High risk cohort study for psychiatric disorders in childhood: rationale, design, methods and preliminary results

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Abstract

The objective of this study is to present the rationale, methods, design and preliminary results from the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders. We describe the sample selection and the components of each phases of the study, its instruments, tasks and procedures. Preliminary results are limited to the baseline phase and encompass: (i) the efficacy of the oversampling procedure used to increase the frequency of both child and family psychopathology; (ii) interrater reliability and (iii) the role of differential participation rate. A total of 9937 children from 57 schools participated in the screening procedures. From those 2512 (random =958; high risk =1554) were further evaluated with diagnostic instruments. The prevalence of any child mental disorder in the random strata and high-risk strata was 19.9% and 29.7%. The oversampling procedure was successful in selecting a sample with higher family rates of any mental disorders according to diagnostic instruments. Interrater reliability (kappa) for the main diagnostic instrument range from 0.72 (hyperkinetic disorders) to 0.84 (emotional disorders). The screening instrument was successful in selecting a sub-sample with "high risk" for developing mental disorders. This study may help advance the field of child psychiatry and ultimately provide useful clinical information. *Copyright © 2014 John Wiley & Sons, Ltd.*

Introduction

In this study we describe the methods and present some preliminary results from the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders. This cohort was designed for the purpose of understanding developmental trajectories of psychopathology and mental disorders. Using a two-stage design we first assessed child symptoms and family history of psychiatric disorders in a screening interview. In the second stage a random sub-sample (aimed to be representative from the community) and a high-risk sub-sample (a sample with children with increased risk for mental disorders) were selected for further evaluation. The evaluation of the sub-samples includes an extensive assessment of environmental and genetic risk factors, brain structure and function and peripheral biomarkers combined with a clinical evaluation of psychiatric disorders and symptoms.

This higher risk sampling was based on the presence of early psychiatric symptoms and high family loading of psychopathology assessed by the screening interview. Using this strategy we hoped to find a higher incidence of mental disorders in this sub-sample, and therefore, to enhance the power to identify developmental trajectories and causal pathways for five main disorders: (1) attention deficit hyperactivity disorder (ADHD); (2) anxiety disorders; (3) obsessive compulsive disorder (OCD); (4) psychosis; (5) learning disorders.

The aim of this report is to provide a detailed description of the study methodology, and to present some preliminary results from the baseline (wave-1) of this ongoing cohort project. Preliminary results are limited to the baseline phase and encompass: (i) the efficacy of the oversampling procedure used to increase the frequency of both child and family psychopathology; (ii) interrater reliability; (iii) the role of differential participation rate.

Methods

Baseline assessment (wave-1) comprised six major steps: (1) *screening* of the families at schools at the registry day (n =9937); (2) *high risk and random selection sampling* (n =2512); (3) a household *parent interview* conducted by a lay interviewer (n =2512); (4) *child evaluation* at schools conducted by a psychologist and a hearing and speech pathologist (n =2401); (5) collection of saliva for *genetic studies* (simultaneously during household interviews for parents and school interviews for children); (6) acquisition of *neuroimaging and collection of blood samples for analyses of biomarkers*.

Screening of the families at the registry day

A total of 57 schools (22 in Porto Alegre and 35 in São Paulo) were included in the study (Figure 1). Porto Alegre and São Paulo are capitals of two Brazilian states. São Paulo is the capital of one of the southeast states of Brazil and the most populated city of the country, with 11,316,149 inhabitants. Porto Alegre is the capital of the southernmost state of Brazil and has 1,409,939 inhabitants. For logistic reasons (specially for the neuroimaging study), only public schools close to the research centers with more than 1000 students in the age of interest were selected to participate.

The enrollment for the screening phase was conducted at public schools during the early registry days. Attendance to schools is compulsory in Brazil for all children 7–14 years old and by law at least one carer is needed to register
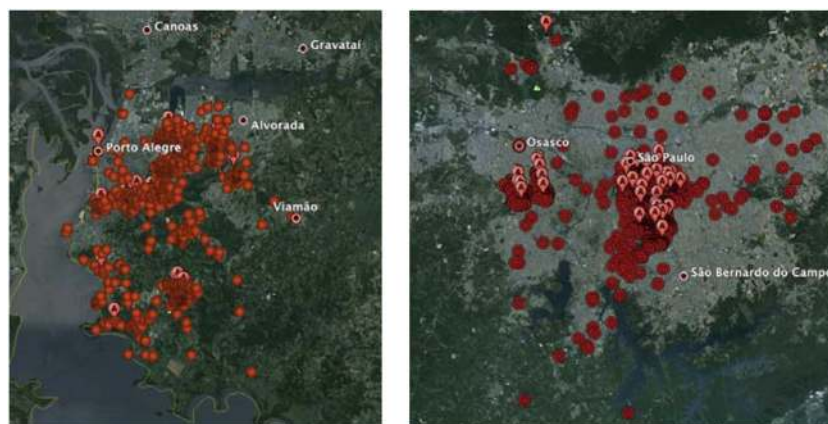
Figure 1. Subjects and schools geographic distribution in Porto Alegre and São Paulo.

the child. Eligible subjects were those: (1) being registered by a biological parent that was a primary carer and could provide sufficient information about the children's behavior; and (2) 6–12 years old at enrollment. All parents present at the selected schools on registry days were invited to participate and those who agreed were interviewed *in loco* or later, by telephone, with a modified version of the Family History Screen (FHS) administered by a lay interviewer (Weissman *et al.,* 2000).

Family History Screen (FHS)

The FHS is an interview used to screen all members of a family for DSM-IV mental disorder symptoms based on the information provided by one family member. In this study, this screening instrument was adapted to allow the collection of information about the index child, his/her biological parents, biological siblings and half-siblings of the index child, instead of asking about family members of the informant.

The FHS is completely structured, with a mean time of administration of approximately 40–60 minutes, assessed by trained interviewers using an electronic data collection system. In Porto Alegre (site 1) 19% of the interviews were performed by telephone and in São Paulo (site 2) all interviews were performed by telephone. At the beginning of the interview, the interviewer asked the informant to make a complete list of all biological first-degree family members of each eligible child. Subsequently, the informant was asked about the presence of DSM-IV screening symptoms for each diagnosis (e.g, "Did anyone on the list feel sad, blue, or depressed for most of the time for two days or more? If yes, who was that?"). The screening question serves as gate to ask about impairment, duration/frequency, and/or exclusion questions, asked only for those individuals who screened-positively (conditional questions). The instrument was adapted for the purposes of this study. Briefly, the version we have used has 48 items, 29 main questions accompanied by 19 conditional questions. It has questions about the main psychiatric syndromes: depression, mania, specific phobia, social phobia, generalized anxiety disorder, panic disorder, agoraphobia, OCD, psychotic experiences, alcohol use and problems due to alcohol use, drug use and problems due to drug use, ADHD, separation anxiety, oppositional defiant disorder, conduct disorder and inhibited behavior towards unfamiliar people.

In total, we were able to interview 9937 children (from 8012 families) and collect information about 45,394 family members. In this phase we obtained information primarily from the biological mother (in 87.6% of the cases) or biological father. The total number of parents approached in the registry day in both states with children in the age range of the project was approximately 12,500.

Training procedures for the screening phase: The research team trained lay interviewers to perform the FHS assessment. The training procedure consisted of two sessions lasting two hours each with lectures about main psychiatric syndromes and symptoms, familiarization with the instrument and ethical/confidentiality issues. We further conducted five simulations using videotaped recorded interviews of real patients and control subjects. Researchers answered interviewers' doubts about rating and instrument procedures (including the digital platform used).

High risk and random selection sampling

Based on the information collected with the FHS, we computed an index of family load for each of the 9937 potential eligible children. This index expresses the percentage of members in the family that screened positively for each of the disorders assessed, adjusted for relatedness.

$$\text{Family Liability Index(FLI)}$$
$$= \frac{BM + BF + \Sigma BS + (\Sigma HS * 0.5)}{2 + n\ BS + (n\ HS * 0.5)}$$

In which: BM, the biological mother is positive for the presence of symptoms; BF, the biological father is positive for the presence of symptoms; BS, the biological sibling is positive for the presence of symptoms; HS, the half-sibling are positive for the presence of symptoms. All variables were coded as zero for absence and one for presence. The relatedness adjustment (0.5) takes into account that half siblings contribute to half of genetic information if compared to biological siblings. This index was constructed based on previous work using this instrument (Milne *et al.,* 2008).

Among the 9937 eligible children, 1500 were randomly selected to compose the *random study sample* (without replacement). Among the remaining children, those who had screened positively for any of the five disorders of interest for this study were ranked according to percentage of members in their families presenting symptoms of the same disorder. We further invited subjects to be enrolled in the second phase of the selection process with replacement until a fixed number of 2512 individuals was achieved (our budget limit), prioritizing those with higher FLI.

Only one child per family was enrolled. In families with more than one child eligible, one of them was chosen

based on a simple randomization procedure. In summary: high-risk selection aimed at those screening positively for any of the five main psychiatric diagnoses of interest (ADHD, anxiety disorders, OCD, psychotic experiences, and learning disorders). Among those, children with a higher number of family members affected were prioritized. A schematic representation of the selection procedure is depicted in the Supplementary Material (Figures S1 and S2).

A total of 2512 subjects selected through the earlier mentioned procedures were comprehensively studied during the parent interview (household interview) and child interview and testing (school evaluation). The flowchart describes the selection procedures (Figure 2).

Household parent interview

The parent interview consisted of: (1) a detailed evaluation of general risk factors for mental disorders; (2) an assessment of childhood psychiatric diagnosis; (3) an assessment of parental diagnosis; (4) questions about child's treatment history and service use.

General risk factors

Questions about risk factors were drawn based on a careful literature review about known major risk factors for mental disorders. The risk factors can be divided in to demographical, prenatal and perinatal, and early life stressors and are presented in Table 1.
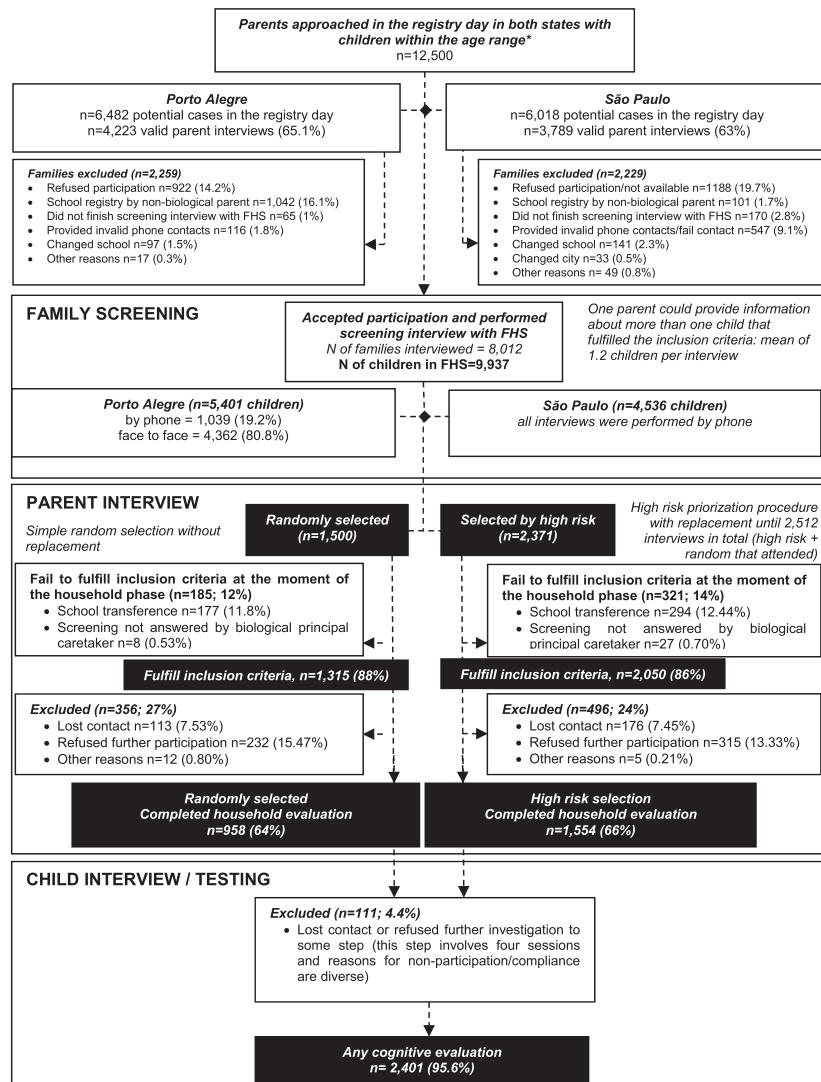

Figure 2. Flowchart of participants in the study.

Table 1. Neuropsychological tasks used in the study

Domain	Tasks	Main function
Computerized tasks		
Basic information processing	Two-choice reaction time (Hogan *et al.,* 2005)	Baseline speed, accuracy, intra-subject reaction time variability. Processing efficiency, cautiousness, motor response/encoding (diffusion model)
Inhibitory-based executive function	Conflict control task (Hogan *et al.,* 2005)	Inhibition of a pre-potent response and initiation of an alternative more appropriate response
	Go/No-Go (Bitsakou *et al.,* 2008).	Inhibition of a pre-potent response
Attention	Attention network task (Fan *et al.,* 2002)	Aspects of alerting, orienting and executive attention
Attention orienting towards threat faces and happy faces	Dot-probe task (500 ms exposure time; 80 trials) (Mogg *et al.,* 1997)	Attention bias towards threat faces and attention bias towards happy faces at initial stages of attention orienting
	Dot-probe task (500 ms and 1250 ms exposure time; 160 trials) (Mogg *et al.,* 1997)	Attention bias towards threat faces and attention bias towards happy faces at initial and late stages of attention orienting
Temporal processing	Time anticipation 400 ms and 2000 ms (Toplak and Tannock, 2005)	Store a time interval in the memory and reproduce it several times without the cue stimuli
	Duration discrimination task (Toplak *et al.,* 2003)	Discriminate the relative length of time intervals through visual stimuli
Delay aversion	Delay reaction task (Sonuga-Barke and Taylor, 1992)	Estimate the relative performance in speed, variability and accuracy in tasks with long time delays if compared to baseline levels
	Choice delay task (Sonuga-Barke and Taylor, 1992)	Preference of immediate less advantageous rewards over delayed more advantageous rewards.
Non-computerized tasks		
General intelligence (estimated)	Wechsler Intelligence Scale for Children (Wechsler, 2002) – subtests vocabulary and block design	General intelligence
Working memory	Digit span forwards and backwards (Wechsler, 2002)	Short-term memory and manipulation capacity of verbal information
	Corsi blocks forwards and backwards (Vandierendonck *et al.,* 2004)	Short-term memory and manipulation capacity of visual-spatial information
Immediate and late non-verbal memory	Rey Osterrieth complex figure test (Rey and Osterrieth, 1993)	Visuo-motor abilities, planning, non-verbal immediate and late visual memory
Visuo-motor abilities	Bender Gestalt task Bender, 1938)	Visuo-motor maturity
Motor functions	Luria motor tasks (Luria, 1973)	Motor coordination
Non-verbal design fluency	Five-point task	Non-verbal design fluency

- Demographics: (i) age; (ii) sex; (iii) socio-economic status (ABEP, 2010); (iv) socio-economic progression since birth; (v) parental marital status; (vi) parental age at birth;
- Prenatal and perinatal: (i) gestational age at birth; (ii) stress during pregnancy; (iii) prematurity, (iv) low birth weight; (v) low birth length; (vi) exposure to tobacco intra-utero and during childhood (quantified);

(vii) exposure to alcohol intra-utero and during childhood (quantified); (viii) gestational infections and clinical conditions (diabetes, hypertension); (ix) delivery conditions; (x) perinatal complications; (xi) psychiatric medications use during pregnancy; (xii) breastfeeding and exclusive breastfeeding time; (xiii) prenatal care;
- Early life stressors: (i) time and quality of contact with caregivers since birth; (ii) bullying perpetration and

victimization; (iii) head trauma; (iv) brain injury; (v) parental warmth and protection [selected questions from Parental Bonding Instrument (Parker, 1990)]; (vi) childhood maltreatment [selected questions from Childhood Trauma Questionnaire (Bernstein *et al.,* 1997)]; (vii) family cohesion, conflict and control [dimensions from the Family Environment Scale (Moos, 1990)].

Child diagnosis and dimensions of psychopathology

Child psychiatric diagnosis was established using the Development and Well-being Assessment (DAWBA, Goodman *et al.,* 2000a). The DAWBA is a structured interview administered by lay interviewers, which also contains the Strength and Difficulties Questionnaire (SDQ, Goodman *et al.,* 2000b) (a 25-item questionnaire providing four risk groups of behavioral and emotional difficulties) and recorded verbatim responses of any reported problems (for further details see http://www.dawba.info). Verbatim responses as well as structured answers are then carefully evaluated by psychiatrists that confirm, refute or alter the initial computerized diagnosis. All questions are closely related to DSM-IV diagnostic criteria and focus on current problems causing significant distress or social impairment. The DAWBA has been translated to several languages, and for the present study the Brazilian Portuguese version (Fleitlich-Bilyk and Goodman, 2004) was administered to the biological parents of all children included in the project. Administrations were performed in accordance with previously reported procedures.

A total of nine certified child psychiatrists performed the rating procedures. All of them were trained and supervised closely by a senior child psychiatrist with extensive experience in rating the DAWBA (BFB). In addition, all cases in which raters had doubts about any specific diagnosis were scaled up and discussed between two child psychiatrists until consensus about the diagnosis was achieved.

In order to perform a reliability analysis of the rating procedure, a sub-sample of 200 subjects received a second rating by a trained child psychiatrist. We selected subjects divided equally into DAWBA bands (Goodman *et al.,* 2011). DAWBA bands represent computer-generated categories based on answers to the DAWBA questions that inform to the rater the probability of a positive diagnosis ($<0.1\%$, $\sim 3\%$, $\sim 15\%$, $\sim 50\%$ and higher than 70%). The second rater was informed that the 200 cases (40 cases from each band) did not represent the population distribution of mental disorders.

In addition to the DAWBA, we also used the Child Behavior Checklist (CBCL) in order to have an assessment of dimensions of psychopathology that have shown to be valid in several cultures (Ivanova *et al.,* 2007).

Parental diagnosis

History of psychiatric disorder in the respondent was assessed using the Mini International Psychiatric Interview (MINI) and the MINI Plus (Amorim *et al.,* 1998; Sheehan *et al.,* 1998). The following modules were used in this research: (1) major depressive episode; (2) manic episode; (3) panic disorder; (4) agoraphobia; (5) social anxiety disorder; (6) alcohol abuse and dependence; (7) drug abuse and dependence; (8) psychotic disorders; (9) generalized anxiety disorder (GAD); (10) ADHD. To assess obsessive-compulsive symptoms dimensionally, we used the Dimensional Yale–Brown Obsessive-Compulsive Scale (Rosario-Campos *et al.,* 2006). At the end of each MINI module we added a four-point response option question ("None", "A Little", "Moderate" and "Severe") about impairment, an item about age of onset of the symptoms, and an item about treatment-seeking.

Child medication, psychotherapy and service use

During household interview, parents were asked on whether the child had ever received any type of treatment for behavioral, attention, learning, or emotional problems, such as fear, anxiety and depression. A positive response would lead to other questions aiming to evaluate the detailed history of medication and psychotherapy treatment. A list of the most common psychiatric medications and their commercial names was presented in order to facilitate communication. We asked additional questions with respect to hospitalization due to psychiatric problems and specific interventions for learning disorders.

Training procedures for the parental interviews: In this phase, training procedures lasted two full days. Lay interviewers attended to instructions provided by clinical psychiatrists from the research team covering the following topics: (1) project structure and design; (2) main aspects of psychiatric syndromes, psychopathology, and risk factors; (3) how to deal with difficult situations/interviews; (4) confidentiality and ethical issues of collecting psychiatric information. Researchers reviewed the full protocol together with the interviewers several times, and simulated difficult situations and potential doubts in role-playing activities. We also asked them to rate videotaped interviews. Given the importance of this procedure, each interviewer was rated by the research team and those not achieving

acceptable retained trained information were excluded from participation in the project. Since this was a household phase, interviews were scheduled and confirmed previously by telephone.

Child interview and testing (school interview)

The child interview and testing comprised: (1) a detailed child evaluation regarding psychosis and psychotic experiences, anxiety and temperament; (2) specific neurocognitive tests; (3) an evaluation of literacy and phonological awareness. For logistical purposes, only participants who remained in the same school of original registry were evaluated, that resulted in a sub-sample of subjects from the screening phase not fulfilling the project entry criteria.

Child evaluation

Trained psychologists read to children the 20 items about positive symptoms and one item about negative symptoms of the Community Assessment of Psychotic Experiences (CAPE, Konings *et al.,* 2006). Two items about difficulty in differentiating reality and fantasy were added. Additionally, psychologists rated an overall clinical judgment using four anchored ratings from the Comprehensive Assessment of At-risk Mental States (CAARMS, Yung *et al.,* 2003). The rating consisted of four questions, with a score from zero to six, related to the following aspects: unusual mental contents, unusual perceptual experiences, speech organization, and blunted affect. Finally, psychologists adjudicated the presence of psychotic symptoms according to the K-SADS-PL (Kiddie–Sads – Present and Lifetime Version) evaluation of delusions and hallucinations (Kaufman *et al.,* 1997).

Since parents tend to underestimate emotional symptoms (Kuhn *et al.,* 2011), we used the child version of the Portuguese Brazilian version of the Screen for Children Anxiety Related Emotional Disorders (SCARED, Isolan *et al.,* 2011) to directly assess anxiety symptoms.

A scale was also used to evaluate a child's temperament, the Early Adolescent Temperament Questionnaire – revised version (EATQ-R, Ellis and Rothbart, 2001). This scale provides measures of Effortful Control, Negative Affect and Surgency.

Neuropsychological evaluation

The neurocognitive tests used in this study are depicted in Table 1. The tests were chosen based on *a priori* hypothesis related to specific cognitive domains for each of the main five disorders investigated.

Intelligence quotient was estimated using the vocabulary and block design subtests of the Weschler Intelligence Scale for Children, third edition (WISC-III, Wechsler, 2002), using the Tellegen and Briggs (1967) method and Brazilian norms (Figueiredo, 2001).

Procedures and computerized tests battery: All computerized tests were administered by mental health professionals previously trained. Tests were performed in 26 notebooks Acer 14 inches Intel Pentium Dual Core T4300 running in Windows 7 Premium software. All computerized neuropsychological tests were programmed using e-prime 2.0. Professionals were instructed to adjust computer to 70% volume, 100% brightness and to perform the tests with the computer linked to a power font. Children were instructed to be 50 cm from the computer screen, which should be kept at a 90° angle to the base of the notebook supported by a fixed structure. Before each computerized task, professionals received a structured instruction to certify that the children were positioned at the center of the computer screen and with both index fingers positioned at the notebook mouse or spacebar. Professionals were instructed to follow narrowly the standard procedures.

To assign tasks between sessions 1 and 2, we used a randomized block approach that takes into consideration the sum of the estimated time sessions in each block of tasks. For half of the children, Block 1 was administered in the first session, and for the other half, Block 2 was administered in the first session.

- Block 1 comprised (1) go/no-go task*, (2) conflict control task, (3) long dot-probe task (500/1200 ms version; 160 trials), (4) two-choice task, (5) delay reaction task* and (6) duration discrimination task*.
- Block 2 involved (1) attention network task*, (2) choice-delay task, (3) short dot-probe task (500 ms; 80 trials) and (4) 400 and (5) 2000 ms time anticipation task. Note: * Indicates tasks with practice trials.

The order of administration of each task within the two blocks was also randomized in five randomly generated sequences that were attributed to each one of the children randomly. We also recoded quality of control of procedural task-related variables (followed random sequence, technical/logistic problems, professional's perception about the understanding of the task, collaboration, motivation, level of noise, impairment of test quality by environmental factors).

Literacy evaluation (reading, writing, mathematics)

The School Performance Test ("Teste de Desempenho Escolar", TDE) (Stein, 1998) assessed literacy. This instrument is

Table 2. Diagnoses compared by selection groups (random versus high risk) in those that had information on the Development and Well-being Assessment (DAWBA)

	Total (n =2512)		Randomly selected (n =958)		Select by high risk (n =1554)		Statistics		
	n	%	n	%	n	%	OR (CI 95%)	χ^2 Yates (df =1)	p-Value
Any disorder	652	26.0	191	19.9	461	29.7	1.694 (1.397–2.053)	28.68	<0.001
Any emotional	335	13.3	93	9.7	242	15.6	1.716 (1.331–2.212)	17.14	<0.001
Separation anxiety	72	2.9	20	2.1	52	3.3	1.624 (0.963–2.737)	2.96	0.087
Specific Phobia	89	3.5	28	2.9	61	3.9	1.357 (0.861–2.139)	1.46	0.227
Social phobia	26	1.0	3	0.3	23	1.5	4.782 (1.432–15.971)	6.78	0.009
Panic disorder	1	0.0	0	0.0	1	0.1	—	—	—
Agoraphobia	4	0.2	0	0.0	4	0.3	—	—	—
PTSD	23	0.9	8	0.8	15	1.0	1.157 (0.489–2.740)	0.014	0.907
OCD	7	0.3	2	0.2	5	0.3	1.543 (0.299–7.968)	0.017	0.895
GAD	47	1.9	17	1.8	30	1.9	1.090 (0.598–1.986)	0.017	0.898
Other anxiety	44	1.8	15	1.6	29	1.9	1.195 (0.638–2.242)	0.161	0.689
Major depression	73	2.9	11	1.1	62	4.0	3.578 (1.874–6.828)	15.967	<0.001
Other depression	8	0.3	1	0.1	7	0.5	4.330 (0.532–35.251)	1.279	0.258
Undifferentiated anxiety/depression	6	0.2	0	0.0	6	0.4	—	—	—
Mania/bipolar	5	0.2	3	0.3	2	0.1	0.410 (0.068–2.459)	0.299	0.585
Any hyperkinetic	274	10.9	79	8.2	195	12.5	1.597 (1.213–2.101)	10.85	<0.001
ADHD combined	105	4.2	29	3.0	76	4.9	1.647 (1.066–2.546)	4.683	0.030
ADHD inattentive	95	3.8	24	2.5	71	4.6	1.863 (1.165–2.981)	6.380	0.012
ADHD hyp-imp	40	1.6	13	1.4	27	1.7	1.285 (0.660–2.503)	0.332	0.565
Other hyperactivity	34	1.4	13	1.4	21	1.4	0.996 (0.496–1.998)	<0.001	>0.999
Any CD/ODD	171	6.8	53	5.5	118	7.6	1.403 (1.004–1.961)	3.65	0.056
ODD	131	5.2	39	4.1	92	5.9	1.483 (1.011–2.176)	3.734	0.053
CD	40	1.6	11	1.1	29	1.9	1.637 (0.814–3.293)	1.518	0.218
Other disruptive	9	0.4	6	0.6	3	0.2	0.307 (0.077–1.230)	2.021	0.155
PDD/Autism									
Autism, NOS	5	0.2	1	0.1	4	0.3	—	4.123*	0.248
Asperger	1	0.0	0	0.0	1	0.1			
Autism	9	0.4	1	0.1	8	0.5			
Tic disorder							—	4.938*	0.176
Other tic	3	0.1	0	0.0	3	0.2			
Chronic tic	7	0.3	2	0.2	5	0.3			
Tourette	9	0.4	1	0.1	8	0.5			
Eating disorder							—	1.588*	0.452
Eating, NOS	9	0.4	2	0.2	7	0.5			
Bulimia nervosa	0	0.0	0	0.0	0	0.0			
Anorexia nervosa	1	0.0	0	0.0	1	0.1			
Psychosis	1	0.0	0	0.0	1	0.1	0.618 (0.600–0.638)	<0.001	>0.999

Note: ADHD, attention deficit hyperactivity disorder; CD, conduct disorder; ODD, oppositional defiant disorder; PTSD, post-traumatic stress disorder; OCD, obsessive compulsive disorder; GAD, generalized anxiety disorder; PDD, pervasive developmental disorder; NOS, not otherwise specified.
*df =3

composed of three subtests: writing (isolated words in dictation); mathematics (oral problem solving and written calculations of mathematical operations); and reading (recognition of words isolated from context). The instrument was elaborated and validated to Brazilian population (Stein, 1998).

Central auditory processing and phonological awareness: The Simplified Assessment of Auditory Processing (Pereira and Schochat, 1997) screened for problems in auditory

function. This is an auditory screening test composed of cochleopalpebral reflex (CPR), sound localization test and a test of memory for non-verbal sounds in sequence. Performance difficulties in sound localization test or in the test of sequenced sounds indicative of harmed auditory processing.

The CONFIAS ("Consciência fonológica instrumento de avaliação sequencial", Phonological Awareness Instrument) (Moojen *et al.,* 2003) test was used to evaluate phonologic processing. It consists of a tool that assesses

Table 3. Comparison of psychiatric diagnoses according to the Mini International Neuropsychiatric Interview (MINI) from the respondent (94.9% mother) between random and high risk samples that attended diagnostic interview (*n* =2512)

	Total (*n* =2512)		Randomly selected (*n* =958)		Select by high risk (*n* =1554)		Statistics		
	n	%	*N*	%	*n*	%	OR	χ^2 Yates (df =1)	*p*-Value
Any	738	29.4	240	25.1	498	32.0	1.411 (1.177–1.691)	13.638	<0.001
Any mood	491	19.5	150	15.7	341	21.9	1.514 (1.225–1.871)	14.493	<0.001
Bipolar	75	3.0	22	2.3	53	3.4	1.502 (0.908–2.486)	2.170	0.141
Unipolar depression	360	14.3	111	11.6	249	16.0	1.456 (1.146–1.851)	9.143	0.002
Recurrent Depression	251	10.0	76	7.9	175	11.3	1.473 (1.111–1.953)	6.933	0.008
Any anxiety	584	23.2	191	19.9	393	25.3	1.359 (1.118–1.653)	9.217	0.002
Panic	175	7.0	49	5.1	126	8.1	1.637 (1.165–2.300)	7.738	0.005
Agoraphobia	288	11.5	95	9.9	193	12.4	1.288 (0.993–1.671)	3.416	0.065
Social anxiety	129	5.1	37	3.9	92	5.9	1.347 (1.060–1.777)	4.739	0.029
GAD	420	16.7	141	14.7	279	18.0	1.268 (1.017–1.581)	4.226	0.040
Any substance	33	1.3	8	0.8	25	1.6	1.942 (0.872–4.322)	2.172	0.141
Alcohol dependence	15	0.6	4	0.4	11	0.7	1.700 (0.540–5.355)	0.423	0.515
Alcohol abuse	6	0.2	1	0.1	5	0.3	3.089 (0.360–26.481)	0.440	0.507
Drug dependence	13	0.5	3	0.3	10	0.6	2.062 (0.566–7.510)	0.697	0.404
Drug abuse	13	0.5	3	0.3	10	0.6	2.062 (0.566–7.510)	0.697	0.404
Other syndromes									
Psychotic syndrome	119	4.8	33	3.5	86	5.6	1.638 (1.087–2.468)	5.224	0.022
Child ADHD	44	1.8	12	1.3	32	2.1	1.676 (0.859–3.270)	1.885	0.170
Adult ADHD	3	0.1	1	0.1	2	0.1	1.238 (0.112–13.668)	<0.001	>0.999

Note: GAD, generalzed anxiety disorder; ADHD, attention deficit hyperactivity disorder; OR, Odds Ratio.

Table 4. Inter-rater agreement for DAWBA clinical ratings (*n* =200)

	Agreement (%)	Expected agreement (%)	Kappa	Standard error	*Z*	*p*-Value	*n* Positive (rater 1/2)
Any disorder	90.95	54.62	0.8007	0.0706	11.34	<0.001	65/73
Any hyperkinetic	92.46	72.66	0.7243	0.0708	10.23	<0.001	31/34
Any emotional	95.48	70.65	0.8459	0.0706	11.98	<0.001	33/38
Any conduct	95.48	83.13	0.7318	0.0709	10.33	<0.001	19/18

Note: DAWBA, Development and Well-being Assessment.

Table 5. Demographics and child psychopathology according to the Family History Screen (FHS) stratified by selection strata, inclusion criteria and participation in the total sample (n =9937) and comparisons between those fulfill versus not fulfill selection criteria and between those evaluated versus non-evaluated in household phase

	Not selected Total (n =6066)		Randomly selected Total (n =1500)		Select by high risk Total (n =2371)		Total (n =9937)		Randomly selected Not fulfill (n =185)		Randomly selected Fulfill (n =1315)		Select by high risk Not fulfill (n =321)		Select by high risk Fulfill (n =2050)		Random with inclusion criteria (n =1315) Not Evaluated (n =357)		Random with inclusion criteria (n =1315) Evaluated (n =958)		High risk with inclusion criteria (n =2050) Not Evaluated (n =496)		High risk with inclusion criteria (n =2050) Evaluated (n =1554)	
	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%	n	%
Respond (father)	850	14.0	195	13.0	196	8.3	1241	12.5	20	10.8	175	13.3	22	6.9	174	8.5	58	16.2	117	12.2	55	11.1	119	7.7
Gender (male)	3036	50.0	792	52.8	1351	57.0	5179	52.1	100	54.1	692	52.6	189	58.9	1162	56.7	188	52.7	504	52.6	274	55.2	888	57.1
State (Porto Alegre)	3455	57.0	750	50.0	1196	50.4	5401	54.4	124	67	626	47.6	226	70.4	970	47.3	143	40.1	483	50.4	198	39.9	772	49.7
Depression	67	1.1	23	1.5	92	3.9	182	1.8	2	1.1	21	1.6	19	5.9	73	3.6	3	0.8	18	1.9	14	2.8	59	3.8
Mania	44	0.7	22	1.5	60	2.5	126	1.3	2	1.1	20	1.5	10	3.1	50	2.4	4	1.1	16	1.7	7	1.4	43	2.8
Panic	166	2.7	69	4.6	245	10.3	480	4.8	11	5.9	58	4.4	40	12.5	205	10	7	2	51	5.3	37	7.5	168	10.8
GAD	95	1.6	39	2.6	157	6.6	291	2.9	4	2.2	35	2.7	21	6.5	136	6.6	8	2.2	27	2.8	20	4	116	7.5
Agoraphobia	207	3.4	82	5.5	293	12.4	582	5.9	13	7	69	5.2	41	12.8	252	12.3	17	4.8	52	5.4	53	10.7	199	12.8
Specific phobia	1403	23.1	408	27.2	959	40.4	2770	27.9	49	26.5	359	27.3	138	43	821	40	83	23.2	276	28.8	184	37.1	637	41
Social anxiety	559	9.2	199	13.3	655	27.6	1413	14.2	28	15.1	171	13	103	32.1	552	26.9	33	9.2	138	14.4	117	23.6	435	28
OCD	395	6.5	217	14.5	847	35.7	1459	14.7	24	13	193	14.7	117	36.4	730	35.6	48	13.4	145	15.1	181	36.5	549	35.3
Psychosis	451	7.4	217	14.5	850	35.8	1518	15.3	27	14.6	190	14.4	132	41.1	718	35	32	9	158	16.5	164	33.1	554	35.6
Alcohol	0	0.0	0	0.0	0	0.0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Drugs	1	0.0	1	0.0	1	0.0	2	0	0	0	0	0	1	0.3	0	0	0	0	0	0	0	0	0	0
Learning	1020	16.8	359	23.9	1032	43.5	2411	24.3	45	24.3	314	23.9	154	48	878	42.8	83	23.2	231	24.1	198	39.9	680	43.8
Language	501	8.3	214	14.3	653	27.5	1368	13.8	32	17.3	182	13.8	111	34.6	542	26.4	33	9.2	149	15.6	103	20.8	439	28.2
Separation	453	7.5	158	10.5	516	21.8	1127	11.3	17	9.2	141	10.7	85	26.5	431	21	25	7	116	12.1	95	19.2	336	21.6
Conduct	77	1.3	19	1.3	86	3.6	182	1.8	2	1.1	17	1.3	23	7.2	63	3.1	2	0.6	15	1.6	8	1.6	55	3.5
ODD	457	7.5	151	10.1	486	20.5	1094	11	20	10.8	131	10	91	28.3	395	19.3	19	5.3	112	11.7	69	13.9	326	21
ADHD	1028	16.9	384	25.6	1126	47.5	2538	25.5	52	28.1	332	25.2	165	51.4	961	46.9	76	21.3	256	26.7	203	40.9	758	48.8

Note: GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; ADHD, attention deficit hyperactivity disorder. All differences between random and high risk group were significant, except for alcohol, drug use and state (compare columns #2 and #3). Italic typeface represents significant differences between proportions in each category of symptoms (p <0.05) – Fulfill versus Not fulfill and Evaluated versus Not Evaluated in each selection stratum. All percentages are presented within columns. Statistics: z-test.

Table 6. Family demographics and family liability index (FLI) according to the Family History Screen (FHS) stratified by selection strata, inclusion criteria and participation in the total sample (n =9937) and comparisons between those fulfill versus not fulfill selection criteria and between those evaluated versus non-evaluated in the household phase

	Not selected Total (n=6066)		Randomly selected Total (n=1500)		Select by high risk Total (n=2371)		Total (n=9937)		Randomly selected (n=1500) Not fulfill (n=185)		Fulfill (n=1315)		Select by high risk (n=2371) Not fulfill (n=321)		Fulfill (n=2050)		Random with inclusion criteria (n=1315) Not Evaluated (n=357)		Evaluated (n=958)		High risk with inclusion criteria (n=2050) Not Evaluated (n=496)		Evaluated (n=1554)	
	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95	p75	p95
Age respectively (years)	40	48	40	50	40	48	40	48	38	49	40	50	39	49	40	48	40	51	40	50	39	48	40	48
Age (years)	10	12	10	12	11	12	10	12	10	12	10	12	11	12	10	12	11	12	10	12	11	12	10	12
Biological siblings	2	3	1	2	2	3	2	3	1	2	1	2	1	3	2	3	1	3	1	2	1	3	2	3
Half siblings	1	3	1	2	1	2	1	2	1	2	1	2	1	2	1	2	0	2	1	3	1	2	1	2
Total	0.75	1	1	1	1	1	0.8	1	1	1	1	1	1	1	1	1	0.8	1	1	1	1	1	1	1
Depression	0	0.25	0	0.33	0	0.4	0	0.33	0	0.33	0	0.33	0	0.4	0	0.4	0	0.33	0	0.33	0	0.33	0	0.43
Mania	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Panic	0	0.33	0	0.37	0	0.5	0	0.33	0.33	0.5	0	0.4	0.22	0.5	0	0.5	0	0.5	0	0.4	0	0.4	0	0.5
GAD	0	0.33	0	0.5	0.29	0.5	0	0.5	0	0.5	0	0.5	0.33	0.5	0.29	0.5	0	0.5	0	0.5	0.25	0.5	0.29	0.5
Agoraphobia	0	0.33	0	0.4	0	0.5	0	0.33	0	0.4	0	0.4	0.14	0.5	0	0.5	0	0.33	0	0.4	0	0.5	0	0.5
Specific phobia	0.33	0.6	0.33	0.6	0.4	0.75	0.33	0.67	0.33	0.5	0.33	0.6	.5	0.67	0.4	0.75	0.33	0.6	0.33	0.64	0.4	0.71	0.4	0.75
Social anxiety	0.13	0.5	0.2	0.5	0.33	0.67	0.25	0.5	0.25	0.5	0.2	0.5	0.33	0.67	0.33	0.67	0	0.5	0.22	0.5	0.33	0.57	0.33	0.67
OCD	0.33	0.5	0.36	0.67	0.5	1	0.33	0.67	0.4	0.75	0.33	0.67	0.5	0.8	0.5	1	0.33	0.67	0.4	0.67	0.5	0.83	0.5	1
Psychosis	0	0.4	0	0.5	0.33	0.67	0.14	0.5	0	0.5	0	0.5	0.33	0.67	0.33	0.6	0	0.5	0.13	0.5	0.25	0.6	0.33	0.6
Alcohol	0	0.33	0	0.5	0.22	0.5	0	0.4	0	0.5	0	0.5	0.25	0.5	0.2	0.5	0	0.5	0	0.5	0.15	0.5	0.2	0.5
Drugs	0	0.29	0	0.33	0	0.4	0	0.33	0	0.5	0	0.33	0.13	0.5	0	0.4	0	0.33	0	0.33	0	0.4	0	0.4
Learning	0.33	0.5	0.33	0.63	0.5	0.75	0.33	0.67	0.33	0.67	0.33	0.6	0.5	0.71	0.5	0.75	0.33	0.57	0.33	0.67	0.5	0.67	0.5	0.75
Language	0	0.33	0	0.44	0.22	0.5	0	0.4	0	0.5	0	0.4	0.25	0.5	0.2	0.5	0	0.5	0	0.4	0	0.5	0.25	0.5
Separation	0	0.33	0	0.5	0.13	0.5	0	0.4	0	0.4	0	0.5	0.25	0.5	0	0.5	0	0.5	0	0.5	0	0.5	0	0.5
Conduct	0	0.33	0	0.4	0	0.5	0	0.33	0	0.4	0	0.4	0.25	0.5	0	0.5	0	0.33	0	0.45	0	0.5	0	0.5
ODD	0	0.33	0	0.5	0.25	0.5	0	0.5	0.2	0.5	0	0.5	0.29	0.5	0.25	0.5	0	0.33	0	0.5	0.17	0.5	0.25	0.5
ADHD	0	0.4	0.11	0.5	0.33	0.5	0.17	0.5	0.18	0.5	0.1	0.5	0.33	0.67	0.33	0.5	0	0.4	0.14	0.5	0.25	0.5	0.33	0.5

Note: GAD, generalized anxiety disorder; OCD, obsessive compulsive disorder; ODD, oppositional defiant disorder; ADHD, attention deficit hyperactivity disorder. Median values returned in a vast majority of zeros and therefore only precentiles 75th (p75) and 95th (p95) are presented. All differences between random and high risk groups were significant, except for respondent age and family liability for mania, (compare columns #2 and #3). Italic typeface represents significant rank differences in each category of symptoms (p <0.05) – Fulfill versus Not fulfill and Evaluated versus Not Evaluated in each selection stratum. Statistics: Independent samples Mann–Whitney test. FLI measures the percentage of family members affected for each psychiatric disorder.

phonologic awareness in sequence and is standardized and validated for use in Brazil. It is composed of two levels (syllable and phoneme), and each level has specific metalinguistic tasks: segmentation, identification, rhyme, and syllable or phoneme exclusion or transposition. The Phonology Test, part of the ABFW Test ("Teste de linguagem infantil nas áreas de fonologia, vocabulário, fluência e pragmática") (Wertzner, 2000), was also used in order to detect the presence of one or more phonologic processes, characterizing phoneme replacements, omissions and/or distortion in the child's speech.

Training procedures for child interview and testing: Psychologists and hearing and speech pathologist conducted child evaluations in this phase. Training consisted of two sessions with a specialized hearing and speech pathologist experienced in the study protocol. Full explanation about the project, instruments, procedures and standardization for the clinical evaluations was provided.

Molecular genetic evaluation

Saliva was collected from the child and both parents using an Oragene© salivary kit. If saliva from one of the biological parents was not available, the brother with the closest age to the child was chosen to provide a saliva sample. More detail about genetic analyses will be provided in specific studies from this cohort.

Neuroimaging and peripheral biomarkers

A sub-sample of approximately 750 subjects was selected to participate in a neuroimaging and blood biomarkers study. A detailed description of the neuroimaging/biomarkers sample and design will be provided elsewhere. Brain magnetic resonance imaging (MRI) was acquired in two centers using a 1.5T General Electric Scanner. The sequences acquired were: (a) high-resolution tridimensional T1-weighted; (b) diffusion tensor imaging (DTI); (c) intrinsic connectivity fMRI; (d) MT ON/OFF. Total scan time was 28 minutes.

Children were invited to arrive one-hour earlier to the exam site and were engaged in a recreational and therapeutic technique in order to reduce exam related distress. Dancing technique and theater games, relaxation, music, games, and various recreational and interactive games were used as a desensitization method. A simulation of the brain scan, using a cloth tunnel on a stretcher with simultaneous presentation of the background noise of each MRI sequence to be performed in the research protocol was also used. Since this is a follow-up study, these procedures were taken to improve the quality of the assessment

and to enhance engagement in future assessments. These procedures were highly successful, since 739 (98%) of children that come to the MRI center finished the MRI scan and 606 (81%) provided blood samples. No anesthetic or sedative medications were used.

After the MRI acquisition, they were invited to provide blood samples. A blood sample was collected for plasmatic biomarkers, mRNA and DNA. Blood samples were stored at 4°C at collecting sites and processed the same day within a four-hour interval for plasma aliquots, which were stored in a freezer at −80°C. EDTA tubes for DNA extraction were stored at 4°C and PAX gene tubes, for RNA extraction, at −20°C after incubating them for at least two hours at room temperature, following manufacturer's instructions.

Ethical considerations

This study was approved by the ethics committee of the University of São Paulo [IORG0004884/National Council of Health Registry number (CONEP): 15.457/Project IRB registration number: 1132/08]. Written consent was obtained from parents of the participants as well as from those participants that were able to read, write and understand the written consent. From others, verbal agreement was obtained. All families were invited for an appointment with a trained psychologist and social worker in case they were interested in receiving the results of the study evaluation and all children identified as being under the need of care were referred for clinical evaluation. Situations involving serious risk of physical or psychological harm received special attention in accordance to competent authorities' guidelines. No compensation or financial incentive was made available for those taking part in the household and school interviews. Compensation for transport expenses was provided for those attending the neuroimaging study.

Statistical analysis

Data is presented as absolute and relative frequencies, and variables with a non-Gaussian distribution are presented with percentiles (50th and 75th; 95th in some cases due to extreme skewness). We compared proportions between samples using Chi-square test (with Yates correction for df =1). For continuous variables with non-Gaussian distribution differences between mean ranks are compared using the independent samples Mann–Whitney U test. Interrater reliability was calculated using Kappa. All tests were two-tailed and we adopted a significance level of 5%.

Results

We report data about: (1) the efficacy of the oversampling procedure; (2) diagnostic reliability; (3) study participation and differences between those individuals who attended household and scholar interviews.

The total sample comprises children with an average age of 9.7 years at the diagnostic phase [standard deviation (SD) =1.92], 53.1% male, included mostly subjects in medium strata of socio-economic status (64.6% medium; 6% low/very low and 29.4% comfortable/high), with a mean number of 1.44 siblings (SD =1.29). The rate of any mental disorders in the random strata was 19.9% if compared to 29.7% in the high-risk strata. Rates for parental and child psychopathology as well as demographic data for each study selection strata are depicted in Tables 2–6.

Efficacy of the oversampling procedure

Adopting the described procedures, we tried to oversample children with psychiatric symptoms and families with high percentage of members affected by psychiatric disorders according to the screening instrument. Here, we evaluate the efficacy of the oversampling procedure comparing groups according to the selection procedure: the random procedure and the high-risk selection procedure.

We found that those in the high-risk group presented a higher number of childhood psychiatric disorders according to the child diagnostic evaluation with the DAWBA (Table 2). We also found that the high-risk group (based on FHS) presented a higher number of parents with psychopathology (the respondent of the household interview) in comparison with the random group as assessed by the MINI (Table 3).

Diagnostic reliability

Diagnostic reliability for the rating procedure of DAWBA resulted in acceptable indexes with agreements ranging from 90% to 95% and Kappa from 0.72 to hyperkinetic disorders to 0.84 for emotional disorders (Table 4).

Attendance to household/scholar interviews

Those children who were selected but failed to fulfill inclusion criteria along the study (e.g. school transference before child evaluation) did differ in some aspects from those that met criteria for being evaluated. They were more likely to be from the Porto Alegre site in both random and high-risk strata. No other differences were found in the random selection group. However, within the high-risk group, those who failed to fulfill inclusion criteria were also more likely to have depressive, psychotic, language, separation anxiety, conduct and oppositional defiant symptoms (Table 5).

Regarding family liability index (FLI), respondents who did not fulfill the criteria were younger and had higher family loading of drug abuse within randomly selected subjects. A lower family loading of generalized anxiety, alcohol, drugs, separation anxiety and conduct was found for those who fulfilled diagnostic criteria within those selected by high-risk (Table 6).

Those who were selected and fulfill inclusion criteria but were not evaluated in the household interview (e.g. refused further participation, not found, etc.) also differed from those evaluated in some specific variables. Within the randomly selected subjects, the non-evaluated were less likely to be from Porto Alegre and to have symptoms of panic, specific phobia, social anxiety, psychosis, language difficulties, separation anxiety, oppositional defiant, and attention deficit hyperactivity symptoms. Within the high-risk group, the non-evaluated were less likely to be from Porto Alegre, to be male and to present panic, generalized anxiety, language difficulties, conduct, oppositional defiant and attention deficit hyperactivity symptoms. Moreover, within randomly selected subjects, those who did not fulfill inclusion criteria were older, had lower FLIs for generalized anxiety, social anxiety, psychosis, learning, oppositional defiant, conduct and attention deficit hyperactivity symptoms. Within the high-risk sample, they had lower FLIs for generalized anxiety, social anxiety, psychosis, language, oppositional defiant and attention deficit hyperactivity symptoms.

Discussion

We described the rationale, methods, design and preliminary results of the High Risk Cohort Study for the Development of Childhood Psychiatric Disorders. Each of the study phases were described in detail, including their instruments, methods and procedures.

The significant efficacy of the oversampling procedure based on the FHS interview evidenced by the higher rate of psychiatric disorders and family psychopathology according to diagnostic instruments (DAWBA and MINI) in the high-risk sub-sample was a key point of this study. This positive result encourages us to think our design will provide advantages in the follow-up phases, since potentially a higher number of subjects, well characterized in terms of clinical and neurobiological measures, will be affected by traits (outcomes) of interest in this study. Despite that, an increase in rates of family and child mental disorders does not necessarily mean higher follow-up risk. However, a series of studies have reported that individual and family psychiatric symptoms and disorders are reliable predictors of psychopathology later in life (Kim-Cohen *et al.,* 2003; Milne *et al.,* 2008; Moffitt *et al.,* 2007).

We showed that whereas those who did not fulfill the inclusion criteria for participation in the study (mainly due to school transference) were found to have more child and family psychopathology, those who did not attended the diagnostic evaluation (mainly due to lost contact or refusal) had lower child and family psychopathology as assessed by the FHS. The participation analysis clearly shows that some family and child psychopathological measures were different between those who failed to fulfill inclusion criteria and those that were not evaluated by the household interview. This underscores that we have to be careful in interpreting prevalence rates in this sample, given its lack of general representativeness for the main population. Indeed, our prevalence rates were somewhat higher than previous studies with representative samples in our country from both south and southeast regions using the same instruments (Anselmi *et al.,* 2010; Fleitlich-Bilyk and Goodman, 2004). Therefore results from our analysis may not be generalized for prevalence purposes. However, this project was designed to be a high-risk cohort, enriched for individual and family psychopathology, and not to assess population prevalence of psychiatric disorders. Still, the slightly higher prevalence rates of psychiatric disorders found when compared to other Brazilian studies, even in the random stratum of our sample, may be accounted to by differences in demographical aspects, such as urbanicity.

Our design has some limitations. First, we needed to select children that lived closely to the research centers in order to carry out the neuroimaging procedures, limiting the representativeness of the sample. Second, in order to keep the enrolled subjects independent from one another, we selected only one child per family, thus children from large families are underrepresented. Third, although five main areas of interest were covered in this study, other important psychiatric disorders such as depression, autism, eating disorders and substance use disorders were not targeted in the oversampling procedure. However, for those outcomes that were measured we believe our cohort will be informative for mental health problems. Finally, although the oversampling procedure with the screening instrument was able to increase the frequency of psychiatric disorders and number of familial cases in the high-risk cohort strata according to diagnostic instruments, it is still not clear if the procedure will increase our power to detect incident and persistent cases of psychiatric disorders.

Our study was specifically designed to combine a longitudinal epidemiological approach with a comprehensive study of gene variants, environmental factors and diverse phenotypes – both clinical and those related to brain structure and functions. We believe studies like the High Risk Cohort Study for Childhood Psychiatric Disorder may help advance the field forward and provide useful information to understand the nature, prevent and treat mental disorders.

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