Cohort Profile: Brazilian High-Risk Cohort for Mental Health Conditions (BHRC)

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Key features

- The Brazilian High-Risk Cohort for Mental Health Conditions (BHRC) was established in 2009 to investigate the developmental trajectories of mental health conditions, integrating clinical, social, genetic, neuroimaging, and environmental assessments. It is unique as one of the most comprehensive population neuroscience studies from a middle-income country.
- Participant screening was performed in 2009-10 across 57 public schools in Porto Alegre and São Paulo, Brazil, with 8,012 caregivers reporting information on 9,937 children aged 6–12 years.
- A total of 2,511 participants were selected for genotyping and deep phenotyping, 958 by random and 1,553 selected by having high risk of mental health conditions based on symptoms and family history.
- Participants received a baseline assessment in 2010-11 and were followed up at regular intervals, including four key waves, in 2013–14, 2018–19, 2019–20 (COVID-19), and 2023–25, with an 83% retention rate after 15 years.
- Currently, the cohort expanded to include three generations: parents, probands and proband's offspring, enabling transgenerational analyses of mental health and cognitive development across three generations.
- Data and resources are available through open-science platforms, with collaboration opportunities accessible via proposal submission (https://osf.io/ktz5h/overview).

Why was the cohort set up?

The "Brazilian High Risk Cohort for Mental Health Conditions (BHRC)", formerly "High risk cohort study for psychiatric disorders in childhood (HRC)"[1], was established to advance the understanding of the developmental trajectories of pediatric mental health conditions by integrating information about behaviors, genes, environments and brain development. BHRC has an accelerated school-based longitudinal design in which children born between 1996 and 2004 were recruited at school in 2009 and 2010 and assessed every two to four years. BHRC is one of the few population neuroscience studies from a middle-income country, integrating in-depth clinical assessments with data on environmental influences, genetics, imaging, cognition, and ecological momentary assessment (EMA), among others[2].

The cohort was established as a collaborative effort among three Brazilian universities: Universidade de São Paulo (USP), Universidade Federal do Rio Grande do Sul (UFRGS) and Universidade Federal de São Paulo (UNIFESP). This was possible through a networking grant from the Brazilian Science and Technology Ministry, which created the National Institute of Developmental Psychiatry for Children and Adolescents (in Portuguese, "Instituto Nacional de Psiquiatria do Desenvolvimento para a Infância e Adolescência", INPD). Participants were recruited at state-funded schools of two Brazilian metropolitan areas: Porto Alegre (South, 1.5 million inhabitants, metropolitan area 4.4 million inhabitants) and São Paulo (Southeast, 11.4 million inhabitants, metropolitan area 22.8 million inhabitants).

Over the past 15 years, the study was funded by multiple sources including Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq), Conselho Nacional de Desenvolvimento Científico e Tecnológico (CAPES), Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP), European Research Council (ERC), UK Medical Research Council (MRC), Banco Industrial do Brasil S/A., and Brazilian Ministry of Health. Additionally, the harmonization between the BHRC and other cohorts has been funded by the National Institutes of Mental Health (NIMH). NIMH also provided support by mentorship

from researchers from the Intramural Research Program to students working with BHRC data.

Who is in the cohort?

The BHRC enrolled participants from 57 state-funded schools (22 in Porto Alegre, 35 in São Paulo), during compulsory registration days, when at least one caregiver must attend by law. Of the approximately 12,500 eligible caregivers, 8,012 enrolled, providing information on 9,937 children (participation: Porto Alegre, 65.1% and São Paulo, 63%). Inclusion criteria were registration in a state-funded school by a biological parent able to provide behavioral information, and child aged 6–12 years. Parents were interviewed in person or by telephone, with a modified Family History Screen (FHS), administered by trained interviewers [1,3]. The FHS was used to generate a family liability index that expresses the percentage of family members who screened positive for a mental health condition, adjusted for degree of relatedness (mother, father and sibling counts as 1.0, half sibling is 0.5). Most interviews involved biological mothers (87.3%), with the remainder completed by biological fathers. Based on the information reported at screening (n=9,937), we recruited two subgroups: random (n=958) and high-risk (n=1,553) samples. Only one child per family was included. The high-risk sample was selected based on the presence of early mental health symptoms and high levels of symptoms in the family as assessed by the family liability index[1]. Recruitment occurred from September 28, 2009, to April 15, 2010.

How often have they been followed up?

Participants have been reassessed over 15 years. Screening was in 2009–2010, followed by baseline (Wave 0: August 2010–June 2011), Wave 1 (October 2013–November 2014), Wave

2 (November 2018–December 2019), and Wave 3 (2023–2025). A special follow-up (Wave C, April 2020–March 2021) evaluated the impact of COVID-19 (Figure 1).

What has been measured?

The BHRC collected a broad, harmonized set of measures to capture psychopathology, development, and context:

- Mental health data assessed via diagnostic interviews, rating scales, parent, self and teacher-reports about psychopathology, temperament, and personality (Supplementary Table S1).
- Exposure to tobacco, alcohol, drugs, screen time, pornography, and addictive behaviors, along with their impact on health and functioning via both self-reports and toxicological hair assays (Supplementary Table S2).
- Cognitive assessments including intelligence quotient, executive function, memory, attention, and attention bias to threats and rewards (Supplementary Table S3).
- Learning assessments including reading speed, accuracy and comprehension, writing, and mathematics (Supplementary Table S4).
- Life events, functioning, and lifestyle including friendship, sleep patterns, well-being, religiosity, physical health, traffic accidents, exposure to violence, and medical diagnosis (Supplementary Table S5).
- Perinatal factors, stressful events and environments, bullying, stigma, and discrimination (Supplementary Table S6).
- Service use including inpatient admission, outpatient services, help-seeking behavior, treatments, and barriers encountered in accessing care (Supplementary Table S7).
- Genetic assessment from biospecimens (saliva and blood) including genomics, transcriptomics, and epigenomics (Supplementary Table S8).

- Neuroimaging assessment including diverse modalities of structural and functional magnetic resonance imaging (Supplementary Table S9).
- Ecological Momentary Assessment including mood, activities, step counts, GPS location and time spend in nature (Supplementary Table S10).

Quality control

From 8-year follow-up onward (Wave 2), all interviews were audio-recorded (Supplementary Table S11) and reviewed for quality control. At the 15-year follow-up, the protocol was further enhanced by including an additional psychiatric interview tailored to severe conditions i.e., intellectual disability, imprisonment, or psychotic disorder (Supplementary Tables S12 and S13).

Assessing biological parents (G1)

Biological parents (Generation 1, G1) initially served as informants about their children (G2). As the cohort matured and G2 participants reached adulthood, G1 participation was expanded: parents were interviewed about their own health, education, and functioning using the same core protocol employed with their offspring. Including both biological parents where possible effectively tripled the number of assessed individuals and enabled family-based analyses (e.g., triads) crucial for disentangling genetic, environmental, and intergenerational mechanisms.

Adding a third generation (G3)

The 15-year follow-up introduced the third generation (G3): the children of the original G2 participants. By November 2024, 458 G2 participants had at least one child, yielding 574 G3 children enrolled. Initial contact identified the child's main caregiver to complete an online

sociodemographic and perinatal questionnaire, followed by a recorded online interview by a trained psychologist focused on the child's emotions, behaviors, and environment (Table S17). Adding G3 allows the cohort to investigate transgenerational associations and inherited susceptibilities with direct measures across three generations.

What has it found?

Mental health conditions are frequent, fluctuate over time, and most Brazilian children with such conditions do not receive needed care. One in five children in the studied cities experience a mental disorder[1], yet only 20% of those receive any form of treatment[4,5], with parental stigma acting as a major barrier to accessing care[6]. Trajectories show waxing and waning patterns of symptoms, with both homotypic and heterotypic transitions. Externalizing conditions, such as Attention-Deficit Hyperactivity Disorder (ADHD) and disruptive behavior disorder, were more prevalent in earlier waves, whereas anxiety and depression were more prevalent in later waves.

Not only symptoms, but positive traits have an important role in educational outcomes. Problems such as low test performance, age-grade distortion, and retention were associated with psychopathology[7]. Positive traits such as eagerness to learn, affection, and caring play a significant role in mitigating negative educational outcomes[8]. They buffer the effects of lower intelligence on learning and reduce the impact of psychopathology on academic performance.

Social determinants and childhood adversity influence mental health, brain activity and development. Poverty, affecting 12% of the sample, is associated with externalizing conditions[9] and later-life criminal convictions[9]. Socioeconomic correlated with spontaneous activity in the right superior temporal gyrus, part of the extended language network[10]. Adversity showed distinct effects: threat-related experiences were tied to psychopathology, while deprivation impaired executive function[11]. Traumatic events with intentional harm were

more strongly associated with psychotic experiences than non-intentional trauma[12]. Parental job loss worsens children's mental health, increasing clinical diagnoses[13].

ADHD involves deficient information processing; biased attention orienting to threats characterizes both anxiety and irritability; and executive functions relate to general psychopathology. While deficits in basic information processing (e.g., processing speed and stimulus discriminability) were specific to the ADHD[14], they were also present in children with subclinical inattention symptoms, providing support for ADHD dimensionality[15]. Impaired basic information processing mediated the relationship between ADHD symptoms and poor reading ability, particularly in younger children[16]. Biases in attention orienting were associated with irritability in children and adolescents[17], beyond their association with anxiety. Finally, impairments in executive function were linked to general psychopathology,[17] rather than specific disorders.

Psychopathology has many dimensions with distinct external correlates. We found psychopathology to have a hierarchical structure, with general and specific dimensions[19]. For example, anxiety disorders can be divided into fear and distress disorders, with distinct cognitive underpinnings[19] and familial transmission patterns[18]. Oppositionality comprises three main dimensions: irritability, headstrong behavior, and hurtfulness, each associated with unique familial and developmental outcomes[20]. Mania has two dimensions: exuberant and undercontrolled, with the latter linked to the most detrimental outcomes[21].

Data-driven classifications of executive function have strong predictive validity. We proposed a data-driven classification of executive dysfunction using cognitive tasks assessing inhibitory control, working memory, and temporal processing[22]. Participants with executive dysfunction reported symptoms spanning several domains of psychopathology and exhibited impairment in multiple settings, including more adverse school events. They also exhibited smaller intracranial volumes and reduced cortical surface areas.

Alzheimer's genetic risk has implications for early development. Genetic risk for Alzheimer's disease may affect early life cognition and hippocampal volumes, supporting previous evidence that some forms of late-life dementia could have developmental roots[23]. We also showed that this genetic risk influences functional connectivity among brain regions susceptible to tau pathology during childhood and adolescence[24].

Aggregated genetic risks have small but consistent effects, which are dependent on the environment. Although the effects of individual genetic variants are modest, their aggregation holds substantial predictive power, especially when moderated by environmental risks [25]. Different polygenic scores appear to impact cognition and brain volume in early development[23], as well as functional connectivity[24], and inhibitory control[22], among other traits. In addition, we found that parents' genetics influence the cognition and educational performance of the offspring, a relationship likely mediated by the parents' phenotypes[26].

Neurodevelopmental correlates of psychopathology include delayed Default Mode Network (DMN) maturation, cerebellum volumes smaller than expected for age, and aberrant ventral striatum connectivity. General child psychopathology was associated with delayed maturation of the Default Mode Network (DMN) using resting state functional connectivity[27], while smaller-than-expected cerebellar volumes for a given age and sex were associated with higher externalizing psychopathology and worse executive function[28]. Aberrant ventral striatum functional connectivity predicted future risk for depressive disorder[29], a finding replicated in an independent sample[30]. Nevertheless, imaging studies revealed relatively low effect sizes, with an aggregate measure of structural brain measures explaining no more than 1–3% of the variance in behavioral traits[31].

Aggregating data is critical for scientific exploration. BHRC data have contributed to numerous important consortia, addressing key gaps in mental health and neurodevelopmental research. For example, it contributed to showing that the diagnosis of ADHD in younger

children within a classroom is no more likely to be disconfirmed over time than that of older children[32]; to the discovery of genes related to PTSD[33]; and to charting brain trajectories of typical development across the lifespan[34]. This is particularly important because most genetic and imaging studies originate from high-income countries, leaving populations from low- and middle-income countries underrepresented. By contributing data to large consortia such as the Psychiatric Genomics Consortium (PGC), Enhancing NeuroImaging Genetics through Meta-Analysis (ENIGMA), Reproducible Brain Charts (RBC)[35], The Methylation, Imaging and NeuroDevelopment (MIND)[36] and others (Supplementary Table S17), BHRC has ensured that findings from Brazil add diversity and depth to global datasets (Figure 2).

What are the main strengths and weaknesses?

Strengths: The BHRC is notable for its comprehensive assessment of mental health phenotypes, encompassing dimensional and diagnostic approaches. Its long-term longitudinal design allows for the study of both typical and atypical neurodevelopmental trajectories, leveraging a wide range of data modalities. These include biological samples (hair, blood, and saliva), genomic (SNP-array, whole genome sequencing, and telomere length), transcriptomic (RNA sequencing) and epigenetic data (DNA methylation array), along with environmental, neuroimaging, physical health, cognitive, and educational assessments. This cohort is particularly notable for its depth of phenotyping within the context of environmental and genomic diversity, reflecting Brazil's highly mixed genetic population[37]. As one of the few extensive cohorts from a low- and middle-income country, the BHRC has achieved a high retention rate of 83%. Analyses of baseline characteristics indicated that attrition across waves was generally limited: respondents and non-respondents did not differ substantially in socioeconomic status or school grade, although maternal education consistently predicted non-response, with children of less educated mothers more likely to be lost to follow-up (Supplementary Table S18). Attrition was also higher among participants with baseline anxiety disorders, whereas other baseline psychiatric conditions did not show consistent

differences. Additionally, at wave 3, a higher proportion of non-respondents were male compared to baseline participants. Importantly, potential selection biases at study entry were previously examined and reported[1], with some differences observed in the high-risk stratum but no systematic biases in the random selection group. This suggests that selection bias is unlikely to have substantially influenced results overall, although the differential attrition by sex, maternal education, and anxiety should be acknowledged.

The cohort has generated 147 publications as of August 2025. A complete list of publications is available at https://osf.io/ktz5h/wiki/Bibliographic%20repository/. Most importantly, the study contributed to capacity building and human resources, with many publications led by students and early-career researchers, including 13 by master's students, 65 by PhD students, 11 by undergraduate research assistants, and 12 by post-doctoral fellows.

Weaknesses: The sample is non-probabilistic and based on urban state-funded schools, which limits the generalizability of findings to the broader population. Additionally, while the BHRCS' primary focus on mental health has enabled in-depth study of psychiatric conditions, this emphasis limits investigations into physical health. Finally, our functional neuroimaging protocol used in waves 0, 1, and 2 (established in 2009) may not meet the current reliability standards required for functional analyses.

Can I get hold of the data? Where can I find out more?

The BHRC is committed to open science. De-identified data can be requested via a brief proposal through the project's Open Science Framework (OSF) page (https://osf.io/ktz5h/). Upon approval by the principal investigators (PIs), data are shared securely. A detailed data dictionary, protocol documentation, wikis, and data-cleaning code are available to facilitate secondary analyses. Researchers interested in collaborating on the project are encouraged to contact Giovanni A. Salum (gsalumjr@gmail.com) and Pedro M. Pan

(pedromariopan@gmail.com). Part of our imaging data is also readily available at https://reprobrainchart.github.io.

Ethics approval

The study was approved by the Brazilian National Ethics in Research Commission (CAAE 13852413010015327 and 74563817.7.1001.5327). For Screening, Wave 0, Wave 1, and Wave 2, written consent was obtained from parents and, when appropriate, assent or consent from participating children. For those unable to read or write, verbal agreement was documented after a researcher explained procedures and answered questions. Families could schedule appointments with study psychologists and social workers to receive results and referrals when indicated. By Wave 3, participants had reached the legal age of consent; consent was obtained directly from them. For participants lacking legal capacity, consent was obtained from parents/guardians with verbal assent from the participant. Situations involving risk of harm received special attention consistent with ethical guidelines.

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Conflict of Interest:

AC declares receiving consulting fees from Knight Therapeutics and EMS pharmaceuticals in the last three years, unrelated to the current study.

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Supplementary material

Supplementary material is available at IJE online

Use of Artificial Intelligence (AI) tools

AI tools were not used in this manuscript.

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Figure captions

Figure 1 - Study Design

Abbreviations:

A. Locations and Sampling
RS – Rio Grande do Sul (Porto Alegre)
SP – São Paulo

B. Instruments and Scales
ABCL – Adult Behavior Checklist
ASR – Adult Self-Report
CAPE – Community Assessment of Psychic Experiences
CBCL – Child Behavior Checklist
CRISIS – The Coronavirus Health Impact Survey
CSSRS – Columbia-Suicide Severity Rating Scale
DAWBA – Development and Well-Being Assessment
ECDI-30 – Early Childhood Development Index (30 items)
EMA – Ecological Momentary Assessment
GAD-7 – Generalized Anxiety Disorder 7-item Scale
GSED – Global Scale for Early Development
K6 – Kessler Distress 6-Item Scale
M-CHAT – Modified Checklist for Autism in Toddlers
MINI – Mini International Neuropsychiatric Interview
m-IPIP – Mini International Personality Item Pool
PHQ-9 – Patient Health Questionnaire-9
SCARED – Screen for Child Anxiety Related Emotional Disorders
SDQ – Strengths and Difficulties Questionnaire
WEMWBS / WEMWB – Warwick-Edinburgh Mental Well-Being Scale
YSR – Youth Self-Report

C. Biological and Digital Measures
EEG – Electroencephalography
GPS – Global Positioning System
MRI – Magnetic Resonance Imaging

Alt text:

Schematic summary of the Brazilian High-Risk Cohort for Mental Conditions (BHRCS). Panel A shows a map of Brazil indicating the two cities from which participants were selected and depicts the selection process, combining high-risk and random selections. Panel B outlines longitudinal design across four waves (2010 to ongoing), indicating generations assessed, questionnaires, biological collections, and neuroimaging. Panel C presents cohort age distribution, MRI scan counts, and retention rates over time.

Figure 2 - Milestones and major findings

Alt text:
Timeline summarizing the development of the Brazilian High-Risk Cohort for Mental Conditions (BHRCS) from 2009 to 2024. It depicts major milestones including cohort creation, partnerships, data collection waves, and key research focuses such as childhood

adversity, brain development, education, depression, anxiety, poverty, and measurement of mental health. The figure highlights institutional collaborations, methodological expansions, and ongoing longitudinal follow-ups leading to the fourth wave of data collection between 2023 and 2024.