement an intervention program for families with mentally ill parents in regular care at multiple sites in Germany and at one site in Switzerland. In the current trial, the program's effectiveness and cost-effectiveness will be evaluated in a randomized-controlled design with a comprehensive health-economic assessment at baseline, 6, 12, and 18 months after baseline assessment. We hypothesize that the CHIMPs intervention improves children's mental health and health-related quality of life compared to the control condition. An important strength of this study is the use of a randomized controlled trial design with a control group receiving treatment as usual. The study design includes a comprehensive health-economic evaluation.

The low-restrictive inclusion criteria allow patients with a variety of psychiatric disorders to take part in the study. Moreover, not only biological parents, but also adoptive parents, foster parents or step parents will be included. This represents an important opportunity to investigate a sample that is representative for this diverse high-risk population in a standard environment.

The CHIMPs family intervention of the present study involves all family members. This setting of the intervention represents an important strength of the study as existing research proves that addressing parents and children jointly produced larger effects of preventive interventions for children of mentally ill parents compared to interventions addressing parents and children individually (23).

In the CHIMPs study, psychopathology will be assessed by multiple perspectives. Most importantly, children's mental health, the primary outcome, will be assessed by a clinical interview by an external rater blind to the family's group assignment. Moreover, psychopathology of the children will be measured by parents' and children's perspectives using the CBCL and the YSR for children 10 years and older. Overall, a wide range of outcome measures (e.g., mental health, health-related quality of life, coping, social support, family relationships) for children and parents will be assessed from multiple perspectives.

As multiple perspectives are estimated to be state-of-the art measuring psychopathology (72, 73) and quality of life (74) in children and adolescents, this assessment presents another clear strength of our study.

The extensive assessment of outcomes will allow for a comprehensive analysis of various risk and protective factors relevant for the interplay between parental mental disorders and children's mental health. This analysis will facilitate the further understanding of transgenerational transmission of mental disorders and the adaptation of existing support programs for families with parental mental health problems. Moreover, this study aims at reducing transgenerational transmission of mental health problems in families with parental mental disorders.

An important implication for practice is that all children participating in the study are screened for mental health problems at the very beginning of study participation. This provides the opportunity for an early identification of children with mental health problems who will subsequently be referred to appropriate offers of assistance. All children and adolescents participating in the intervention or the control group with indication for individual support like e.g., psychiatric treatment or psychotherapy will obtain the corresponding referral.

Difficulties could arise from the multicenter design of this study. The combination of both university and supply clinics could lead to differences in the recruitment process. For this reason, possible center effects will be analyzed and treated accordingly during the statistical analysis.

As a large number of therapists from different therapeutic approaches will lead the CHIMPs program, it could be difficult to perform the intervention in a reliable standardized manner. To ensure adherence to the manual, the process and the methods of each session will be documented and analyzed for compliance with the manual.

Experience from this trial will be used to revise the existing manual. The financing of the intervention in regular care beyond the duration of the study will be discussed with health-insurance representatives as part of the study. An important aim of the study is to not only evaluate the CHIMPs intervention in the participating study centers, but to implement it into regular care throughout Germany.

The support provided to families with mentally ill parents should be comprehensive and integrative and therefore oriented toward all family members as the psychosocial and medical starting points for the affected families are equally complex. If successful, the CHIMPs intervention could be the first program for mentally ill parents and their children to be implemented nationwide into regular practice; this could be an important and future-oriented contribution to the improvement of a family-oriented support system for this particular risk group.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Hamburg Medical Council as well as by the Ethics Committees of all participating study sites. Written informed consent to participate in this study was provided by the participants' legal guardian/next of kin.

AUTHOR'S NOTE

The full trial protocol can be accessed at Silke Wiegand-Grefe, Department of Child and Adolescent Psychiatry and Psychotherapy, University Medical Center Hamburg-Eppendorf, Hamburg, Germany.

AUTHOR CONTRIBUTIONS

SW-G is the principal researcher of this project. SW-G and AP-C have developed and evaluated the CHIMPs intervention. AP-C, SW-G, and BF have drafted the manuscript. BF and MB are responsible for the data and study management in the coordination study center. SW-G, RK, K-TK, KK, KW, and ML were significantly involved in the conception of the study and participated in its design with study advisory by AP-C. CN, KA, and SW are responsible for the realization of the project at their study sites. AD and KW wrote the paragraph on statistical methods. SW-G, BF, KW, and MB are responsible for the data and study management. All authors contributed to the editing of the manuscript and have read and approved the final manuscript.

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ORIGINAL RESEARCH
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Predictors in ASD: The Importance of Parents' Perception

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Several predictors may influence children's developmental trajectories with Autism Spectrum Disorder (ASD), and parents' concerns may play an important role. This study aimed to investigate developmental trajectories of two groups of children with ASD to understand predictive factors, including parental perception. We examined the clinical features of a sample of 55 children with ASD at 3 and 6 years of age in two moments of evaluation to understand this process. We used the Autism Diagnostic Observation Schedule, (ADOS) in both moments. We selected two groups based on ADOS results at moment two: one group with a worse outcome (ADOS results above 8) and one group with a better outcome (ADOS results below 8 in the second moment). We also selected questions from a questionnaire (elaborated by the authors and used in clinical practice) applied to parents to understand if early parents' concerns may help to predict ASD prognosis. We found a significant association between imitation and playability and the child's prognostic. Also, Interactive Gestures, Beginning of Joint Attention, Reciprocity, and Pleasure in Interaction might help identify positive case evolution. Our findings are significant in early intervention program development, not only with direct intervention with the child but also including the parents' involvement in the intervention.

Keywords: parent's concerns, predictors, autism spectrum disorder, early intervention, autism

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INTRODUCTION

The Diagnostic and Statistical Manual of Mental Disorders (DSM 5) describes autism as a developmental disorder characterized by severe and pervasive impairment in several areas of development, including reciprocal social interactive skills, communication skills, and stereotyped behavior, interests, and activities.

ASD (Autism Spectrum Disorders) includes Autistic disorder, Asperger Syndrome, and Pervasive Developmental Disorders not otherwise specified (PDD-NOS). Still, they are not individualized in DSM-5, which provides for only ASD in different levels of severity. It is difficult to predict the disease evolution in early childhood. A marked impairment in emotional competence and social interaction is noted from early stages because emotions are essential to regulate social interactions, which, in turn, influence emotional development. A substantial body of research suggests that children with ASD express emotions differently, and there are autism-specific deficits in emotion perception and understanding (1). There are no consistent indications of a correlation between emotional competencies, social competencies, and ASD subtypes (2). It would be interesting to study some of these features with reliable instruments to define prognosis in the early stages (3).

During the second and third years of life, symptoms of autism usually spread to multiple areas of functioning. While typical infants develop a remarkable growth in social, communication, and

imaginative play competence, infants with autism show syndrome-specific difficulties in these areas (4, 5). Developmental theory links imitation and play, and these two areas may represent a core impairment in ASD (6). They can help discriminate children with ASD from other disabilities from a very early age (7). We believe that these areas may be improved with parents' training to stimulate interaction and social communication, and we think parent's concerns may help in early diagnosis and intervention.

Charman (8) demonstrated that early joint attention and imitation, measured at 20 months of age, were related to social and communication evaluated with Autism Diagnostic Interview-Revised (ADI-R) at 42 months. It has also been found that initial IQ and language at age six were associated with the Adaptive Behavior composite score of the Vineland Adaptive Behavior Scale (VABS) (9) at age 14. Charman (8) enhanced the many significant associations between Non-verbal IQ language and ADI-R, reciprocal social interaction and Non-verbal Communication scores at age 3, and communication and socialization scores of VABS at age 7.

Very early intervention may help to improve existing difficulties and prevent or attenuate subsequent neurodevelopmental disturbances arising from early impoverished socio-emotional interactions in the first years of life (10). Unfortunately, early diagnosis and specific strategies related to early intervention in ASD are still tricky. Understanding the nature and timing of symptoms may be critical in predicting developmental trajectories within ASD and contributing to early diagnosis and intervention planning (11).

This study examined the clinical features of 55 children with ASD, aiming to understand some aspects that can predict different developmental trajectories in children with ASD, including parent's perception. Children were evaluated at 3 and 6 years of age with ADOS and parents' questionnaires.

The current study investigates developmental trajectories of two child groups with ASD trying to understand some predictive factors in order o adjust better intervention strategies.

METHODS

Participants and Procedure

We included a total of 55 children with ASD in this study. These children were evaluated at three years of age and again evaluated at 6 years of age. The children were recruited from a Psychiatric child consultation in a General Hospital in Porto, Portugal.

The study is part of an investigation work approved by the Centro Hospitalar de São João's Health Ethics Committee. The study complies with the relevant national and institutional committees' ethical standards on human experimentation and the Helsinki Declaration of 1975, as revised in 2008. All parents signed an informed consent according to the Helsinki and Oviedo Conventions.

Diagnosis of ASD was initially given by independent clinicians (psychiatrists, pediatricians, and psychologists) with many years of experience.

DSM-5 was used for diagnosis at the time sampling around 2 years of age.

All children were evaluated with ADOS as a symptom of severity measure. We also gave parents a questionnaire (semi-structured interview elaborated by the authors and used in clinical practice) to understand their first concerns related to their children to understand if these concerns may predict clinical evolution. All children were evaluated 3 years later with ADOS. We selected two groups based on the global results of ADOS at moment two: in the best group were included all children with scores below 8, and in the worst group were included all children with scores above 8. These cut-offs are in line with the classification algorithm for autism and autism spectrum.

All the children had a psychoeducational intervention, at least 4 hours per week, with educator, occupational, and speech therapy, and they had no associated co-morbidity. It was not the purpose of this study to evaluate the type of intervention, and the use and type of medication were not considered in this study.

We selected the variables that were more relevant according to clinical features and literature (4, 5, 7, 8): Joint (or Shared) Attention, Reciprocity, Interactive Gestures, and Pleasure in Interaction (in ADOS). We also investigated potential correlations of ADOS results with the parent's questionnaire.

Instruments

The Autism Diagnostic Observation Schedule (ADOS) (12) is an instrument for diagnosing and assessing autism. The protocol consists of several structured and semi-structured tasks that involve social interaction with the examiner to assign the subject's behavior and relate it with predetermined observational categories and quantitative scores associated with ASD.

All the evaluations were conducted by psychologists with an ADOS specialization (from the University of Barcelona), strictly following the author's instructions.

The parents' questionnaire consisted of a semi-structured interview, developed explicitly for these study, based on clinical features, with 30 questions (open and closed) to understand the parent's perspective about the moment of concern (age), type of concern, supports involved, and child's evolution. We only used closed questions (yes or no) about specific symptoms like Social Impairment, Communication (verbal and non-verbal), and Imitation and Playability to identify some potential prognosis predictors.

Data Analysis

Statistical analyses were performed using SPSS software®. Descriptive analysis was performed using proportions in categorical variables and means and standard deviations in the continuous variables with normal distribution. The Fisher Exact test was used to test the significance of the associations, the Pearson and Spearman tests were used for the correlations between the variables, and we also used Logistic Regressions. We considered 0.05 as the level of significance.

RESULTS

Participants

A sample of 55 participants was analyzed in this study, with 46 male and 9 female children. The 55 children with ASD were

TABLE 1 | ADOS results obtained in both evaluation moments.

	Mean (SD)	*p*
Total ADOS 1	11.29 (3.588)	<0.001
Total ADOS 2	8.58 (2.14)	

Significant results at the confidence level of 95% confidence.

evaluated at 3 years of age and again at 6. Participants' average age at the time of the first evaluation was 3.4 (SD = 0.55) years for girls and 3.8 (SD = 0.44) years old for boys. At the second evaluation, the mean age of the participants was 6.5 (SD = 1.46) and 7.3 (SD = 1.73) years old for girls and boys, respectively.

ADOS

In the two time periods analyzed, we observed a significant decrease in the mean ADOS score of the second evaluation ($p < 0.001$) (**Table 1**).

In the ADOS evaluation, the relationship between the score in the first evaluation and the total score in the second evaluation was marked in the interview process carried out with the parents: Beginning of Joint Attention and Pleasure in Interaction.

Regarding the item of Shared Attention, it was verified that it does not significantly impact the total score of the first evaluation ($\chi^2 = 0.15$, $p = 0.13$), with results divided in the middle, as we can see in **Table 2**.

However, this association becomes significant over time, presenting an essential indicator of a good prognosis for the second evaluation. Only 19% of the children with a null score in this item in the first evaluation scored over 8 in the second evaluation ($\chi^2 = 17.46$, $p < 0.001$).

Regarding the Pleasure in Interaction item, we observed a similar phenomenon, with no statistically significant association between the result of the item in the total score of the first evaluation, but with the association gaining robustness over time, with a $\chi^2 = 23.21$, $p < 0.001$, in relation to the total of the second evaluation, where only 8% of the results equal to 0 in this item at the time of the first evaluation had a total score higher than 8 at the time of the second evaluation.

Both items correlate significantly with the ADOS total in the second moment of evaluation, representing the item Pleasure in Interaction as a more robust predictor, $r > 0.7$ (**Table 3**).

We did not find a statistically significant association between the items Interactive Gestures and Reciprocity in the total of the second ADOS evaluation. Still, we can observe significant correlations between items, as shown in **Table 4**.

Parents' Questionnaire

It was found that the parents who identified earlier changes correspond to the cases with worse evolution before the child's one year of age. In the milder cases, parents cared more about the difficulty in speaking or socializing from the age of 2 years. There was essential concern with language and socialization (the answer yes means there is inadequate behavior). The results agree with the data identified in clinical practice and the ADOS. It was verified that the milder cases did not show apparent limitations at 2 years either in imitation ability or pleasure in playing with the adult.

In the questionnaire applied to the parents, it is possible to verify two indicators with a significant association with ADOS evaluation in the second moment: Imitation and Play, as shown in **Table 5**. Thus, parents' perceptions of the child's behavior seem to be better with lower instrument scores.

In the logistic regression, Playability and Imitation were included as predictors of a good result on ADOS evaluation, and the results were significant for this regression: $\chi 2_{(2)} = 10.91$, $p < 0.01$. Thus, the Omnibus test presents statistically significant results, thus confirming the predictive value of these variables in ADOS' second evaluation. The Hosmer and Lemeshow test showed the value of $X^2 = 4.67$ and $p = 0.67$, demonstrating the importance of the Imitation and Playability variables as predictors.

DISCUSSION

We noticed that the best outcome group had better scores on all items in the first and second evaluation, which may have a predictive value. In the worse outcome group, we always found severe impairment in socialization and communication. Still, we also found impairment in Playability and Imitation in moment 1, which results are different from the best outcome group. High stability has been reported for clinical diagnosis made by expert professionals, supported by standard criteria for ASD, as reported in other studies (8).

These findings are similar to other studies. Charman (2005) (8) demonstrated many significant associations between language and ADI-R Reciprocal Social Interaction and Non-verbal Communication scores, at age 3, and VABS Communication and Socialization domain scores at age 7.

The results from our study suggest that some scores observed with ADOS evaluation: Interactive Gestures, Beginning of Joint Attention, Reciprocity, and Pleasure in Interaction, might help with identifying developmental trajectories, namely, of a favorable prognosis, for children with lower scores in the specified items, independently of the total obtained in the scale.

In this study, parents' Imitation and Playability perceptions of the child are also robust possible predictors of favorable developments, as we can see in **Table 5**. Few studies have evaluated the relationship of early parental concerns with prognosis. Ozonoff et al.'s (6) study highlights the importance of early parental concerns' with certain early behaviors that may have predictive value in diagnosing ASD. Sacrey (13), in 2015, draws identical conclusions through a study in which a questionnaire was applied to parents of children at risk of ASD. All of them were evaluated at three years to identify the highest and lowest risk.

These data point to the need to evaluate such items considering the information given by the parents and the observation in consultation.

It also draws attention to the need and advantage of screening tests at pediatric and family doctor visits to detect early warning signs and provide timely guidance to at-risk children and their parents to begin early intervention.

TABLE 2 | Score frequency per item in children with ADOS total >8.

	Evaluation 1		Evaluation 2	
	0	**>0**	**0**	**>0**
Joint attention	51% ($n = 27$)	49% ($n = 26$)	19% ($n = 5$)	81% ($n = 21$)
Pleasure in interaction	44% ($n = 23$)	56% ($n = 30$)	8% ($n = 2$)	92% ($n = 24$)

TABLE 3 | Correlation values between the first evaluation results in the identified items and the total of the second evaluation.

	Total ADOS 2	Joint attention	Pleasure in interaction
Total ADOS 2	1	0.68**	0.77**
Joint attention		1	0.74**
Pleasure in interaction			1

*Significant results at the confidence level of 95% confidence; **$p < 0.001$.*

TABLE 4 | Pearson's correlation values between the first evaluation results and the total of the second evaluation.

	Interactive gestures	Joint attention	Reciprocity	Pleasure in interaction	ADOS 2
Interactive gestures	1	0.59**	0.73**	0.65**	0.69**
Joint attention		1	0.71**	0.74**	0.68**
Reciprocity			1	0.73**	0.74**
Pleasure in interaction				1	0.77**

*Significant results at the confidence level of 95% confidence; **$p < 0.001$.*

TABLE 5 | Frequency of results in percentage, by a total of ADOS in the second moment of evaluation.

		ADOS		
		>8	**<8**	**X^2**
Imitation	**Adequate**	56.0%	93.1%	***p* < 0.05**
	Inadequate	44.0%	6.9%	
Playability	**Adequate**	36.0%	82.8%	***p* < 0.05**
	Inadequate	64.0%	17.2%	
Social impairment	**Adequate**	96.6%	96.0%	$p = 0.71$
	Inadequate	3.4%	4.0%	
Communication	**Adequate**	38.7%	41.4	$p = 0.53$
	Inadequate	61.3%	58.6%	

Significant results with a 95% confidence level are shown in bold.

Landa (12) enhanced that evidence suggests that young children with ASD benefit from early intervention and programs to teach parents to implement child-interaction strategies with parent-coaching supervising.

According to Vivanti (14), the response to early intervention in autism is variable. It reflects the need to report data about the association between predictor and outcome variables because we know so little about this. We need reliable instruments to measure what is related to adaptive capacities and educational strategies and evaluate previous family structures and resources to understand the difference in the outcome.

Cohen (9) studied a retrospective analysis of the trajectories of adaptive skills and severity symptoms in ASD subgroups and confirmed the prediction that each subgroup had different trajectories depending on the type of adaptive behavior. His finding suggests that this instrument may have a helpful prognostic value for clinical application.

Based on these results, coupled with the data from the literature highlighting the importance of the early development of social competencies (1, 7, 8), we can conclude that early diagnosis and intervention are essential. However, integrating the parents' contribution throughout the process is also

very important. From our clinical experience, we observe that when the parents are involved from the beginning in therapy, with acceptance and adequate understanding of the diagnosis, the whole intervention runs better and more successfully.

These findings may be helpful to implement parent training interventions that help parents interact and communicate with their toddlers with ASD, participating throughout all the processes of daily life. We can also understand these findings as a good alternative to promote the development of their child's social and communicative skills (12) and could de be an essential contribution to their clinical evolution.

Further investigation is necessary to replicate results and develop more reliable instruments to define subtypes and prognosis early.

One limitation of this study is the sample size that might be considered small and with a heterogeneous group of children, meeting different profiles. Nevertheless, our study had rigorous diagnostic criteria and only included diagnosed ASD children, confirmed by clinical observation. It could be helpful in further research, with a larger sample, to add another instrument in the second evaluation to compare the results to correlate with possible predictive elements. Also, this study did not evaluate the effect of the intervention on the outcome of groups. It could be interesting in future studies to analyse controlled variables related to family resources and type of intervention. As it was not the purpose of our research and due to the small sample size, we did not detail and analyse the type of pharmacological treatment of the patients. Evaluations represent a particular moment in time, which needs to be considered when interpreting and generalizing results. Further investigation is necessary to replicate results and to develop more reliable instruments to define subtypes and prognosis in the early stages.

DATA AVAILABILITY STATEMENT

The datasets presented in this article are not readily available because they are confidential confidential but they can be made available upon request to the parents with mediation through the authors. Requests to access the datasets should be directed to: alda.coelho@chsj.min-saude.pt.

AUTHOR CONTRIBUTIONS

All authors contributed to the article and approved the submitted version.

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