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An Explanatory Model to Predict Pediatric Psychosis Spectrum Based on Parent Psychiatric Profile and Children and Adolescents Comorbid Disorders as a Mediator Construct

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Abstract

Objective: Psychosis is one of the most vital disorders in children and youths. The definite pathophysiology of schizophrenia and other psychotic disorders in the growth period has remained ambiguous. Therefore, the purpose of the current study was to investigate the predictive value of parental psychiatric disorders and the mediator role of comorbid disorders of children and youths.

Method: The sample, consisting of 29884 individuals aged between 6 to 18 years old from the Iranian population, were selected by multistage cluster sampling during September 22, 2016 to January 3, 2018. Parents were requested to complete a survey around their potential psychiatric disorders, based on their Millon's Clinical Multiaxial Inventory-III (MCMI-III). The Semi-Structured Interview (Kiddie-SADS-Present, Lifetime Form (K-SADS-PL)) was utilized to analyze psychiatric disorders concurring to the DSM.

Results: The fit indices of the model show that the research model has a good fit and the psychiatric disorders of parents directly and indirectly through comorbid disorders are effective on the psychosis symptoms of children and adolescents (RMSEA=0.06, CFI=0.89, PGFI=0.75, PNFI=0.75).The incidence of Schizotypal Personality Disorder, Anxiety, Bipolar Spectrum Disorder, PTSD, Schizophrenia Spectrum and Delusional Disorder were statistically higher in parents of psychotic children and adolescents. However, Borderline Personality Disorder was more frequent among their mothers while Alcohol Dependency and Drug Dependency were significantly more prevalent among their fathers.

Conclusion: The outcomes of our study showed that there were statistically significant differences between the mean scores of each scale assessed by Millon's inventory between parents of psychotic versus non-psychotic pediatric cases. In addition, psychiatric disorders were more common among children and youths with psychosis spectrum in comparison with the general population.

Key words: *Adolescence; Environmental Effects; Genetic Effects; Psychiatric Disorders; Psychos' Spectrum*

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Psychoses are among the most crucial disorders in children and youths (1). The unequivocal pathophysiology of schizophrenia and other psychotic disorders in children and teenagers has remained unclear. Psychotic disorders are influenced by multiple risk factors including genetic vulnerability; although any specific gene is not proposed to be solely in charge, except a few genes with small penetration (2, 3). Family, twin, and adoption studies have indicated that close relatives of schizophrenics are at an elevated risk of a group of disorders such as schizoaffective disorder, schizotypal and paranoid personality disorders, and affective disorders with psychotic features, in addition to schizophrenia itself (4-6). Conversely, the presence of psychiatric disorders in a first-degree relative may be a risk factor for schizophrenia. It has been appeared that a few psychiatric disorders are more prevalent in relatives of schizophrenics than in lineages of normal populace, including schizophrenia (5.8% versus 0.6%), schizotypal personality disorder (unequivocal, 14.6% versus 2.1%; likely, 12.1% versus 6.5%), and paranoid personality (7.3% versus 2.3%) (7). In another study, 34% and 48.6% of psychotic patients had a familial history of psychiatric disorder, respectively, including 6% bipolar disorder, 5.7% major depression, 1.8% schizoaffective disorder, 18.4% schizophrenia, 13% unspecified schizophrenia spectrum and other psychotic disorders, 0.4% obsessive-compulsive disorder, and 2.5% mental retardation (8). Kendler *et al.* also reported a lifetime incidence of 13.9 percent schizotypal personality disorder among the parents of schizophrenic children. The parent-child concordance rate was twofold that of siblings concordance among the first-degree relatives (5).

Another risk factor is psychiatric disorder during childhood and adolescence. Earlier studies have shown a higher likelihood of an early age of onset of schizophrenia in individuals with a history of psychiatric disorders at childhood or adolescence (9, 10). This correlation may indicate a common neurodevelopmental pathogenesis between schizophrenia and pediatric psychiatric disorders (11). Attention Deficit/Hyperactivity Disorder (ADHD) is also found to be related to an increased risk of rate of schizophrenia by four times, as shown in two separate studies (12). Moreover, two long-term follow-up studies showed that 3.4% of children and adolescents affected by psychiatric disorders would eventually receive a diagnosis of schizophrenia (11).

Children living with drug-abusing fathers are more likely to develop a psychiatric disorder and involve in destructive behaviors later in life (13). Children of alcoholic fathers are also at a higher risk of experiencing psychopathologies (14). Trauma in childhood, especially sexual assault, and maltreatment are related with the risk of expression of psychotic symptoms in children, with the risk increasing cumulatively according to the number and type of traumas (15-17).

Psychotic symptoms in childhood are rare but of serious clinical importance, persisting into adulthood. The peak age of onset for schizophrenia and bipolar disorder, as two prevalent forms of psychotic disorders, occurs in adolescence (18). They influence biological, social, and psychological aspects of developmental processes that pave the way for explosion of psychotic disorders. However, it seems that certain early childhood developmental deficits may lead to psychotic disorders (19). Hence, we need to find protective factors and preventive interventions that can avert the worst manifestations of childhood and adolescence psychosis spectrum.

As far as we could find, there is limited literature focusing on the prediction of childhood and adolescence psychosis spectrum. The existing research so far have mainly investigated cognitive and biological risk factors in adolescents and adults with small sample sizes such as perinatal complications (20), presence of negative symptoms (21) poor general functioning (22), gray matter deficits in the prefrontal cortex (23), and executive function impairments (24). According to the background of the research investigation, it seems that parental psychiatric disorders exert influence on the occurrence of children's psychological disorders due to genetic or environmental effects. This influence may indirectly manifest itself in children's psychological disorders. Therefore, the aim of the current paper was to explore the predictive significance of parental psychiatric disorders for pediatric psychosis spectrum as well as for children and adolescents' own comorbid disorders as mediators. Until our review of literature, this has been the first study investigating the combination of different variables and with such a large sample size. The identification of these variables helps clinicians to understand the fundamental risk factors and to manipulate or manage them.

Materials and Methods

The sample included 29884 people aged between 6 to 18 years old, encompassing Iranian children and youths. This study was part of a national project executed across Iran and included residents of each area independently. The Morals Committee of National Institute for Medical Investigate Development (NIMAD) affirmed and Tehran University of Medical Sciences funded this study (funding No. 940906). Participants were categorized into six groups based on gender and age (6-9, 10-14, 15-18 yrs.) and were selected from thirty provinces (with one exception) using a cluster multistage sampling strategy. Applying this method, 170 chunks were randomly collected from both urban and rural areas, agreeing to post-office codes relatively. Six cases were chosen from each bunch, with three cases from each gender and age bunch (6-9, 10-14, 15-18). The parents were asked to complete a questionnaire regarding their potential

psychiatric disorders, based on their Millon's Clinical Multiaxial Inventory-III (MCMI-III). Inclusion criteria were as follows: being a citizen of Iran (in each region, those who have resided in the respective province for at least one year are eligible to participate in the project) and being between the ages of 6 and 18. Children and youths with serious physical sicknesses were excluded. In addition, children and adolescents affected by any chronic physical disability or medical disorder were also excluded.

We utilized semi-structured interviews (Kiddie-SADS-Present, Lifetime Adaptation (K-SADS-PL)) to identify psychiatric disorders according to the Diagnostic and Statistical Manual of Mental Disorders, 4th Edition, Text Revision (DSM-IV-TR) criteria. The validity and reliability of the K-SADS were confirmed by Joan Kaufman *et al.* The test-retest reliability was inside the range of 0.77 to 1.00 for present and lifetime assessment of diverse psychiatric disorders, and the level of the inter-rater reliability in diagnosing the disorders was between 93% to 100%. Ghanizadeh *et al.* detailed the sensitivity and specificity of the Persian form of the K-SADS to be compelling. They detailed a test-retest reliability of 0.56-0.81 to analyze distinctive psychiatric disorders, and the inter-rater reliability was at the level of 0.69 (25). Millon's Clinical Multiaxial Questionnaire was filled by parents. MCMI-III consists of three modifier scales and 14 clinical scales for personality disorder assessment: (a) eleven personality clinical scales; (b) three severe personality pathology scales (used for 18-year-olds and above) (26). Sharifi reported the positive and negative predictive power of 0.92 – 0.98 and 0.93- 0.99, respectively and the diagnostic power for all scales ranged between 0.58 and 0.83 (27). Chegini *et al.* also reported desirable positive and negative predictive powers and test-retest reliability of 0.611 – 0.793, 0.795 – 0.972, and 0.64 – 0.89, respectively, calculated across 311 patients and 463 healthy cases. In addition, Cronbach's alpha was calculated across all 774 cases (28).

Full details of the selection criteria and procedures have been reported in our published protocol article (29).

Interviewer preparing and information collection

Information collection was conducted by 250 skilled clinical clinicians throughout the whole country during September 22, 2016 to January 3, 2018. Before starting the sampling, all the interviewers were asked to participate in the K-SADS-PL training course conducted by the psychiatrist. Interviewers were also trained on interview strategies and information collection methods so that they could collect the best type of information from the families. In this study, both children and parents, especially mothers, responded to two interviewers in order to make a high-quality diagnosis based on the DSM-IV. Also, during the study, the research executive group took the interviewer group to all the provinces to get a better sample. Furthermore, the executive directors of the research randomly checked some sample people to double check the quality of the work. Moreover, during information collection and execution stage, attempts were made to decrease the information bias by involving educated psychologists all through the country to administer the approved Persian form of the K-SADS-PL. In this study, the duration of each interview was between 30 and 90 minutes. The inter-rater reliability in this study was 0.91, which indicates a good reliability coefficient. Table 1 displays participants' demographic information.

Table 1. Demographic Information of the Sample and Their Parents

		M(SD)/N(P)	Min-Max Score
Mother age		38.20(6.68)	20-65
Father age		43.19(7.67)	23-75
age		11.83(3.78)	6-18
Sex	Girls	15251(51)	-
	Boys	14633(49)	-
Types of settlement	Rural	4965(16.6)	-
	Urban	24919(83.4)	-
Total		29884(100)	-

Results

This study included 29884 samples, 49% boys, having a mean age of 11.83 years and a standard deviation (SD) of 3.41 years. 83.4% of the participants resided in cities, while 16.6% lived in rural areas. Regarding the parents, the range of age for the mothers was 20-65 with a mean of 38.20 and SD of 8.73, and for the fathers the age range was 23-75 with a mean of 43.19 and SD of 7.47.

Descriptive data about psychiatric disorders in the parents are summarized in Table 2. The scores of the parents of psychotic children and youths for all of the scales of Millon's inventory were different in comparison with the parents of non-psychotic samples. The prevalence of Schizotypal Personality Disorder, Anxiety, Bipolar Spectrum Disorder, PTSD, Schizophrenia Spectrum and Delusional Disorder were statistically higher in these parents. Borderline Personality Disorder was more frequent among the mothers while Alcohol Dependency and Drug Dependency were significantly more prevalent among the fathers. In addition, psychotic children and adolescents also suffered from comorbid disorders with a significantly higher rate than the general population (Table 3).

Table 2. Descriptive Statistic for Interval Variables in the Model for Predicting Psychiatric Disorders of Children and Adolescents Based on Parental Disorders

		General Population	With Psychos	P value
		Mean(SD)	Mean(SD)	
Mother psychiatric disorder	Schizotypal personality disorder	20.74(18.75)	27.52(21.04)	0.002
	Borderline personality disorder	24.19(18.37)	28.45(20.83)	0.045
	Anxiety	25.73(21.79)	33.19(22.75)	0.003
	Bipolar spectrum disorder	18.92(19.34)	29.35(26.08)	< 0.001
	Alcohol dependency	18.32(12.29)	20.55(13.82)	0.118
	Drug dependency	16.25(13.26)	18.25(14.01)	0.192
	Post-traumatic stress disorder	15.44(20.02)	25.71(27.13)	< 0.001
	Schizophrenia spectrum	25.65(21.19)	32.31(24.62)	0.007
	Delusional disorder	21.66(18.79)	28.97(21.02)	0.001
Father psychiatric disorder	Schizotypal personality disorder	19.94(20.13)	29.80(20.43)	< 0.001
	Borderline personality disorder	23.74(20.23)	27.86(20.17)	0.083
	Anxiety	24.76(24.06)	34.14(24.14)	0.001
	Bipolar spectrum disorder	15.30(21.20)	26.05(24.01)	< 0.001
	Alcohol dependency	16.49(17.65)	23.79(17.13)	< 0.001
	Drug dependency	18.52(18.26)	25.27(16.88)	0.001
	Post-traumatic stress disorder	14.67(21.14)	21.68(19.44)	0.003
	Schizophrenia spectrum	26.93(22.74)	35.60(22.52)	0.001
	Delusional disorder	21.66(22.50)	26.57(19.18)	0.059

We evaluated the role of parental psychiatric disorders and comorbid psychiatric disorders in childhood and youths to build an influential model that quantifies the impact of risk factors and mediators predicting pediatric psychosis spectrum. As shown in Table 5, parental psychiatric disorders have both direct and indirect effects on the incidence of psychosis in their children, with a more prominent emphasis on direct effects.

The results of model analysis and implementation of goodness-of-fit showed that some fitness indices confirm the explanatory model, while others do not. These indices examine how closely the model fits the data. The Chi-square goodness-of-fit test did not confirm the model. It should be reminded that the Chi-square test is sensitive to sample size, with greater sample sizes leading to greater test power. Hence, the Chi-Square test would be able to distinguish minor differences between predicted and observed covariance. In this way, a model that has goodness-of-fit may not meet the Chi-square criteria for fitness due to these minor differences.

Therefore, it is recommended to use other alternatives or supplement goodness-of-fit indices (6). Consequently, other goodness-of-fit statistics were calculated and reported too. The Root Mean Square Error of Approximation (RMSEA) goodness-of-fit index indicates the remaining average between the observed covariance of the sample and the expected covariance.

According to Meyers *et al.*, a value of less than 0.08 demonstrates a good fit between the observed model and the expected model, while values above 1 indicate the

non-fit of the model. According to Meyers, a high degree of fit is desirable for research using the Comparative Fit Index (CIF).

Table 3. Descriptive Statistic for Categorical Variables in the Model for Predicting Psychiatric Disorders of Children and Adolescents Based on Parental Disorders

	General Population		With Psychos	
	N (P)	CI 95%	N (P)	CI 95%
Depression disorder	490(1.7)	1.5-1.8	18(24.7)	15.7-34.8
Social phobia	565(1.9)	1.7-2.1	12(16.4)	9.4-25.9
Specific phobia disorder	909(3.1)	2.9-3.3	7(9.3)	4.6-18.0
Agoraphobia	631(2.1)	2.0-2.3	8(10.7)	5.5-19.7
Generalized anxiety disorder	717(2.4)	2.2-2.6	17(22.7)	14.7-33.3
Post-traumatic stress disorder	184(.6)	.5-.7	6(8.5)	3.7-16.4
Tic disorder	340(1.1)	1.0-1.3	8(10.7)	5.5-19.7
Attention Deficit Hyperactivity disorder	1147(3.9)	3.6-4.1	19(25.7)	16.9-36.2
Oppositional defiant disorder	1078(3.6)	3.4-3.8	28(37.8)	17.3-48.6
Epilepsy	541(1.8)	1.7-2.0	9(12)	6.4-21.3
Total	29809	-	75	-

Table 4. Standardized Regression Weights for Variables in the Model for Predicting Psychiatric Disorders of Children and Adolescents Based on Parental Disorders

Criteria		Predictors	Regression Weights	P value	Indirect Effect
Comorbid Disorders	<---	Mothers psychiatric disorders	0.061	< 0.001	-
Comorbid Disorders	<---	Fathers psychiatric disorders	0.017	0.026	-
Children and adolescents' Psychosis	<---	Mothers psychiatric disorders	0.012	0.044	0.002
Children and adolescents' Psychosis	<---	Fathers psychiatric disorders	0.017	0.017	0.001
Children and adolescents' Psychosis	<---	Comorbid Disorders	0.031	< 0.001	-

A CIF value above 0.90 indicates a very good fit, and a value between 0.80 and 0.89 shows a good fit (30). The same is true for NFI and IFI. Parsimonious adjustment indicators, which adjust the GFI and NFI indicators with PNFI and PGFI, indicate the goodness-of-fit for the model when their values are above 0.50 (31). According to the results and explanations, both of the models are presented to explain the childhood and adolescence

psychosis spectrum based on the model variables. The structural coefficients obtained from the two models are listed in Table 4.

Table 5. Goodness of Fit Indexes for Two Model of Predicting Psychiatric Disorders of Children and Adolescents Based on Parental Disorders

The Goodness of Fit Indexes	X^2	$\frac{\chi 2}{df}$	$RMSEA^1$	CFI^2	NFI^3	IFI^4	$PNFI^5$	$PGFI^6$
Expected value	P > 0.05	Less than 3	Less than 0.1	More than 0.95	More than 0.90	More than 0.90	More than 0.50	More than 0.50
Explain model	< 0.001	132.70	0.066	0.89	0.88	0.88	0.75	0.75

Discussion

Our study investigated the correlation between childhood and adolescence psychosis spectrum in children and adolescents and parental psychiatric disorders, as well as their own comorbid disorders as a mediator construct. Compatible with our hypotheses, the outcomes of our study showed that not only were there statistically critical differences between the mean scores of each scale assessed by Millon's inventory among parent of psychotic versus non-psychotic pediatric cases, but psychiatric disorders were found to be more common among children and adolescents with psychosis spectrum in comparison with the general population. Conclusively, we could create a model that suitably fits our data. Our results indicate that parental psychiatric disorders can predict comorbid disorders in psychotic children and adolescents, and vice versa.

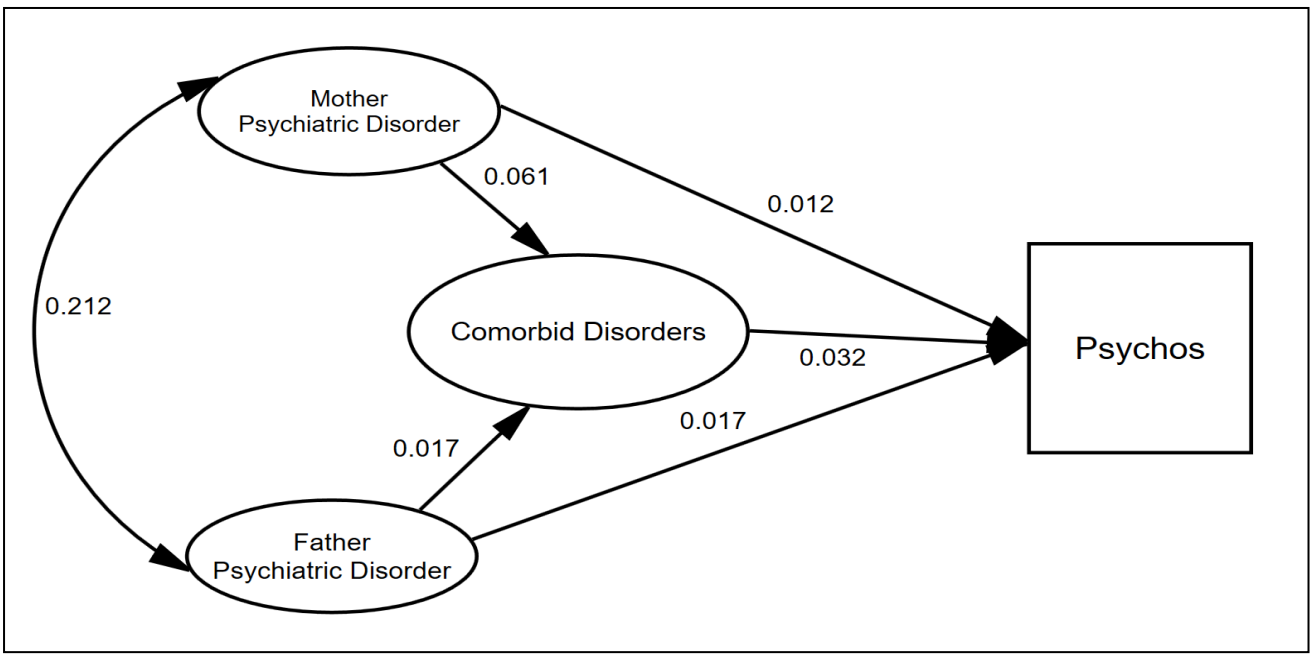

Figure 1. Explain Model to Predict Childhood and Adolescence Psychosis Based on Parental Disorders with the Mediation of Comorbid Disorders

These findings align with the study of Parnas *et al.* which revealed that 25 percent of children who had schizophrenic parents of any type, developed schizophrenia (32). In another longitudinal study, Goodman followed children with disturbed parents since birth up to 5 years; schizophrenic mothers provided a poorer environment, characterized by less play incitement, less opportunities to learn, and fewer emotional and verbal experiences than depressed and normal mothers (33). Parenting skill (an 'environmental' experience) and a variety of shared genetic predispositions may influence the incidence of psychosis in childhood (34). An increasing number of studies illustrate that child abuse and mistreatment may also be a risk factor for the expression of psychotic disorders in children (35, 36). A comprehensive meta-analysis indicated that a history of maltreatment by parents during childhood is more frequent among psychotic patients than in the general population (37, 38).

McGrath *et al.* found that psychiatric disorders in both male and female parents were related to an increased chance of psychotic episodes in their children (33). This finding may reflect communal genetic liabilities and/or impact of harmful environmental experiences (e.g. suboptimal childrearing). Other studies, such as those by Kelleher & Cannon in 2011 and Jeppesen *et al.* in 2015, have also reported an association between a family history of mental disorders and the lifespan prevalence of the expression of psychosis (39).

There is a complex interplay of genetic and ecological elements that can contribute to the growth of psychiatric disorders in children of parents with personality disorders (6). Children of parents with personality disorders may inherit certain genetic vulnerabilities that increase their risk of developing psychotic disorders. For example, studies have found that children of parents with depression and personality disorders are more likely to cultivate depression or bipolar disorder (8). Certain genetic differences may elevate the hazard of developing multiple psychiatric disorders, which can further complicate the picture for children of affected parents. Children of parents with psychiatric disorders may be exposed to stressful or traumatic environments that increase their risk of developing psychiatric disorders (12). Parental disorders can also impact family problems and relationships, which can subsidize the development of psychiatric disorders in children. For example, parents with depression may have difficulty providing emotional support and stability for their children, which can increase the risk of anxiety or mood disorders in their children (33). Children of parents with personality disorders may be more likely to develop similar disorders themselves. This is because certain personality traits and behaviors may be passed down genetically or learned through observation and imitation (29). Parents with personality disorders may struggle with emotional regulation, which can create a chaotic or unstable home environment for their children. This can elevate the risk of anxiety and mood disorders in children, who may have difficulties to cope with the stress and unpredictability of their home life (1). These parents may struggle to form healthy attachments with their children, which can impact children's capacity to create healthy relationships afterward in life. Children may struggle with trust issues, fear of abandonment, or difficulty regulating emotions in relationships (37). Comorbid disorders, or the presence of two or more disorders in an individual, can have significant effects on children's psychiatric disorders. For example, if a child has both anxiety and depression simultaneously, they may experience more severe symptoms and a poorer overall prognosis compared to having only one of these disorders. Comorbid disorders can also make it more difficult to accurately diagnose and treat a child's psychiatric disorder, as symptoms may overlap or be difficult to distinguish from one another (25).

Limitation

This study has some limitations. The participants were children and young people aged between 6-18 years, but this population may not be representative of other age groups. Moreover, clinical personality patterns might have had different effects on them. Due to the voluntary nature of participation, the fathers were less willing to participate in the study, and the sample was restricted, reducing the generalizability of the results. Multigenerational families, as a common lifestyle in Iran, have been abolished except in a few rural areas that have not been assessed as a risk factor, because of the added complexity of data analysis and their limited cooperation. Among other important limitations was the non-utilization of the MCMI-IV. A longitudinal study design would have been more appropriate for the questions of the research, rather than the cross-sectional method that we used. However, we tried to minimize the effect of this limitation by categorized selection based on age. Considering age control also did not alter the contribution of independent variables.

Conclusion

The practical conclusion derived from our results is the necessity of paying special attention to the mental well-being of high-risk children and adolescents. The existence of any disorder in parents should be considered a potential risk factor, and conducting follow-ups and screening for the children of psychiatric patients, in addition to monitoring themselves, will lead to less personal problems related to the disorders that may affect them in the long run. Furthermore, such assessments can reduce the huge financial burden on health systems during decades. In addition, as mentioned in the introduction, the early discovery of psychosis in children and youths may improve their prognosis. Such children from families with parental psychiatric disorders also need to be assessed regarding the risk of child neglect and maltreatment. Creating a psychiatric

profile for each child since the pre-school age, including periodic screenings and such risk factors, may make a great improvement in the visage and well-being of communities in coming days.

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Conflict of Interest
None.

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