The importance of clinical factors beyond psychosocial adversity and sex, on clinical outcome in a population at risk for ADHD.

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Looking beyond psychosocial adversity and sex: Clinical factors associated with ADHD and other psychiatric disorders in a non-Caucasian sample of high-risk siblings

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Highlights

- Our study found a 12-fold higher recurrence risk for ADHD in high-risk siblings.

- High psychosocial adversity and male sex significantly increase ADHD risk in siblings.

- HPAd increases ADHD risk, and it is linked to other psychopathologies.

- Males in high-risk siblings show a higher ADHD probability.

- A holistic understanding involves evaluating beyond HPAd and sex.

Manuscript

Looking beyond psychosocial adversity and sex: Clinical factors associated with ADHD and other psychiatric disorders in a non-Caucasian sample of high-risk siblings.

Short title:

The importance of clinical factors beyond psychosocial adversity and sex, on clinical outcome in a population at risk for ADHD.

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Authors' contribution: CALJ and JDPO wrote the study protocol and design. JDPO, JVE, and MMZ conducted psychiatric interviews with the participants. JVE reviewed all the surveys and cleaned the database. JEM performed statistical analyses. LPC, JEM, MMZ, JVE, CALJ, and JDPO contributed to data analysis and manuscript writing. All authors contributed to and approved the final manuscript, and it has not been published in any other journal or scientific publication. All authors are responsible for all aspects of the work, and also, they are responsible for the integrity of every part of the work. The authors declare that they did not use any AI technology.

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This study complied with the regulations for research involving human subjects, as mandated by Colombian laws and the Declaration of Helsinki of 2013. The study

was approved by the ethics committees of the participating centers (Certificate of the Medical Research Institutes dated May 24, 2013).

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Abstract

This study examined the association of clinical factors, independent of sex and high psychosocial adversity (HPAd), with the presence of ADHD or other mental disorders, specifically within a middle-income country with a non-Caucasian population. A multi-centric cross-sectional study was conducted in three sites in Colombia. Our study recruited trios of an ADHD proband, one sibling, and one parent. We used valid instruments for assessing parents and siblings. The sample included 223 siblings, an average age of 12.3 (SD 3.9), and 51.1% Females. The

ADHD recurrence risk ratio (λ) was 12. The clinical factors mainly associated with the presence of ADHD, independent of sex and HPAd, were 1) Pregnancy and childbirth complications, 2) Delayed psychomotor development, 3) Temperament, and 4) Sleep disturbances. Our research showed that, independently of HPAd and the male sex, there were other clinical factors associated with ADHD and other psychiatric disorders in this population. These findings need to be replicated in similar populations globally.

Keywords: Risk factor; Psychopathology; Latinos; Developing countries; Child development; Adolescent; Environment;

1. Introduction

The Attention-Deficit Hyperactivity Disorder (ADHD) is a neurodevelopmental disorder that persists throughout life (American Psychiatric Association, 2013). It has a global prevalence of 7.2% and has become one of the leading reasons for mental health consultations in children and adolescents (Thomas et al., 2015).

The interplay between genetic and environmental factors may manifest distinctively, thereby providing valuable insights into the underlying mechanisms of ADHD (Faraone et al., 2024; Steinhausen, 2009). Twin studies suggest an average concordance of 75% in monozygotic twins (Faraone et al., 2000). Furthermore, siblings of ADHD patients have a recurrence risk ratio (λ) of around nine, meaning

siblings of ADHD probands are nine times more likely to develop ADHD than the general population (Chen et al., 2008). This recurrence is even higher when there is a comorbidity in ADHD probands, reaching a λ of 26.2 in these siblings (Faraone et al., 2000). These findings identify these siblings of ADHD probands as a high-risk population, often called "siblings at high risk" (SHR). Studying SHR offers the advantage of not only identifying the transmission of ADHD as a diagnosis in siblings. Additionally, this model allows for partial control of genetic factors shared with the proband and in-depth investigation of environmental factors (Wade et al., 2015).

Despite genetic influences, environmental factors have a role crucial in comprehending ADHD's multifaceted development. There are a great variety of environmental factors, on one hand, high psychosocial adversity (HPAd) significantly contributes to the onset of mental disorders like ADHD (Gómez-Cano et al., 2021). Sir Michael Rutter emphasized that the cumulative effect of psychosocial adversity increases risk for mental disorders (Rutter, 1999). Other studies confirm the additive impact of adversities on mental health outcomes in at-risk individuals (Benjet et al., 2009, 2011; Østergaard et al., 2016). Some findings indicated that higher environmental adversity correlated with increased ADHD risk and comorbidity in girls and boys, with boys showing more vulnerability to adverse cognitive and interpersonal outcomes. In the presence of psychosocial adversity, the male sex not only confers a higher vulnerability to ADHD but also to other psychiatric disorders (Biederman et al., 2002). On the other hand, some studies point out clinical factors involved in the etiology of ADHD, such as pregnancy complications like preeclampsia and low Apgar scores (Sauver et al., 2004), delivery complications

such as cesarean section, low birth weight, premature birth, and low Apgar scores (Halmøy et al., 2012), cesarean section births (Chen et al., 2023), psychomotor development delays in fine and gross motor skills (Marín-Méndez et al., 2017; McLeod et al., 2014), high activity, difficult temperament (Gurevitz et al., 2014), and sleep problems (Loram et al., 2023) among others.

Despite these advances reported in the international literature in understanding environmental factors associated with the development of ADHD, there remain unresolve issues. Most of the reported results come from samples of subjects predominantly concentrated on the caucasian populations and from high-income countries, resulting in constrained applicability of findings to other demographic groups. The non-caucasian populations may encounter unique socio-economic and cultural influences that can impact the expression, diagnosis, and management of ADHD (Yang et al., 2011). Furthermore, the non-caucasian populations demonstrate heightened genetic diversity compared to caucasian counterparts (Liu et al., 2020). Moreover, although 90% of children and adolescents reside in middle- and low-income nations, only approximately 10% of publications in international scientific literature focus on this demographic (Kieling et al., 2011). Hence, prioritizing studies addressing this population is imperative.

Finally, various studies have demonstrated that siblings of ADHD patients do not necessarily inherit ADHD itself but may inherit other mental disorders (Yang et al., 2011). Some authors conducted studies in the caucasian population compared with control siblings, and they determined the heightened risk for mental disorders

in SHR (Faraone et al., 1996; Geller et al., 2007; Larsson et al., 2013; Schuler et al., 2012; Steinhausen et al., 2012). Otherwise, reports within the non-caucasian populations are limited (Keshavarzi et al., 2014; Palacios-Cruz et al., 2014; Yang et al., 2011), and though they conclude a similar prevalence of SHR for developing ADHD compared to studies in the caucasian populations, these studies occur within environments with different psychosocial adversity components.

Considering all mentioned above, we aimed to investigate the association between clinical factors and the likelihood of ADHD or other mental disorders in SHR, controlling for psychosocial adversity and sex, specifically within a middle-income country with a non-caucasian population.

2. Methods

Prior approval by the scientific and ethical committees of the participating centers (Certificate of the Medical Research Institutes dated May 24, 2013) and by Colombian laws and the Helsinki Declaration of 2013, we conducted a multi-centric, cross-sectional, analytical study in Colombia at three public health sites: San Vicente Fundación Hospital in Medellín, San Juan de Dios Clinic in Manizales, and the Child Psychology Service at IPS Universidad CES in Sabaneta. We collected the sample in these three polluted and overcrowded urban cities. Their population has high socioeconomic inequality, and the majority live in a low socioeconomic stratum with high population density, which can lead to high levels of psychosocial adversity.

The PHARCE Project (Spanish acronym: *"Psicopatología en Hermanos Alto Riesgo según Contexto adverso Enfrentado"*) is an initiative to study at-risk populations for ADHD such as SHR (Gómez-Álzate et al., 2021).

2.1. Participants

Once the informed consent of the parents and the voluntary informed assent of the minors were obtained, we recruited for our study "triplets," which consisted of an ADHD proband, one SHR, and one parent participant (PP). First, over three years, we identified these triplets from the centers' databases, and then we contacted possible candidates by phone to confirm eligibility. Clinicians with at least 15 years of experience made ADHD diagnoses based on DSM 5 criteria through a clinical interview applied to multi-informant children/adolescents and their parents. A child and adolescent psychiatrist (JDPO) with 25 years of experience verified that probands met DSM-5 criteria. For each proband, we selected one SHR who met the inclusion criteria of being between six and 21 years old and sharing the same biological mother as the proband.

Clinical evaluators who participated in this study decided to include children and adolescents if they had sufficient cognitive capacity to understand the instructions, reliably answer the clinical interview, and fill out the scales. Additionally, the parent had to be fluent in Spanish, capable of reading and writing, and willing to participate in the study voluntarily. We excluded trios in which either the proband or SHR had a severe comorbidity that better explained the ADHD symptoms. We

excluded probands and siblings who were institutionalized. We also eliminated triplets where a parent could not provide the necessary information.

2.2. Instruments

In the evaluation of triplets, we use the same instruments for the siblings, both ADHD probands and SHR. We utilized a standardized data collection sociodemographic questionnaire (SocDemQ) designed by Palacios et al. (2014) for a previous SHR study in Mexico.

To confirm the clinical diagnosis of ADHD, in addition to being based on the DSM-5 criteria, we decided to rely on the scale ADHD Rating Scale version for DSM-IV (ADHD-RS-IV) (Zhang et al., 2005). ADHD-RS-IV has been validated in Spanish and is commonly used in multiple studies to diagnose ADHD (Vallejo-Valdivielso et al., 2019). This scale is a self-administered format, but we decided that the clinicians used the ADHD-RS-IV. The scale has shown moderate inter-rater reliability, with an ICC higher than 0.6 in different studies and adequate internal consistency, with reports of Cronbach's α between 0.79 and 0.83.

We used the Brief Psychiatric Evaluation Scale – Modified Adolescent Clinic (BPRS C-25) (De la Peña, 2003) to evaluate the presence of psychiatric symptoms in children. The BPRS has been validated in a Mexican sample and has demonstrated adequate inter-rater and test-retest reliability with ICC values of 0.824

and 0.661, respectively. We used the BPRS-C score as another measure to demonstrate the severity of psychopathology in SHR.

To determine the global level of functioning in our clinical sample, we decided to use the Children's Global Assessment Scale (CGAS) (Shaffer et al., 1983). The CGAS measure provides a global rating on a scale of 0-100 in a hypothetical health-disease continuum. A higher CGAS score corresponds to better functioning. We determined the worst level of functioning over the past three months for both probands and SHRs.

In the case of PP, since one of the criteria of Rutter's psychosocial adversity index is psychopathology, we used the following clinimetric instruments for that purpose. The Mini-International Neuropsychiatric Interview (MINI) (Sheehan et al., 1998) validated in Spanish (Bobes J., 1998) was used to assess and diagnose psychiatric disorders in PP. The instrument's specificity for the disorders we studied ranges between 72% and 97%, with kappa coefficients of 0.88 to 1.0 for inter-rater reliability and between 0.76 and 0.93 for test-retest reliability. We used two sections of the Structured Clinical Interview for DSM-5 Disorders-Clinician Version (SCID-5-CV)) (Shabani et al., 2021) to diagnose borderline personality disorder (BPD) or antisocial personality disorder in the PP. The instrument demonstrated sensitivity and specificity greater than 80% for most diagnoses, with kappa coefficients greater than 0.80. We used the Adult ADHD Self-Report Scale (ASRS) (Kessler et al., 2007) alongside the MINI interview to support the diagnosis of current ADHD in PP. The scale has adequate internal consistency with Cronbach's α between 0.63 and 0.72

and test-retest reliability between 0.58 and 0.77. It has been validated in the Mexican population (Reyes-Zamorano et al., 2009).

The Family APGAR scale assesses family functioning and has been validated in Colombia (Forero et al., 2006)*.* The accepted cut-off point to determine if family dysfunction existed was <7. The scale has demonstrated adequate internal consistency, with Cronbach's α: 0.79. Only children completed the scale.

2.3. Procedures

Clinicians gathered participants' age, sex, educational attainment, family's socioeconomic status, number of family members, and other related information through *SocDemQ* (Palacios-Cruz et al., 2014). During the interview with the PP, the clinicians investigated the personal history of SHR to assess personal antecedents (See Appendix 1). The team conducted clinical interviews with ADHD probands, their SHR, and their PP. The team obtained lifetime diagnoses after these interviews.

ADHD probands, SHR, and PP completed scales under the supervision of a psychologist with at least eight years of clinical experience (JVE). The average duration of the evaluation was three hours. Besides, we organize a board review led by a child psychiatrist (JDPO). The Board certified the diagnoses of ADHD in probands and SHR and excluded dubious cases.

We used five of six Rutter's indicators for the assessment of HPAd (Biederman et al., 2002): a) *Low socioeconomic level* is equivalent to the lowest levels on the graduated scale of socioeconomic strata (levels 1 and 2). In Colombia, the scale ranges from level 1=, the lowest, to level 6=, the highest; b) **L*arge family*** was considered a household with three or more children; c) *Parental criminality*, we looked at the legal background or behavior of the PP. We considered it positive if the PP had a history of criminal proceedings or an antisocial personality disorder; d) *Psychiatric disorders in the PP*, it was considered positive if the PP had at least two psychiatric disorders during the parenting period; e) *Family conflict* was determined if there were two or more of the following: a single-parent family, more than one verbal argument per month at any time in the children's lives, physical violence by one of the parents at least once every six months, marital discord that led to parental separation, and a score of 6 points or less on the family APGAR. According to a previous study by Benjet et al. (2009) in Latin America, we determined that three or more adversity factors were HPAd, and f) Institutionalization was not considered for our study.

2.4. Data analysis

For the exploratory analysis of the data, we proceeded with the general evaluation to identify atypical, extreme, or missing data and obtain general descriptive data. Treatment for missing data was carried out through simple imputation if there was a maximum of 15% of the data for each independent variable.

After this, the normal distribution of the data was evaluated through the Kolmogorov-Smirnov test since there were more than 50 observations per variable.

As the objective of our current report, first, we performed the univariate or descriptive analysis of the categorical variables of the study, and an analysis of proportions and frequency distributions was carried out. The variables to analyze were a) sex, b) HPAd, and c) factors associated with ADHD, in addition to HPAd, according to Rutter (Østergaard et al., 2016; Rutter, 1999), such as perinatal history, history of complications in pregnancy, complications in childbirth, delayed psychomotor development, report of sleep disturbances, mother's age range at the time of birth and socioeconomic level, d) comorbid mental disorders in axis I defined by the DSM-5 criteria. For continuous and ordinal variables, dispersion and central tendency measures were used. These variables were: a) age of onset of ADHD, b) age of the mother at the time of birth, c) severity of ADHD, and d) number of comorbid disorders.

According to the study's objective, in the bivariate analysis, Pearson's X2 and linear trend and Fisher's exact test were used (2x2 and 3x2 contingency tables), using as independent variables: a) sex and b) HPAd. Additionally, as dependent variables: siblings with ADHD (SWA) versus siblings with another psychiatric disorder (SAPD) versus siblings without psychiatric disorder (SWPD). In this way, in the first step, unadjusted odds ratios were obtained using logistic regression analysis for the prediction of each outcome variable for each independent variable, and in the second step, logistic regression analysis was used to determine the magnitude of

the association adjusted by sex (male), and having three or more psychosocial adversities (HPAd), according to the Rutter indicators.

We calculated λ for our sample by dividing the incidence of ADHD in SHR by the incidence of ADHD in the country, which is 2.6%, according to the latest study in Colombia (Gomez Restrepo et al., 2015). Besides, the recurrence-risk ratio of disease in siblings λ was calculated for ADHD. The statistic λ was defined as the probability of an individual having the disease given that one of the siblings also has it, divided by the population prevalence of the disease.

For type I error, statistical significance was established when p<0.05, for type II error β = 0.20, and statistical power was established at 0.80 (1 − β). The IBM SPSS Statistics 22 statistical package was used to analyze the data, and the R Project was used to prepare the graphs and tables.

3. Results

The sample consisted of 223 trios. The siblings had a mean age of 12.3 (SD 3.9), and 51.1% (N=114) were female. The λ for ADHD was 12. Only 31.4% (n=70) of siblings presented ADHD (group SWA), followed by 30.9% (n= 69) who had another psychopathology (group SAPD), and 37.7% (n=84) who did not present either ADHD or other mental health conditions (group SWPD). It is worth mentioning that only 24.2% (N=54) reported HPAd. Among SWA (N=70), 62.9% (N=44) had an ADHD combined presentation, and the rest had a predominantly inattentive presentation.

When comparing clinical and sociodemographic characteristics among the three groups, significant differences were observed in the SWA group compared to the other two groups **(see Table 1 and Table 2)**, particularly about the likelihood of being male (SWA 61.4% vs SWPD 44%; $p < 0.05$, OR = 5.9, 95% CI 2.4 to 17.1, vs SAPD 42%, OR 2.2, 95% CI 1.1 to 4.4). Pregnancy complications were more likely to be associated with SWA when compared to SWPD or SAPD (SWA 31.4% vs SWPD 14.3%, $p < 0.05$, OR 2.8, 95% CI 1.3 to 6.2 vs SAPD 15.9%, OR 2.4, 95% CI 1.1 to 5.6). Complications during childbirth were significantly more frequent in SWA when compared to SWPD or SAPD (SWA 31.4% vs SWPD 7.1%, $p < 0.01$, OR 6.0, 95% CI 2.4 to 17.1 vs SAPD 11.6%, OR 1.0, 95% CI 0.4 to 2.4). The report of delayed psychomotor development was significantly about three times more frequent in SWA when compared to SWPD. The association mentioned above was even more pronounced when compared to SAPD (SWA, 20%; SWD 8.3%, OR 2.8, 95% CI 1.1 to 7.7; SAPD 4.4%, OR 5.5, 95% CI 1.7 to 24.7).

Please insert Table 1 and Table 2 here.

When adjusting for sex and HPAd, most of the associations remained significant. It is striking that the alterations in psychomotor development only remained significant when comparing SWA versus SAPD, with almost five times higher likelihood of finding these alterations in SWA (OR 4.7, 95% CI 1.4 to 21.8). The association of a history of sleep disturbances remained significant only in favor of SWA compared to the other two groups (SWA vs. SWPD OR 4.2, 95% CI 1.7 to

11.7; vs SAPD OR 2.6, 95% CI 1.1 to 7.0). Lastly, the association of a history of alcohol or tobacco use remained significant in favor of SWA when compared to the other two groups (SWA vs SWPD OR 12.3, 95% CI 5.0 to 34.5; vs. SAPD OR 4.1, 95% CI 1.9 to 9.4). For more detailed information about these results, **see Appendix 2 and Appendix 3**.

When individually comparing mental disorders among SWA versus SAPD (**see Table 3**), presenting an ODD was four times more likely in SWA (SWA, 50% vs. SAPD 18.8%, OR 4.3, 95% CI 2.0 to 9.5). Also, presenting an SLD had a probability greater than three times in favor of those siblings with ADHD (SWA 14.3% vs. SAPD 4.4%, OR 3.7, 95% CI 1.1 to 16.9). These associations showed statistical significance for both disorders, even after controlling for sex and HPAd (ODD: OR 3.4, 95% CI 1.6 to 7.8; SLD: OR 4.4, 95% CI 1.2 to 21.4).

Please insert Table 3 here.

4. Discussion

Our study aimed to investigate, in siblings of probands with ADHD from a middle-income country, the association of risk factors beyond sex and HPAd, as per the criteria established by Rutter and colleagues (Østergaard et al., 2016; Rutter, 1999), and the clinical status of these siblings at the time of clinical evaluation, specifically whether they exhibited ADHD, another psychiatric disorder, or no signs of psychopathology. Our results demonstrated that irrespective of HPAd and sex

(male), parental reports of complications during pregnancy, birth complications, and delayed psychomotor development were significantly associated with a higher likelihood of being present in high-risk siblings with ADHD or another psychiatric disorder compared to those without psychopathology. This association was notably more significant in siblings with ADHD, especially when compared to those with other psychiatric disorders (SAPD). Our findings enable us to discuss four specific points below.

4.1. Risk for SHR for ADHD

As expected, we confirm that in this SHR population, the most frequent psychopathology was ADHD. It had a recurrence risk of 12 (Chen et al., 2008; Gomez Restrepo et al., 2015), surpassing the λ of 9 reported by Yang (2011). Approximately 31.4% exhibited ADHD, aligning with previous studies, notably Yang et al.'s initial study reporting a 34% rate (Yang et al., 2011). Similar percentages were observed across high- and middle-income countries, which had a rate of 45.2 (Palacios-Cruz et al., 2014). However, variations in SHR studies, considering sample origin and exposure to HPAd, must be considered. This finding leads us to acknowledge the importance of the study's design characteristics, which enable us to investigate new variables while controlling for well-documented variables like HPAd or shared genetic factors.

The "sibling of probands with ADHD model" proves invaluable for studying health conditions with complex etiologies where heritability is a significant contributor. This model enhances our understanding of neurodevelopment

processes and psychopathology genesis, even in the early stages (Wade et al., 2015).

Beyond psychopathology figures, it is noteworthy that over 35% of SHR did not exhibit any mental disorder. These "resilient" individuals share psychosocial and biological adversities with probands. Future longitudinal studies in these high-risk populations should prioritize investigating mechanisms influencing the absence of ADHD or other psychopathologies. The SWPD group, comprising siblings who share part of the genetic material of the ADHD probands, was chosen as the control group. We made this decision based on the fact that these participants did not develop psychiatric disorders, making them an ideal reference group to contrast the clinical outcomes in the other two groups (SWA and SAPD) in the presence of clinical risk factors.

Our subsequent purpose was to determine the association between psychosocial adversity, male sex, and other psychosocial risk factors with the clinical status of individuals in this sample.

4.2. Psychosocial adversity and the male sex increase the risk of presenting ADHD in the SWA group.

We observed in the SWA group an increased risk of ADHD associated with HPAd and male sex. Elevated psychosocial adversity heightened the likelihood of developing ADHD, as seen in studies on children, adolescents, and the SHR

population (Benjet et al., 2011; Brown et al., 2017; Gómez-Cano et al., 2021). Additionally, HPAd is correlated with an increased risk of other psychopathologies beyond ADHD.

HPAd lacks a standardized definition and is explored through various lenses, including Adverse Childhood Experiences (ACEs). These events play a crucial role in mental disorders' development from childhood to adulthood (Edwards et al., 2003; Schilling et al., 2007). Specifically, some studies have shown that individuals with ADHD report a higher frequency of exposure to adverse psychosocial events (Østergaard et al., 2016). However, not all kinds of adversity equally affect individuals. For example, one study revealed that all psychosocial adversity indicators, except family size, showed a significant association with the presentation of ADHD (Biederman et al., 2002). Subsequent research (Reimelt et al., 2021) has confirmed that there is no relationship between the number of siblings and the risk of developing ADHD. These findings lead us to reflect on what other clinical risk factors may be involved in ADHD.

The multifactorial etiological model of ADHD has generated varied perspectives on the role of psychosocial adversity. Some studies suggest a linear relationship, with an increased risk correlating with the number of adversity factors (Faraone et al., 2019). However, evidence from middle-income countries proposes a non-linear risk, peaking at three adversities beyond which the effect plateaus (Benjet et al., 2010); otherwise, there is a marginal effect on the risk of developing

any mental disorder after that threshold. Hence, our study adopted a cutoff of three or more adversities as a risk factor for any mental disorder.

Evolution in understanding the role of sex in ADHD considers a "reference bias" against women. Males in our study exhibited a higher probability of ADHD compared to the other groups. While some attribute this to a genuine higher risk in males (Keshavarzi et al., 2014; Ma et al., 2015; Palacios-Cruz et al., 2014; Silva et al., 2014; Yang et al., 2011), others suggest a possible selection bias (Biederman et al., 2005). Another possibility is how parents perceive ADHD in women; one study indicates that parents do not seek help until additional behavioral or emotional issues occur (Mowlem et al., 2019). Significantly, the male sex, coupled with psychosocial adversity, not only heightens vulnerability to comorbidities but is also associated with poorer global functioning (Biederman et al., 2002). Consequently, we considered the joint presence of HPAd and the sex to assess other candidate variables.

4.3. Exploring risk factors for ADHD beyond psychosocial adversity and sex

One of our primary contributions was demonstrating that certain clinical risk factors remained independent of HPAd and male sex.

Pregnancy complications were more prevalent in the SWA group, which is true even compared to the SAPD group. While some studies found no association between pregnancy complications and ADHD (Sauver et al., 2004), a recent meta-analysis linked certain factors like preeclampsia and low Apgar scores to ADHD (Bitsko et al., 2022). Our results indicated an association between birth

complications and ADHD, independently of HPAd and male sex. This aligns with previous findings, highlighting the impact of factors such as low birth weight, premature birth, and low Apgar scores on ADHD risk (Halmøy et al., 2012). Additionally, meta-analyses suggest a connection between cesarean section births and neurodevelopmental disorders, including ADHD (Chen et al., 2023).

Association with psychomotor development delays remained significant in the SWA group compared to the SAPD group. This supports previous findings that link preschoolers' learning difficulties to delayed psychomotor development, suggesting potential predictive value in motor performance during the first 5 or 6 years for later ADHD symptoms (Marín-Méndez et al., 2017; McLeod et al., 2014). While systematic reviews note methodological heterogeneity, recent research emphasizes the positive link between fine and gross motor skills and academic performance, irrespective of ADHD risk (Havmoeller et al., 2019).

Our results show an association between parents' reports of difficult temperament during early years and ADHD, even when controlling for HPAd and male sex. This finding aligns with a retrospective study indicating difficult temperament before 18 months as part of the predictive model for ADHD (Gurevitz et al., 2014). High activity, a component of difficult temperament, persists in siblings of ADHD probands, emphasizing its role as a risk factor (Andersson-Konke et al., 2023).

Sleep disturbances, reported in 28% of SHR, were three times more common in the SWA group compared to the other two groups. Literature supports the link between sleep problems and a wide range of mental health conditions, including ADHD (Loram et al., 2023). A recent systematic review suggests that early identification of sleep disorders is crucial, recommending interventions to improve behavioral outcomes in these children (Bondopadhyay et al., 2022). Based on the above, we can conclude that both sleep problems and difficult temperament are symptoms that should be considered in the early detection of ADHD in this high-risk population.

Contemporary research unveils that ADHD inheritance is not exclusive, carrying the risk of other mental disorders. Our study expands its focus beyond ADHD, delving into the risk for various psychiatric disorders in SHR. This holistic approach enhances our understanding of the complex interplay of factors influencing ADHD and related conditions in this population.

4.4. Risk of other psychiatric disorders in the SHR

In this SHR sample, ADHD was the most common psychopathology, followed by ODD, GAD, MDD, and SAD. Similar risks were observed in other studies in caucasian (Christiansen et al., 2008; Faraone et al., 1996; Geller et al., 2007; Larsson et al., 2013; Schuler et al., 2012; Sobanski et al., 2010; Steinhausen et al., 2012) and non-caucasian populations (Keshavarzi et al., 2014; Palacios-Cruz et al., 2014; Yang et al., 2011). SHR not only had a higher likelihood of ADHD but also

reported these disorders more frequently than siblings without ADHD or the general population.

Our analysis revealed a greater incidence of ODD and SLD in the SWA group when compared to the SAPD group, even after adjusting for sex and HPAd. Several authors have controlled only for male sex, but few for sex and HPAd (Biederman et al., 2002; Palacios-Cruz et al., 2014). Our findings are in line with the studies mentioned above that concluded that in these siblings, the presence of ADHD increases the risk of presenting comorbidities such as ODD and SLD. Comorbidity of ADHD with ODD indicates a reserved prognosis, emphasizing the need for early identification, especially during behavioral therapy.

SWA exhibited a 12-fold higher risk of alcohol and tobacco use compared to SWPD and a 4-fold higher risk than SAPD. Notably, no heightened risk for substance use disorder was found in SWA. Age plays a role, suggesting that these comorbidities may emerge during adulthood, emphasizing the importance of preventive measures (Yang et al., 2011). This would be an additional reason to work preventively with populations of SHR. This concept becomes increasingly relevant when reviewing studies related to unmet needs, as they suggest that individuals with undiagnosed ADHD face an elevated risk of developing disruptive disorders, substance use disorders, and other conditions.

In summary, our study delves beyond established factors, highlighting pregnancy complications, birth issues, psychomotor delays, temperament, and

sleep problems as independent risk factors for ADHD in SHR. It is essential to acknowledge the limitations of our study: 1) we only assessed one parent to obtain information from the non-participating parent, which could have limited the scope of our conclusions. 2) the mean age of the participant children was 12 years, which is a low age risk for mental disorders such as MDD, BD, or SUD. A follow-up study of this population could provide a more accurate understanding. 3) we have a clinical sample, making it challenging to generalize our findings to the broader community, and 4) However, we included several sociodemographic, clinical, and psychosocial factors in our analysis; we did not incorporate genetic factors that play a significant role in developing mental disorders.

On the other hand, we must mention some strengths of our study. 1) we employed self-report questionnaires and clinical interviews to enhance the credibility of the results. Moreover, the assessment team received guidance, and an experienced child and adolescent psychiatrist scrutinized the evaluations. 2) we utilized the RIA for psychosocial adversity assessment and adopted previous studies' definitions to ensure our findings' comparability. 3) there is a scarcity of research investigating SHR and HPAd as potential factors in ADHD etiology, and 4) conducting studies in non-caucasian populations from middle-income countries is crucial for promoting equity in scientific research and healthcare. Every individual, regardless of their ethnic background, deserves evidence-based healthcare that takes into account their characteristics.

We recommend future research exploring subclinical symptoms, prenatal and perinatal factors, ACEs, and resilience in SHR. A holistic clinical perspective, viewing families as cohesive units, is crucial for understanding challenges related to ADHD care and education. Lastly, we strongly advocate for a family approach that can offer invaluable insights into understanding the dynamics of familial tensions and challenges related to the care and education of children with ADHD.

4.5. Conclusions

Our study demonstrates a significant association between HPAd and the likelihood of SHR developing ADHD and other psychiatric disorders within low to middle-income countries. It also showed that independently of HPAd and male sex, there were other factors associated with a higher risk of ADHD and other psychiatric disorders in these SHRs, such as complications during pregnancy, childbirth, report of psychomotor development alterations, temperament, and sleep problems were associated with a higher risk of ADHD and other psychiatric disorders like ODD and SLD.

Furthermore, our study highlights the intricate interplay between sex, HPAd, and psychiatric risk. Males in the group of SHR with ADHD demonstrated a notably higher probability of ADHD, aligning with some previous research. However, sex's exact role remains complex within a multifactorial etiological model. This research underscores the significance of family-based screenings, early interventions targeting precursor deficits, and further investigations into the comprehensive role of psychosocial adversity in this context.

Acknowledgment

Table 1 - Clinical and Sociodemographic Characteristics of High-Risk Siblings, by Groups (SWPD, N=84), (SAPD, N=69), (SWA, N=70).

Variable	SWPD	SAPD	SWA
	Mean (SD)	Mean (SD)	Mean (SD)
Age (years)*	12.6 (4.0)	13.1 (4.0)	11.2 (3.5)
Family APGAR score**	8.6 (1.6)	8.1 (1.8)	7.7 (1.7)
BPRS C-25 score**	1.4 (1.8)	7.6 (5.1)	14.8 (7.2)
ADHD-RS-IV score**	2.7 (4.7)	4.1 (4.1)	36.0 (10.8)
CGAS score**	92.3 (12.6)	76.1 (16.1)	55.1 (13.7)
Number of lifetime mental disorders**	-	1.7 (1.1)	3.4 (1.6)

Note: Standard deviation (SD)
ANOVA: * p < 0.05, ** p < 0.01

SWA: siblings with attention-deficit/hyperactivity disorder; SAPD: siblings with another psychopathology; SWPD: siblings with neither attention-deficit/hyperactivity disorder nor other mental conditions; SD: Standard deviation; Family APGAR: scale for assessment of family functioning; BPRS C-25: brief psychiatry rating scale children 25 items; ADHD-RS-IV: attention-deficit/hyperactivity disorder rating scale forth; CGAS: Children's Global Assessment Scale; Standard deviation (SD); ANOVA *p-value < 0.05

Table 2 - Clinical, Sociodemographic, and Psychosocial Adversity Characteristics of High-Risk Siblings, by Groups (SWPD, N=84), (SAPD, N=69), (SWA, N=70), adjusted for sex and psychosocial adversity.

	SWPD N (%)	SAPD N (%)	SWA N(%)	OR NOT ADJUSTED (CI 95%)	OR ADJUSTED (CI 95%)
Perinatal history					
Male*	37 (44.0)	29 (42.0)	43 (61.4)		
SWPD[1] vs SAPD				1.7 (0.5-5.4)	
SWPD[1] vs SWA				5.9 (2.4-17.1)	
SAPD[1] vs SWA				2.2 (1.1-4.4)	
Maternal age of risk for pregnancy*	18 (21.4)	11 (15.9)	29 (41.4)		
				0.7 (0.3-1.6)	0.7 (0.3-1.6)
SWPD[1] vs SAPD				2.6 (1.3-5.3)	3.6 (1.7-7.9)
SWPD[1] vs SWA				3.7 (1.7-8.6)	6.3 (2.6-16.5)
SAPD[1] vs SWA					
Complications during pregnancy*	12 (14.3)	11 (15.9)	22 (31.4)		
				1.1 (0.5-2.8)	1.1 (0.5-2.8)
SWPD[1] vs SAPD				2.8 (1.3-6.2)	3.4 (1.5-8.4)
SWPD[1] vs SWA				2.4 (1.1-5.6)	2.9 (1.2-7.2)
SAPD[1] vs SWA					
Complications during childbirth*	6 (7.1)	8 (11.6)	22 (31.4)		
				1.7 (0.6-5.4)	1.7 (0.6-5.3)
SWPD[1] vs SAPD				6.0 (2.4-17.1)	5.2 (2.0-15.5)
SWPD[1] vs SWA				1.0 (0.4-2.4)	1.1 (0.4-2.8)
SAPD[1] vs SWA					
Psychomotor delay	7 (8.3)	3 (4.4)	14 (20.0)		
SWPD[1] vs SAPD				0.5 (0.1-1.9)	0.5 (0.1-1.9)
SWPD[1] vs SWA				2.8 (1.1-7.7)	2.4 (0.9-7.0)
SAPD[1] vs SWA				5.5 (1.7-24.7)	4.7 (1.4-21.8)
Dificult temperament*	13 (15.5)	15 (21.7)	31 (44.3)		
SWPD[1] vs SAPD				1.5 (0.7-3.5)	1.6 (0.7-3.7)
SWPD[1] vs SWA				4.3 (2.1-9.5)	4.9 (2.2-11.1)
SAPD[1] vs SWA				2.8 (1.4-6.1)	3.0 (1.4-6.6)
Personal medical history					
Sleep problems in the preschool	7 (8.3)	8 (11.6)	20 (28.6)		

stage**					
SWPD[1] vs SAPD				1.4 (0.5-4.3)	1.5 (0.5-4.5)
SWPD[1] vs SWA				4.4 (1.8-11.9)	4.2 (1.7-11.7)
SAPD[1] vs SWA				3.0 (1.3-7.9)	2.6 (1.1-7.0)
Feeding problems	12 (14.3)	6 (8.7)	12 (17.1)		
SWPD[1] vs SAPD				0.6 (0.2-1.6)	0.6 (0.2-1.5)
SWPD[1] vs SWA				1.2 (0.5 a 3.0)	1.2 (0.5-3.2)
SAPD[1] vs SWA				2.2 (0.8 a 6.6)	1.9 (0.7-6.1)
Allergies	6 (7.1)	5 (7.3)	6 (8.6)		
SWPD[1] vs SAPD				1.0 (0.3-3.5)	1.0 (0.3-3.6)
SWPD[1] vs SWA				1.2 (0.5-3.0)	0.9 (0.3-3.2)
SAPD[1] vs SWA				2.2 (0.8-6.6)	0.9 (0.2-3.3)
Hospitalizations	22 (21.4)	26 (37.7)	21 (30.0)		
SWPD[1] vs SAPD				1.7 (0.9-3.4)	1.7 (0.8-3.4)
SWPD[1] vs SWA				1.2 (0.6-2.4)	1.0 (0.5-2.2)
SAPD[1] vs SWA				0.7 (0.3-1.4)	0.5 (0.2-1.1)
Surgical interventions*	18 (21.4)	26 (37.7)	28 (40.0)		
SWPD[1] vs SAPD				2.2 (1.1-4.6)	2.3 (1.1-4.7)
SWPD[1] vs SWA				2.4 (1.2-5.0)	2.2 (1.1-4.7)
SAPD[1] vs SWA				1.1 (0.6-2.2)	0.9 (0.4 a 1.9)
Traumatic brain injury	0 (0.0)	2 (2.9)	2 (2.9)		
SWPD[1] vs SAPD				0.0	
SWPD[1] vs SWA				0.0	
SAPD[1] vs SWA				1.0 (0.1-8.4)	
Fractures	15 (17.9)	11 (15.9)	15 (21.4)		
SWPD[1] vs SAPD				0.9 (0.4-2.0)	0.9 (0.4-2.0)
SWPD[1] vs SWA				1.3 (0.6-2.8)	1.1 (0.5-2.4)
SAPD[1] vs SWA				1.4 (0.6-3.5)	1.1 (0.4-2.8)
Chronic medical conditions	3 (3.6)	4 (5.8)	7 (10.0)		
SWPD[1] vs SAPD				1.7 (0.4-2.0)	1.5 (0.3-8.9)
SWPD[1] vs SWA				3 (0.8-14.3)	2.1 (0.5-10.6)
SAPD[1] vs SWA				1.8 (0.5-7.2)	1.1 (0.3-4.8)
Pharmacological treatment**	7 (8.3)	15 (21.7)	34 (48.6)		

SWPD[1] vs SAPD				3.1 (1.2-8.5)	3.1 (1.2-8.7)
SWPD[1] vs SWA				10.4 (4.2-27.6)	12.3 (5.0-34.5)
SAPD[1] vs SWA				3.4 (1.6-7.3)	4.1 (1.9-9.4)
Alcohol or tobacco use*	13 (15.5)	24 (34.8)	20 (28.6)		
SWPD[1] vs SAPD				2.9 (1.4-6.5)	3.0 (1.4-6.7)
SWPD[1] vs SWA				2.2 (1.0-4.9)	2.5 (1.1-5.8)
SAPD[1] vs SWA				0.8 (0.4-1.5)	0.9 (0.4-1.8)
Drug use	2 (2.4)	4 (5.8)	6 (8.6)		
SWPD[1] vs SAPD				2.5 (0.5-18.6)	2.3 (0.4-17.0)
SWPD[1] vs SWA				2.5 (0.8-26.8)	2.4 (0.5-17.6)
SAPD[1] vs SWA				1.5 (0.4-6.2)	1.1 (0.3-4.6)
Psychosocial adversity					
Low socioeconomic status*	11 (13.1)	19 (27.5)	22 (31.4)		
SWPD[1] vs SAPD				2.5 (1.1-5.9)	
SWPD[1] vs SWA				3.0 (1.4-7.1)	
SAPD[1] vs SWA				1.2 (0.6-2.5)	
Large family*	29 (34.5)	18 (26.1)	34 (48.6)		
SWPD[1] vs SAPD				0.7 (0.3-1.3)	
SWPD[1] vs SWA				1.8 (0.9-3.4)	
SAPD[1] vs SWA				2.7 (1.3-5.5)	
Family conflict**	26 (31.0)	36 (52.2)	40 (7.1)		
SWPD[1] vs SAPD				2.4 (1.3-4.8)	
SWPD[1] vs SWA				3.0 (1.6-5.8)	
SAPD[1] vs SWA				1.2 (0.6-2.4)	
Parental criminality	5 (6.0)	7 (10.1)	10 (14.3)		
SWPD[1] vs SAPD				1.8 (0.5-6.3)	
SWPD[1] vs SWA				2.6 (0.9-8.8)	
SAPD[1] vs SWA				1.5 (0.5-4.3)	
Participant parent with 2 or more	28 (33.3)	25 (36.2)	38 (54.3)		
psychiatric disorders*				1.1 (0.6-0.2)	
SWPD[1] vs SAPD				2.4 (1.2-4.6)	
SWPD[1] vs SWA				2.1 (1.1-4.2)	
SAPD[1] vs SWA					
Family with 3 or more adversity factors**	11 (13.1)	14 (20.3)	29 (41.4)		
				1.7 (0.7-4.1)	

SWPD[1] vs SAPD	4.7 (2.2-10.7)
SWPD[1] vs SWA	2.8 (1.3-6.7)
SAPD[1] vs SWA	

χ^2 test for independence: * $p < 0.05$, ** $p < 0.01$

Table 3 - Diagnoses of High-Risk Siblings, by Groups (SAPD, N=69), (SWA, N=70), adjusted for gender and psychosocial adversity.

	SAPD N (%)	SWA N (%)	OR (IC al 95%)
Oppositional defiant disorder **	13 (18.8)	35 (50.0)	3.4 (1.6 a 7.8)
Conduct disorder	1 (1.45)	6 (8.57)	3.9 (0.5 a 67.0)
Separation anxiety disorder	14 (20.3)	14 (20.0)	0.8 (0.3 a 2.0)
Generalized anxiety disorder	24 (34.8)	17 (24.3)	0.8 (0.3 a 1.7)
Social anxiety disorder	7 (10.1)	8 (11.4)	1.2 (0.4 a 3.8)
Obsesive -compulsive disorder	5 (7.25)	2 (2.86)	0.4 (0.0 a 2.3)
Major depressive disorder	15 (21.7)	20 (28.6)	1.3 (0.6 a 3.1)
Persistent depressive disorder	1 (1.45)	1 (1.43)	1.4 (0.0 a 37.4)
Bipolar disorder	0 (0.0)	2 (2.86)	-
Tic disorder	14 (20.3)	13 (18.6)	0.7 (0.3 a 1.7)
Elimination disorder	5 (7.25)	8 (11.4)	1.7 (0.5 a 6.2)
Substance use disorder	3 (4.35)	8 (11.4)	2.0 (0.5 a 6.2)
Specific learning disorders*	3 (4.35)	10 (14.3)	4.4 (1.2 a 21.4)
Language disorder	2 (2.90)	6 (8.57)	2.9 (0.6 a 21.4)
Sleep disorder	7 (10.1)	15 (21.4)	2.1 (0.8 a 6.2)
Panic disorder	2 (2.90)	0 (0.0)	-
Autism spectrum disorder	1 (1.45)	1 (1.43)	0.8 (0.0 a 22.9)

test for independence: * p < 0.05, ** p < 0.01

Appendix 1. Personal Antecedents Variables

Maternal age at risk for pregnancy (under 20 years or over 35 years), complications during pregnancy (threatened preterm labor, placenta previa, hypertension or gestational diabetes, duration less than 36 weeks), complications during childbirth (prolonged labor, use of forceps, indication of cesarean section due to cephalopelvic disproportion), child's complications at birth (indicators such as cyanosis, hypotonia, meconium), perinatal complications (prematurity, low birth weight under 2500 g, perinatal asphyxia, respiratory diseases, neonatal infection), psychomotor retardation (head control after four months, sitting without support after six months, crawling after 12 months, walking after 18 months), difficult temperament (emotional intensity, irregularity, limited adaptability, intense sensitivity, persistence, frustration intolerance, high energy), enuresis (presence of nocturnal bedwetting after the age of five), encopresis (primary or secondary encopresis after the age of four), sleep problems in the preschool stage (insomnia, nightmares, night terrors, sleepwalking, daytime hypersomnia), feeding problems (selective eating, texture sensitivity, marked appetite problems, specific eating disorders), allergies (allergic reaction to any medication used), hospitalizations (hospitalizations for any non-psychiatric medical cause), surgical interventions (history of any surgical intervention), traumatic brain injury (only considered with loss of consciousness exceeding 20 minutes), fractures (including soft tissue injuries and bone fractures), chronic medical condition (asthma, diabetes, chronic kidney disease, inflammatory bowel disease, rheumatoid arthritis), pharmacological treatment (only considered the lifetime use of psychopharmacological treatment prescribed for psychiatric disorders), alcohol or tobacco use (history of experimental use of either), drug use (any experimental use of psychoactive substances). History of abuse (physical, sexual, psychological abuse or neglect), and overcrowding (presence of three or more occupants per room).

Appendix 2 - Clinical and Sociodemographic Characteristics of High-Risk Siblings, by Groups (SWPD, N=84), (SAPD, N=69), (SWA, N=70).

	Odds ratio not adjusted (CI 95%)			Odds ratio adjusted by gender and adversity (CI 95%)		
	SWPD[1] vs SAPD	SWPD[1] vs SWA	SAPD[1] vs SWA	SWPD[1] vs SAPD	SWPD[1] vs SWA	SAPD[1] vs SWA
Male*	1.7 (0.5-5.4)	5.9 (2.4-17.1)	2.2 (1.1-4.4)	-	-	-
Maternal age at risk for pregnancy**	0.7 (0.3-1.6)	2.6 (1.3-5.3)	3.7 (1.7-8.6)	0.7 (0.3-1.6)	3.6 (1.7-7.9)	6.3 (2.6-16.5)
Complications during pregnancy*	1.1 (0.5-2.8)	2.8 (1.3-6.2)	2.4 (1.1-5.6)	1.1 (0.5-2.8)	3.4 (1.5-8.4)	2.9 (1.2-7.2)
Complications during childbirth**	1.7 (0.6-5.4)	6.0 (2.4-17.1)	1.0 (0.4-2.4)	1.7 (0.6-5.3)	5.2 (2.0-15.5)	1.1 (0.4-2.8)
Psychomotor delayed**	0.5 (0.1-1.9)	2.8 (1.1-7.7)	5.5 (1.7-24.7)	0.5 (0.1-1.9)	2.4 (0.9-7.0)	4.7 (1.4-21.8)
Difficult temperament **	1.5 (0.7-3.5)	4.3 (2.1-9.5)	2.8 (1.4-6.1)	1.6 (0.7-3.7)	4.9 (2.2-11.1)	3.0 (1.4-6.8)
Enuresis	1.0 (0.3-3.5)	2.4 (0.9-7.4)	2.4 (0.8-7.9)	1.0 (0.3-3.6)	2.1 (0.7-6.6)	1.9 (0.6-6.6)
Encopresis	-	3.2 (0.7-22.5)	-	-	-	-
Sleep problems in the preschool stage**	1.4 (0.5-4.3)	4.4 (1.8-11.9)	3.0 (1.3-7.9)	1.5 (0.5-4.5)	4.2 (1.7-11.7)	2.6 (1.1-7.0)
Feeding problems	0.6 (0.2-1.6)	1.2 (0.5-3.0)	2.2 (0.8-6.6)	0.6 (0.2-1.5)	1.2 (0.5-3.2)	1.9 (0.7-6.1)
Allergies	1.0 (0.3-3.5)	1.2 (0.5-3.0)	2.2 (0.8-6.6)	1.0 (0.3-3.6)	0.9 (0.3-3.2)	0.9 (0.2-3.3)
Hospitalizations	1.7 (0.9-3.4)	1.2 (0.6-2.4)	0.7 (0.3-1.4)	1.7 (0.8-3.4)	1.0 (0.5-2.2)	0.5 (0.2-1.1)
Surgical interventions*	2.2 (1.1-4.6)	2.4 (1.2-5.0)	1.1 (0.6-2.2)	2.3 (1.1-4.7)	2.2 (1.1-4.7)	0.9 (0.4-1.9)
Traumatic brain injury	-	-	1.0 (0.1-8.4)	-	-	-
Fractures	0.9 (0.4-2.0)	1.3 (0.6-2.8)	1.4 (0.6-3.5)	0.9 (0.4-2.0)	1.1 (0.5-2.4)	1.1 (0.4-2.8)
Chronic medical condition	1.7 (0.4-7.7)	3 (0.8-14.3)	1.8 (0.5-7.2)	1.5 (0.3-8.9)	2.1 (0.5-10.6)	1.1 (0.3-4.8)
Pharmacological treatment**	3.1 (1.2-8.5)	10.4 (4.2-27.6)	3.4 (1.6-7.3)	3.1 (1.2-8.7)	12.3 (5.0-34.5)	4.1 (1.9-9.4)
Alcohol or tobacco use*	2.9 (1.4-6.5)	10.4 (4.2-27.6)	3.4 (1.6-7.3)	3.1 (1.2-8.7)	12.3 (5.0-34.5)	4.1 (1.9-9.4)
Drug use	2.5 (0.5-18.6)	2.5 (0.8-26.8)	1.5 (0.4-6.2)	2.3 (0.4-17.0)	2.4 (0.5-17.6)	1.1 (0.3-4.6)

1 Reference group

χ^2 test for independence: * p < 0.05, ** p < 0.01

Appendix 3 - Psychosocial Adversity Characteristics of High-Risk Siblings, by Groups (SWPD, N=84), (SAPD, N=69), (SWA, N=70).

	Odds ratio (CI 95%)		
	SWPD1 vs SAPD	SWPD1 vs SWA	SAPD1 vs SWA
Low socioeconomic status*	2.5 (1.1-5.9)	3.0 (1.4-7.1)	1.2 (0.6-2.5)
Large family*	0.7 (0.3-1.3)	1.8 (0.9-3.4)	2.7 (1.3-5.5)
Family conflict**	2.4 (1.3-4.8)	3.0 (1.6-5.8)	1.2 (0.6-2.4)
Parental criminality	1.8 (0.5-6.3)	2.6 (0.9-8.8)	1.5 (0.5-4.3)
Participant parent with 2 or more psychiatric disorders*	1.1 (0.6-.2)	2.4 (1.2-4.6)	2.1 (1.1-4.2)
Family with 3 or more adversity factors**	1.7 (0.7-4.1)	4.7 (2.2-10.7)	2.8 (1.3-6.7)

[1] Reference group
χ^2 test for independence: * $p < 0.05$, ** $p < 0.01$

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Graphical abstract
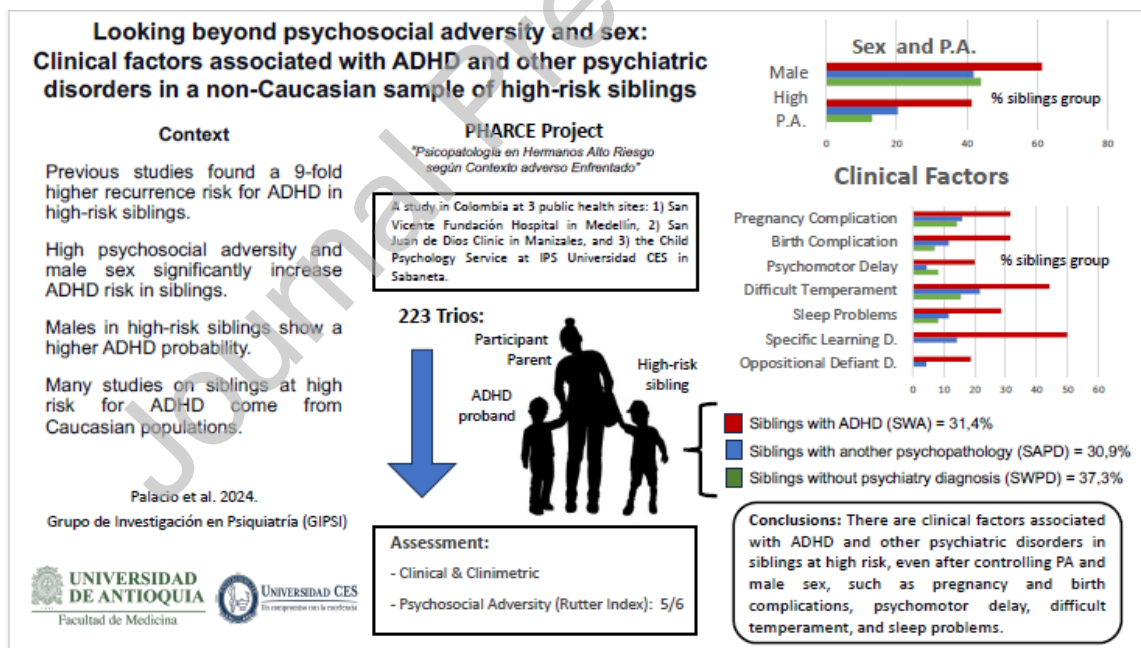
Declaration of interests: None.

This study complied with the regulations for research involving human subjects, as mandated by Colombian laws and the Declaration of Helsinki of 2013. The study was approved by the ethics committees of the participating centers (Certificate of the Medical Research Institutes dated May 24, 2013).