

Prenatal and perinatal factors associated with ADHD risk in school children: EPINED epidemiological study

ABSTRACT

Objective: To assess the relationship between pre and perinatal factors and ADHD in childhood, adjusting for several confounders.

Method: 6720 scholars participated in a double-phase epidemiologic cross-sectional study (Epidemiological Study of Neurodevelopmental Disorders, EPINED). A sample of 646 (ADHD risk, ASD risk, and controls) were assessed with the Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version for performing ADHD diagnosis (DSM-5 criteria). Associations between prenatal, perinatal and postnatal factors and ADHD (n=168), subclinical ADHD (n=88) and non-ADHD (n=310) were analysed using logistic regression models for each ADHD presentations.

Results: Gestational diabetes ($p=.012$), instrumental delivery ($p=.011$), family history of psychopathology ($p=.033$) and maternal ADHD phenotype ($p=.023$) were associated with ADHD, specifically with hyperactive-impulsive and combined presentations. No factors were related to the inattentive presentation.

Conclusion: Metabolic disorder in the pregnancy, difficulties in childbirth and ADHD family phenotype were related to ADHD, specifically with hyperactive-impulsive presentation.

Key words: *ADHD diagnosis; ADHD presentations; risk factors.*

INTRODUCTION

Attention deficit hyperactive disorder (ADHD) is a pervasive neuropsychological disorder that manifests in inattention and overactivity that significantly interferes with the child's functioning in family, social and/or academic settings (Bowling, Tiemeier, Jaddoe, Barker, & Jansen, 2018; DuPaul & Langberg, 2015; Owens, Zalecki, Gillette, & Hinshaw, 2017). According to clinical patterns, ICD-11 and DSM 5 criteria distinguish between predominantly hyperactive-impulsive, inattentive and combined presentations (APA, 2013; WHO, 2019). ADHD begins in the early years of life, but usually persists until adolescence or adulthood. It frequently co-occurs with other neurodevelopmental or emotional and behavioural disorders, which worsens the ADHD clinical course and prognosis (Lara et al., 2009; Reale et al., 2017; Shea, Lee, Lai, Luk, & Leung, 2018). ADHD is a frequent disorder and its prevalence has increased considerably in recent years (Atladdottir et al., 2015; Giacobini, Medin, Ahnemark, Russo, & Carlqvist, 2018). The latest data suggest that the prevalence of ADHD in children and adolescents is around 6-7% (Sayal, Prasad, Daley, Ford, & Coghill, 2018; Thomas, Sanders, Doust, Beller, & Glasziou, 2015). In the Spanish population, Canals, Morales-Hidalgo, Jané, and Domènech (2018) and Ezpeleta, De La Osa, and Domènech (2014) found a prevalence of 2-5% among pre-schoolers, while in the adolescent population the prevalence was around 7% (Catalá-López et al., 2012). The impaired behavioural and neuropsychological functioning of ADHD children is associated with functional and morphological abnormalities in the fronto-striatal circuits. Specifically, several studies have observed a reduced volume and/or activity of grey and white matter and slower maturation of the prefrontal cortex, caudate and cerebellum, which underlies the reduced brain functioning and impaired communication in numerous neural tracts (Arnsten & Pliszka, 2011; Nagel et al., 2011; Nakao, Radua, Rubia, & Mataix-Cols, 2011).

Although ADHD is a widely researched disorder, the underlying aetiology is not well understood. However, the evidence highlights its multicausality since genetics as well as neurological and environmental factors contribute to the pathogenesis of the disorder (Akutagawa-Martins, Rohde, & Hutz, 2016; Azeredo, Moreira, & Barbosa, 2018; Palladino, McNeill, Reif, & Kittel-Schneider,

2019). The heritability of ADHD ranges between 54 and 70% (Brikell, Kuja-Halkola, & Larsson, 2019; Eilertsen et al., 2018). Previous research has found that some DNA variants are associated with ADHD, including the serotonin (5HTT) and dopamine (DAT1) transporter genes, the D4 and D5 dopamine receptor gene (DRD4 and DRD5), the serotonin 1B receptor gene (HTR1B) and a gene coding for a synaptic vesicle regulating protein known as SNAP25 (Gizer, Ficks, & Waldman, 2009).

In spite of this evidence, other studies have reported the important role played by some environmental factors in the onset and development of the disorder (Golmirzaei et al., 2013; McLaughlin et al., 2014), estimating that environmental factors account for between 10 and 40% of variance in ADHD (Banerjee, Middleton, & Faraone, 2007; Smidts & Oosterlaan, 2007). ADHD is associated with some adverse prenatal conditions that affect foetal development, such as maternal smoking, psychosocial stress, depression and maternal age at delivery, as well as various mental illnesses during pregnancy (Motlagh et al., 2010; Park et al., 2014; Silva, Colvin, Hagemann, & Bower, 2014; Sourander et al., 2019). It has also been associated with adverse birth outcomes, such as being small for gestational age (SGA), prematurity, low Apgar score and low birth weight (Halmøy, Klungsøyr, Skjærven, & Haavik, 2012; Heinonen et al., 2010; Lindstrom, Lindblad, & Hjern, 2011; Mick, Biederman, Prince, Fischer, & Faraone, 2002; Perapoch et al., 2019; Perricone, Morales, & Anzalone, 2013; Sucksdorff et al., 2015). However, a recent review showed that, whereas there is considerable evidence that prematurity is an ADHD risk factor, the role of birth weight and type of delivery is less clear (Sciberras, Mulraney, Silva, & Coghill, 2017). In fact, a substantial number of studies have found no evidence of birth weight as a predictor of ADHD (Silva, Colvin, Hagemann, & Bower, 2014). However, maternal age at delivery and being a firstborn have been associated with ADHD (Canals et al., 2018; Halmøy et al., 2012; Sciberras et al., 2017).

An adverse psychosocial environment and parenting practices such as low parental education and socioeconomic status (SES), negative parenting, maltreatment and family discord or parental lifelong psychiatric disorders have also been associated with ADHD (Counts, Nigg, Stawicki,

Rappley, & Von Eye, 2005; Pauli-Pott et al., 2017; Rivas-Juelas, de Dios, Benac-Prefaci, & Colomer-Revuelta, 2017; Rowland et al., 2018; Thapar, Cooper, Jefferies, & Stergiakouli, 2012). However, longitudinal research into the causal relationship between family psychosocial adversity and ADHD has produced relatively mixed findings (Keownn, 2012; Lifford, Harold, & Thapar, 2008). Freitag et al. (2012) noted that whereas the ADHD inattentive presentation was strongly influenced by psychosocial risk factors, the ADHD hyperactive-impulsive presentation was predominantly related to biological risk factors, which could be the origin of the confusing results.

Faced with this scenario, other studies suggest that the most accurate ADHD aetiological approach is the gene-environment interaction (GxE) (Tarver, Daley, & Sayal, 2014). This approach is based on the premise that the aetiology of complex disorders is the result of the interactions between genetic factors and environmental conditions. This could explain why some children are susceptible to environmental risks while others are resilient to them. It would also explain the mixed results concerning the ADHD risk factors (Franke et al., 2018; Palladino et al., 2019; Wermter et al., 2010).

In conclusion, the evidence suggests that ADHD is a complex disorder with great heterogeneity and multicausality in its aetiology. Consequently, it is difficult to state a real causal relationship between these risk factors and ADHD development. Although it can be inherited, the aetiology of ADHD cannot be explained only by genetic factors (Thapar, Cooper, Eyre, & Langley, 2013).

The aim of the present study is to research the potential role of several pre and perinatal factors in ADHD and explore differences between ADHD presentations. We also explore the differences between ADHD severity (ADHD clinical diagnostic and ADHD subclinical manifestations). Given the reported data, we hypothesize that adverse prenatal conditions, such as maternal nutritional status and tobacco smoke exposure, adverse birth outcomes, and an ADHD family phenotype, will be risk factors for ADHD, regardless of other individual and socio-family variables.

METHODS

Sample and study design

The sample was drawn from the EPINED study, which is a double phase epidemiologic cross-sectional study to determine the prevalence of ADHD, autism spectrum disorders (ASD) and social communication disorder (SCD) in school population of the province of Tarragona (Spain). Methodological data have been previously described (Morales-Hidalgo, Roigé-Castellví, Hernández-Martínez, Voltas, & Canals, 2018).

Students from 66 ordinary schools (public and private) from Preschool Education (4 to 5 years old) and Primary Education (10 to 11 years old) participated in the study. In the first phase, 6720 students [3382 boys (50.3%) and 3338 girls (49.7%)] were invited to participate in the EPINED study and teachers answered the ADHD and ASD screening questionnaires. Of the initial sample of 6720 students, 3286 were from Preschool Education [mean age = 4.99, $SD = 0.48$; 1632 females (49.7%)] and 3434 were from Primary Education [mean age = 10.94, $SD = 0.45$; 1705 females (49.7%)]. Of the whole sample, 3613 (53.8%) families agreed to participate in the first phase of the study and answered the parent questionnaires (screening procedure).

For the ADHD screening we used the *Conners Early Childhood Global Index* (Conners EC GI) for pre-schoolers and *Conners 3 ADHD Index* (Conners 3 AI) for school-age children (parent and teacher report in both cases). In addition, parents and teachers answered a brief sociodemographic questionnaire. Children whose Conners scores were above T65 on the parent and teacher reports and children with previous ADHD diagnosis were considered at risk of ADHD. All children at risk of ADHD, ASD and SCD were invited to participate in the second phase of the study. Additionally, a sample of children without the risk by a ratio of 2:1 randomized by school, age and sex was also individually assessed.

A total of 646 students [407 males (63.0%), 239 females (37.0%)] participated in the second phase of the study. Of these, 252 were from Preschool Education and 394 from Primary Education. Most

of the participating families were autochthonous (83.0%, 536) and 57.7% (373) of the families had a middle SES level, 16.3% (105) had a high SES and 14.4% (91) had a low SES level.

The second phase of the study included a child cognitive assessment and a parent structured interview to complete the diagnostic procedure. Parents also completed an *ad-hoc* questionnaire that asked about family sociodemographic characteristics and other prenatal, perinatal and postnatal data. The ADHD diagnosis was made by experienced research team members according to data obtained in the assessment in relation to the DSM 5 criteria.

The study was approved by the Catalan Department of Education and the Research and Ethics Committees at the Sant Joan University Hospital of Reus (Spain). Informed consent was obtained from all parents of participating children, and the children assented verbally to participate. All the schools requested to participate agreed to collaborate in the study.

Instruments

The *Conners Early Childhood Global Index* (Conners EC GI; Conners & Goldstein, 2009) and *Conners 3 ADHD Index* (Conners 3 AI) (Conners, 2008) are brief scales composed of 10 items scored on a 4-point Likert scale. The items are based on DSM 5 criteria and are designed to determine the presence of ADHD-related symptoms in infants and children in the last month. Both instruments include parent and teacher report forms. The Conners EC GI can be answered by parents and teachers of infants aged 2-6 years old and is derived from the original version of the Conners Early Childhood Index. The Conners EC GI provides two subscales (restlessness-impulsivity and emotional lability or reactivity) and both have a cut-off for elevated scores ($T \geq 65$) and for very elevated scores ($T \geq 70$). The Conners 3 AI assesses the ADHD symptomatology of children aged 6 to 18 years old and is drawn from the Conners Rating Scale 3rd Edition. The total ADHD score has a cut-off for elevated scores ($T \geq 65$) and for very elevated scores ($T \geq 70$). In this study, we administered the Spanish version of these instruments. The internal reliability of Conners EC GI was $\alpha = .92$ and $\alpha = .97$ for the parent and teacher forms respectively (Morales-Hidalgo, Hernández-Martínez, Vera, Voltas, & Canals, 2017). For Conners

3 AI, the internal reliability was $\alpha = .96$ for the parent and $\alpha = .98$ for the teacher report forms (Morales-Hidalgo et al., 2017).

The *Kiddie-Schedule for Affective Disorders & Schizophrenia, Present & Lifetime Version* (K-SADS; Kaufman et al., 1997) is a semi-structured clinical interview widely used to assess psychopathology in children and adolescents. This interview collects information on current (within the last 6 months) and past episodes based on DSM criteria. We administered the validated Spanish version to parents, and the Kappa coefficients were between good and excellent, showing values of $\kappa = 0.76 - 1$ and specifically, $\kappa = 0.91$ for the ADHD scales (Ulloa et al., 2006). The K-SADS-PL gives an ADHD diagnosis for the inattentive presentation to those children who show six or more manifestations related with attention problems. The ADHD hyperactive-impulsive presentation is get when six or more manifestations of hyperactivity and impulsivity are present, and the ADHD combined presentation when there are 12 or more manifestations (6 of inattention and 6 of hyperactivity-impulsivity). For each presentation, is need that manifestations are present in at least two settings (home, school, with friends) and prior to 12 years old. The oppositional defiant disorder and tic disorder were also assessed with the K-SADS-PL, as they are frequent co-occurring problems in ADHD.

For assessing infant and child intelligence capabilities we used the *Wechsler Intelligence Scale for Children* (WISC-IV; Wechsler, 2005) for children form Primary Education and *Wechsler Scales of Intelligence for Preschool and Primary School* (WPPSI-IV; Wechsler, 2012) for infants of Preschool Education.

For detecting the ADHD parental phenotype, mothers and fathers completed the *World Health Organization Adult ADHD Self-Report Scale* (ASRS-18; Kessler et al., 2005), which is an auto-informed questionnaire to assess the current presence of ADHD symptoms in adults. It is composed of 18 items: 9 items of inattention and 9 items of hyperactivity. We used the total score of the scale as a continuous quantitative variable.

Risk variables

Data about sociodemographic and family characteristics and prenatal and perinatal factors were collected through a questionnaire designed ad-hoc. Specifically, we collected retrospectively information on birth weight, gestational age, type of delivery, hypoxic problems at birth, maternal smoking habits, maternal weight gain, diabetes and hypertension during pregnancy, and breastfeeding duration. This questionnaire also collected the family history of mental illness (indicating the presence of psychopathology in 1st and 2nd grade relatives), child chronic illness and parental provenance (ethnicity). Finally, the family socio-economic level was calculated according to the Hollingshead Index (Hollingshead, 2011).

ADHD case definition

Participating children classified as “*clinical ADHD or ADHD*” received ADHD diagnosis according to DSM 5 criteria (three presentations of ADHD) based on the information collected in the K-SADS-PL interview. We also considered as “*clinical ADHD*” those children who received an ADHD diagnosis previous to the study but presented a remission of some symptoms during the current assessment due to pharmacological or psychological treatment. Children were classified as “*subclinical ADHD*”, when they presented between four or five manifestations of ADHD on the K-SADS-PL for any of the ADHD presentations. Children included in clinical or subclinical ADHD groups may have other comorbid neurodevelopmental disorders, such as language and learning disorders (previously diagnosed by clinical and psycho-pedagogical services), intellectual disabilities (data from Weschler Intelligence scales, or previous clinical data and school interference), ASD and oppositional-defiant disorder.

Finally, the “*Non-ADHD*” group was formed by children who did not reach previous criteria in the K-SADS-PL interview and had not previously been diagnosed with ADHD or other neurodevelopmental disorders (ASD, language disorders, learning disorders, intellectual disabilities) or syndromes.

Statistical analyses

We described data related to ADHD presentations (separated into clinical and subclinical diagnosis groups) according to age group (Preschool and Primary Education) and sex (using frequencies and percentages).

We used Chi-Square and ANOVA analyses to examine the differences between ADHD groups (*Non-ADHD*, *subclinical* and *clinical ADHD*) in relation to obstetric, individual, family socio-demographic characteristics and comorbidities. In addition, Chi-Square and t-student tests were performed to compare the subclinical and clinical ADHD groups.

We then carried out logistic regressions to test which variables were associated with an ADHD diagnosis in children. Different logistic regression models were performed using the enter method in all cases. In the first model, pre and perinatal variables (gestational hypertension, diabetes, tobacco exposure, weight gain, gestational age, birth weight, type of delivery, perinatal hypoxia and breastfeeding duration), adjusted by sex and age, were included as potential predictors. In the second model we added to the previous pre and perinatal variables the ethnicity, the first-born status of children, and the family psychopathological history as potential ADHD risk factors and family SES as a covariate. In the third model, the maternal and paternal ADHD phenotypes (scores on ASRS questionnaire) were added to the previous variables. The ADHD phenotypes were introduced in a separate model because we did not obtain the questionnaires from all parents, which substantially decreased the potential sample. We carried out the same procedure (using the same models) for the inattentive ADHD presentation, the hyperactive-impulsive and combined presentations and for the subclinical ADHD group. Participants with an intellectual disability (total IQ equal or below than a score of 75 obtained on the Weschler Intelligence Scale) were excluded from the analyses. Data were analysed using SPSS 22.0.

RESULTS

Regarding the ADHD diagnosis, in the second phase of the study 26.2% (168) of the participating children were diagnosed as ADHD and 13.6% (88) as subclinical ADHD. Of the ADHD diagnosed children, 9.1% (59) showed the inattentive presentation, 3.7% (24) the hyperactive presentation and 13.3% (86) the combined presentation. Data about ADHD presentations and ADHD diagnosis groups according to age groups and sex are shown in Table 1.

INSERT TABLE 1 ABOUT HERE

Table 2 shows data about individual, family and obstetric variables and the differences between ADHD diagnosis groups. There are significant differences between ADHD diagnosis groups in terms of maternal weight gain during pregnancy, perinatal hypoxia, child total IQ and chronic illness, SES level, family psychopathologic history, and maternal ADHD phenotype (ASRS score). Non-ADHD children predominantly came from families with a high SES level and had higher total IQ. Higher ADHD severity was related to child chronic illness, maternal ADHD phenotype, and family psychopathologic history. Children with ADHD have more have a higher risk of perinatal hypoxia than subclinical ADHD children. Moreover, when we compare the subclinical and clinical ADHD groups, we can observe that the two groups differ in perinatal hypoxia ($p = .027$), total IQ ($p = .034$) and family psychopathological history ($p = .042$). Regarding comorbidity, as seen in Table 2, children with ADHD diagnosis showed a higher prevalence of comorbid ASD and intellectual disability than subclinical ADHD children. However, subclinical ADHD children showed more learning disorders than ADHD children.

INSERT TABLE 2 ABOUT HERE

Logistic regression models were conducted to examine which variables were associated with clinical and subclinical ADHD diagnosis. As children with other neurodevelopmental disorders were excluded from the non-ADHD group, children with intellectual disability were also excluded from clinical and subclinical groups in the logistic regression analyses. For subclinical ADHD, the first model (which included pre and perinatal variables, sex and age of children) explained 9.8% of the variance ($p = .031$) and only a greater weight gain during pregnancy was significantly

associated ($p = .017$). The second model, which added the sociodemographic variables to previous pre and perinatal factors, explained 15.5% of the variance ($p = .015$), and the subclinical ADHD diagnosis continued to be associated with weight gain during pregnancy ($p = .009$). However, the third model (in which the maternal and paternal ADHD phenotypes were added) was not significant (see Table 3).

Data from logistic regression models for the ADHD diagnosis (all presentations) are shown in Table 3. The first model explained 13.6% of the variance ($p = .000$), and only the child's age ($p = .000$) was associated with ADHD diagnosis. Model 2, which includes socio-familial variables, explained 20.5% of the variance ($p = .000$). The child's age ($p = .000$), the type of delivery ($p = .044$), lower family SES ($p = .001$) and having a family member with a mental illness ($p = .020$) were associated with ADHD diagnosis. Model 3, which included parental ADHD phenotypes explained 34.1% of the variance ($p = .000$), and gestational diabetes ($p = .012$), instrumental delivery ($p = .011$), having a family psychopathological history ($p = .033$) and the maternal ADHD phenotype ($p = .023$) were associated with ADHD diagnosis.

INSERT TABLE 3 ABOUT HERE

The analyses of the inattentive ADHD presentation and hyperactive-impulsive and combined ADHD presentations are shown in Table 4 and 5 respectively. For the inattentive presentation, model 1 explained 21.2% of the variance ($p = .000$), and the variable of being older ($p = .000$) was the only associated variable. The second model explained 31.6% of the total variance ($p = .000$), and inattentive ADHD was associated with the child's age ($p = .000$) and low family SES ($p = .008$). The third model explained 42.0% of the variance ($p = .004$), and being older ($p = .007$) was associated with inattentive ADHD (see Table 4).

INSERT TABLE 4 ABOUT HERE

Table 5 shows the logistic regression models for the hyperactive-impulsive and combined presentations. Model 1 explained 9.6% of the variance ($p = .037$), being older ($p = .017$) and male ($p = .027$) were associated with the hyperactive-impulsive and combined ADHD presentations.

Model 2 explained 16.9% of the variance ($p = .007$), and low SES ($p = .013$), having a family member with a mental illness ($p = .034$) and being first-born ($p = .043$) were associated factors. Finally, model 3 explained 35.9% of the variance ($p = .003$), and gestational diabetes ($p = .019$), having a family member with a mental illness ($p = .016$) and the maternal ADHD phenotype ($p = .008$) were associated with both the hyperactive-impulsive and combined ADHD presentations.

DISCUSSION

The present study researches the role played by potential risk factors in ADHD diagnosis in a community school sample. Although it has been demonstrated that ADHD is a highly heritable neurodevelopmental disorder and there is a wide range of genetic factors involved in its aetiology (Arnsten & Pliszka, 2011; Nagel et al., 2011; Nakao et al., 2011), the effect of some environmental variables should not be ignored. The results of the present study support that in addition to the ADHD specific parental phenotype and the family psychopathological background, prenatal and perinatal factors are also associated with child ADHD diagnosis.

In our sample, ADHD (both clinical and subclinical) was more diagnosed among boys than girls, in agreement with previous literature (Canals et al., 2018; Kim et al., 2017). In addition, ADHD diagnosis was higher in school-age children than in preschool children, which is consistent with prevalence data (Canals et al., 2018; Catalá-López et al., 2012; Thomas et al., 2015). Moreover, the hyperactive-impulsive presentation was more prevalent in preschoolers than in older, unlike the inattentive presentation. These results support that ADHD is an early-onset disorder and their manifestations change throughout development (Martel, Levinson, Langer, & Nigg, 2016).

In addition, the results showed differences between subclinical and ADHD groups. In the subclinical group there were more subjects with inattentive manifestations and with less problems at birth (instrumental delivery and hypoxic problems) than in the clinical group. The frequency of chronic illness in children, the family psychopathological background, the SES level and the

maternal ADHD phenotype increased in relation to ADHD severity (non ADHD-subclinical and clinical), which gives further evidence of the relationship between these factors and the risk of neurodevelopmental disorders (Canals et al., 2018; Perapoch et al., 2019; Sourander et al., 2019; Sucksdorff et al., 2015). Hypoxic problems only occurred in 2.9% of the total sample, and a little more than half of the cases were among ADHD children.

The logistic regression models showed that weight gain during pregnancy was the only risk factor of subclinical ADHD diagnosis (only in the first and second models). In the case of ADHD diagnosis, the results showed that family psychopathological history and maternal ADHD phenotype were associated with ADHD, as well as other factors that can presumably alter neurodevelopment, such as an instrumental delivery and gestational diabetes (considering all presentations). These data are in agreement with those of Halmøy et al. (2012), Henionen et al. (2010), Talge et al. (2016) and Sucksdorff et al. (2015), who state that adverse birth outcomes are risk factors for ADHD. However, some studies have found no associations between adverse outcomes and ADHD diagnosis (Sciberras et al., 2017; Silva et al., 2014). These differences could be explained by the criteria used for ADHD diagnosis; while we consider the ADHD diagnosis according to the DSM criteria, other studies may use the presence of ADHD symptomatology without fulfilling the diagnostic criteria.

Our results also showed no significant association between prenatal smoke exposure and ADHD diagnoses at childhood. These results contrasted with previous evidence (He, Chen, Zhu, Huan, & Ke, 2017; Huang et al., 2018; Roigé-Castellví et al., 2019) which found that children who were prenatally exposed to tobacco smoke have a greater risk of presenting ADHD related symptoms. That our study did not find an association could be because data about tobacco consumption were collected retrospectively, while the other studies used cohorts followed from pregnancy.

The results about the family psychopathological history (indicating a possible genetic risk) were in line with previous results that suggest that children with psychopathological antecedents are at risk of developing ADHD (Breux, Brown, & Harvey, 2017; Cheung, Aberdeen, Ward, & Theule, 2018; Homan et al., 2019; Leijdesdorff, van Doesum, Popma, Klaassen, & van Amelsvoort, 2017;

López Seco et al., 2015; Uchida, Spencer, Faraone, & Biederman, 2018). Moreover, our data also demonstrated that the maternal, but not paternal ADHD phenotype was associated with later child ADHD diagnosis, which is in agreement with the results of other authors (Auerbach, Zilberman-hayun, Atzaba-Poria, & Berger, 2017; Breaux et al., 2017; Joelsson et al., 2017). The literature provides evidence that ADHD is a heritable disorder and there are several genetic factors and DNA risk variants involved in the emergence of ADHD (Stergiakouli et al., 2015). Therefore, that the presence of ADHD child symptomatology in first-degree relatives increases the risk of developing ADHD could be expected to be due to shared genetic factors that contribute to the onset of ADHD (Faraone & Larsson, 2019).

The pattern of sex-specific differences in parental ADHD phenotype could have different explanations. It could be due to specific genetic factors that depend on female genetic characteristics, based on the mitochondrial genome or X-chromosomal factors (Cederlöf et al., 2014; Chinnery & Schon, 2003), or it could be explained by environmental factors, such as mothers with ADHD symptoms having more difficulties in the parenting practices involved in caring for and bringing up their offspring (Babinski et al., 2016; Breaux et al., 2017; Park, Hudec, & Johnston, 2017). In addition, women with ADHD symptoms frequently show daily-life impairments related to having professional, relationship and personal-life problems; are more likely to engage in risky sexual behaviours, so they may have unwanted pregnancies or teenage pregnancies; and are more likely to engage in other risk-related behaviours like smoking, drinking and drug use during pregnancy (Eddy, Jones, Snipes, Karjane, & Svikis, 2019; Isaksson, Stickley, Kopolov, & Ruchkin, 2018; Joelsson et al., 2017; Kaye et al., 2014). These women could also be undergoing treatment with ADHD medication, which is associated with birth defects, neonatal morbidity and disorders related to the central nervous system (Anderson et al., 2018; Nörby, Winblad, & Källén, 2017). In this case, the association would be due to the indirect effect of some other prenatal factors related to child ADHD development. Thus, both genetic and environmental factors, perhaps through epigenetic mechanisms, could play an important role.

In addition, this study found that the ADHD presentations showed different associated factor patterns. We observed that the hyperactive-impulsive and combined presentations were associated with biological factors, while the inattentive presentation was not associated with these factors and models only showed an increase of ADHD symptoms related with age. These results are consistent with those of Freitag et al. (2012) which showed that only the ADHD hyperactive-impulsive presentation was predominantly related to biological risk factors. Similarly, the study carried out by Stawichi (2006) also reported a specific pattern of family transmission for the inattentive and combined presentations. However, these authors concluded that there is a shared process for the two presentations and another one specific to each presentation and discuss the possible association with different neurobiological pathways.

In accordance with our results, some previous studies have also associated gestational diabetes with child ADHD (Nomura et al., 2012; Xiang et al., 2018). The underlying pathways that link gestational diabetes and child ADHD are still unknown; however, some studies propose epigenetics as a possible explanation, by which gestational diabetes influences the cell and organ development of the foetus, which interacts with postnatal environmental factors (Franzago, Fraticelli, Stuppia, & Vitacolonna, 2019; Ornoy, Reece, Pavlinkova, Kappen, & Miller, 2015). Specifically, Ruchat et al. (2013) reported a wide range of placenta and cord blood genes that were methylated differently in children exposed to gestational diabetes. However, Chandna et al. (2015) also suggested a proinflammatory status due to hyperglycaemia (as a result of diabetes) disturbing brain development, and consequently child behaviour, by activating the receptor for advanced glycation end-products, whose expression is higher in psychiatric disorders. Other studies suggest that gestational diabetes interferes in child neurobehavior through other pregnancy complications, because maternal hyperglycaemia is a risk factor for adverse pregnancy outcomes, such as oxidative stress, hypoxia, apoptosis, low birth weight, preeclampsia and caesarean delivery (Catalano et al., 2012; Metzger, Coustan, & Trimble, 2019; Ornoy et al., 2015). Finally, the latest evidence shows the role the microbiome plays as an underlying mechanism linking

gestational diabetes and child ADHD outcomes, since the maternal microbiome status may be modified by diabetes (Cortez et al., 2019; Wang et al., 2018).

One strength of this study is that the results were obtained from a wide and representative scholar sample, which allows us to generalize the findings found to the general population. We excluded children with other neurodevelopmental disorders in the non-ADHD group, which implies that it is a group of healthy children. Moreover, we categorized the ADHD group into clinical diagnosis and subclinical ADHD manifestations in addition to the ADHD presentations (inattentive versus hyperactive-impulsive and combined). Another strength is that we research the association between several prenatal and perinatal factors and control for potential confounders, such as family risk of ADHD, ethnicity, SES level and the child's total IQ.

As limitations, we should mention that, as it is a cross-sectional study, pregnancy conditions and obstetric data were collected retrospectively with the bias that this entails. In addition, we do not have maternal IMC information before pregnancy or any anthropometric reference prior to pregnancy, which would give us a reference index with which to compare weight gain during pregnancy. Another limitation was that although the size of the sample was large, only a few subjects were diagnosed with the hyperactive presentation and therefore we could not carry out the specific analyses for this presentation. Finally, not all parents (fathers and mothers) provided information about the ADHD symptomatology. In conclusion, this study provides new evidence of the association of prenatal and perinatal factors, such as metabolic disorder in the pregnancy, difficulties in childbirth and ADHD family phenotype with childhood ADHD. We suggest that subclinical syndromes may have different associated factors in relation to ADHD clinical, at the same time that there may be specific factors according to ADHD presentations.

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Table 1.

Descriptive data regarding ADHD (clinical and subclinical) presentations.

	SUBCLINICAL ADHD (n = 88)				CLINICAL ADHD (n = 168)			
	All ADHD presentation	Inattentive	Hyperactive - impulsive	Combined	All ADHD presentations	Inattentive	Hyperactive-impulsive	Combined
Total sample	13.6 (88)	51.1 (45)	23.9 (21)	25.0 (22)	26.0 (168)	35.1 (59)	14.3 (24)	50.6 (86)
Preschool Education	33.0 (29)	13.8 (4)	48.3 (14)	37.9 (11)	21.4 (36)	8.3 (3)	36.1 (13)	55.6 (20)
Primary Education	67.0 (59)	69.5 (41)	11.9 (7)	18.6 (11)	78.6 (132)	42.4 (56)	8.3 (11)	49.2 (65)
Male	62.5 (55)	50.9 (28)	18.2 (10)	30.9 (17)	67.3 (113)	31.0 (35)	14.2 (16)	54.9 (62)
Female	37.5 (33)	51.5 (17)	33.3 (11)	15.2 (5)	32.7 (55)	43.6 (24)	14.5 (8)	41.8 (23)

Data are presented in % (number subjects)

Table 2.

Obstetric, individual and family sociodemographic data for each ADHD group.

	Non-ADHD (n = 310)	SUBCLINICAL ADHD (n = 88)	ADHD (n = 168)	χ^2 / F	<i>p</i>
PREGNANCY OUTCOMES					
Hypertension ^a	4.5 (14)	4.5 (4)	4.2 (7)	0.36	.982
Diabetes ^a	6.1 (19)	5.7 (5)	7.7 (13)	0.586	.746
Tobacco exposure ^a	18.1 (56)	20.5 (18)	26.8 (45)	5.01	.082
Gain of weight (Kg.) ^b	12.47 (5.94)	14.86 (7.66)	13.93 (7.58)	4.08*	.018
PERINATAL OUTCOMES					
Gestational age (weeks) ^b	38.90 (2.39)	39.26 (2.32)	38.55 (2.91)	2.13	.120
Birth weight (gr.) ^b	180.70 (562.66)	3281.31 (616.12)	3.161 (313.59)	1.14	.321
Type of delivery (instrumental) ^a	41.3 (128)	37.5 (33)	47.6 (80)	3.73	.155
Perinatal hypoxia ^a	2.3 (7)	0 (0)	5.4 (9)	6.84	.033
Breastfeeding duration (months) ^b	7.35 (9.68)	6.53 (9.28)	6.19 (10.31)	.737	.479
CHILD CHARACTERISTICS					
Sex (female) ^a	41.9 (130)	37.5 (33)	32.7 (55)	3.93	.140
Total IQ (score) ^b	104.61 (12.74)	98.72 (13.47)	94.74 (14.33)	30.91	.000
(excluding children with intellectual disability)	104.61 (12.74)	99.77 (12.48)	97.46 (11.74)	18.28	.000
Chronic illness ^a	6.5 (20)	11.4 (10)	14.3 (24)	8.23	.016
First-born status ^a	54.8 (170)	42.0 (37)	44.6 (75)	0.60	.741
FAMILY AND SOCIODEMOGRAPHIC DATA					
Ethnic (autochthonous) ^a	86.5 (268)	85.2 (75)	83.3 (140)	.149	.928
Family SES (score) ^{b, 3}	33.93 (12.81)	38.05 (12.33)	39.45 (12.67)	9.94	.000
Family member with mental illness ^{b, a}	14.5 (45)	17.0 (15)	28.6 (48)	14.22	.001
Maternal ADHD phenotype (score) ^{b, 4}	16.77 (9.07)	21.18 (9.66)	23.09 (11.43)	9.78	.000
Parental ADHD phenotype (score) ^{b, 3}	16.61 (10.47)	16.98 (9.88)	19.76 (10.70)	2.20	.113
COMORBIDITY					
Autism spectrum disorder	-	5.7 (5)	7.1 (12)	50.51	.000
Tic disorder	-	0 (0)	2.4 (4)	8.07	.089
Oppositional defiant disorder	-	2.3 (2)	5.4 (9)	8.27	.082
Learning disorder	-	6.8 (6)	5.4 (9)	25.31	.000
Intellectual disability	-	3.4 (3)	8.9 (15)	28.31	.000

a. ANOVA: Mean (SD) and F value

* *Brown-Forsythe*b. Chi-Square: Percentage (n) and χ^2

Note: 1. *Wechsler Scales of Intelligence*; 2. *Wechsler Intelligence Scale for Children (WISC-IV)*; 3. *Hollingshead Index*; 4. *World Health Organization Adult ADHD Self-Report Scale (ASRS)*.

Table 3.

Factors associated with subclinical and ADHD diagnosis (*all presentations*).

	Subclinical manifestations			Clinical ADHD		
	β	Odds ratio (95% CI)	<i>p</i>	β	Odds ratio (95% CI)	<i>p</i>
MODEL 1						
Maternal gain of weight	0.050	1.051 (1.009 – 1.095)	.017	-	-	-
Child age	-	-	-	0.018	1.018 (1.010 – 1.026)	.000
MODEL 2						
Maternal gain of weight	0.067	1.069 (1.017 – 1.124)	.009	-	-	-
Type of delivery	-	-	-	0.564	3.040 (1.758 - 1.016)	.044
Child age	-	-	-	0.017	1.017 (1.009 - 1.026)	.000
Family SES level (score)	-	-	-	0.040	1.041 (1.017 - 1.065)	.001
Family member with mental illness	-	-	-	0.775	2.170 (1.131 - 4.163)	.020
MODEL 3						
Maternal gain of weight	0.083	1.086 (1.006 – 1.173)	0.35	-	-	-
Diabetes	-	-	-	3.093	22.034 (1.956 – 248.177)	.012
Type of delivery	-	-	-	1.111	3.037 (1.290 - 9.299)	.011
Child age	-	-	-	0.016	1.016 (1.003 – 1.030)	.018
Family member with mental illness	-	-	-	1.194	3.301 (1.099 – 9.920)	.033
Maternal ADHD phenotype	-	-	-	0.051	1.053 (1.007 – 1.100)	.023

Logistic regression models (only significant predictors are presented).

Note: 95% CI, 95% confidence interval.

Variables introduced in model 1: *gestational hypertension, diabetes, tobacco exposure, gain of weight, gestational age, birth weight, type of delivery, perinatal hypoxia, breastfeeding duration, sex and age.*

Variables introduced in model 2: *variables introduced in model 1 and first-born status of children, family SES, ethnicity and psychopathological antecedents.*

Variables introduced in model 3: *variables introduced in model 2 and parental ADHD phenotype.*

Table 4.

Factors associated with inattentive presentation of ADHD.

	β	Odds ratio (95% CI)	<i>p</i>
Model 1 (pre-perinatal variables)			
Child age	0.039	1.040 (1.020 – 1.060)	.000
Model 2 (with sociodemographic variables)			
Child age	0.040	1.041 (1.020 – 1.061)	.000
Family SES level	0.047	1.048 (1.012 – 1.086)	.008
Model 3 (with parental ADHD phenotype)			
Child age	0.049	1.050 (1.014 – 1.088)	.007

Logistic regression models (only significant predictors are presented).

Note: 95% CI, 95% confidence interval.

Variables introduced in model 1: *gestational hypertension, diabetes, tobacco exposure, gain of weight, gestational age, birth weight, type of delivery, perinatal hypoxia, breastfeeding duration, sex and age.*

Variables introduced in model 2: *variables introduced in model 1 and first-born status of children, family SES, ethnicity and psychopathological antecedents.*

Variables introduced in model 3: *variables introduced in model 2 and parental ADHD phenotype.*

Table 5.

Factors associated with hyperactive-impulsive and combined presentations of ADHD.

	β	Odds ratio (95% CI)	<i>p</i>
Model 1 (pre-perinatal variables)			
Child sex	-0.681	0.506 (0.277 - 0.926)	.027
Child age	0.010	1.010 (1.002 – 1.019)	.017
Model 2 (with sociodemographic variables)			
Familial SES level	0.036	1.037 (1.008 – 1.067)	.013
First-born status	0.673	1.959 (1.022 – 3.756)	.043
Family member with mental illness	0.845	2.327 (1.067 – 5.076)	.034
Model 3 (with parental ADHD phenotype)			
Diabetes	3.300	27.113 (1.710 – 429.962)	.019
Family member with mental illness	1.727	5.623 (1.385 – 22.824)	.016
Maternal ADHD phenotype	0.074	1.077 (1.020 – 1.137)	.008

Logistic regression models (only significant predictors are presented).

Note: 95% CI, 95% confidence interval.

Variables introduced in model 1: *gestational hypertension, diabetes, tobacco exposure, gain of weight, gestational age, birth weight, type of delivery, perinatal hypoxia, breastfeeding duration, sex and age.*

Variables introduced in model 2: *variables introduced in model 1 and first-born status of children, family SES, ethnicity and psychopathological antecedents.*

Variables introduced in model 3: *variables introduced in model 2 and parental ADHD phenotype.*