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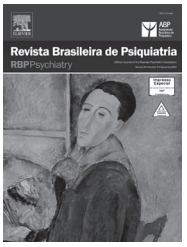

ORIGINAL ARTICLE

Is there an association between perinatal complications and attention-deficit/hyperactivity disorder-inattentive type in children and adolescents?

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DESCRIPTORS
Attention-Deficit Hyperactivity Disorder - predominantly inattentive type; Prenatal, Delivery and Early Postnatal Complications; Environmental Factors.

Abstract
Objective: The objective of the present study is to investigate the association between attention-deficit/hyperactivity disorder (ADHD), predominantly inattentive type (ADHD-I) and prenatal, delivery and early postnatal complications (PDPC). *Method:* In a case-control design, we assessed a sample of 124 children and adolescents with ADHD-I and 124 non-ADHD controls (6-17 years old) from both a non-referred (n = 200) and a clinical sample (n = 48). Cases and controls, matched by gender and age, were systematically evaluated through structured diagnostic interviews. Prenatal, delivery and early postnatal complications (PDPC), as well as potential confounders were evaluated by direct interview with biological mothers. *Results:* Conditional logistic regression analysis showed that children and adolescents whose mothers presented more PDPC had a significantly higher risk for ADHD-I (p = 0.005; OR = 1.25; CI 95%: 1.1-1.5). *Conclusions:* In a case-control study, we expanded to ADHD-I previous findings suggesting the association between perinatal factors and broadly defined ADHD. Due to the preventable nature of some of these PDPC, our results have clear impact in public mental health policies.

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DESCRITORES:
Transtorno de déficit de atenção/hiperatividade predominantemente desatento;
Complicações no período pré-natal, perinatal e pós-natal imediato;
Fatores ambientais.

Existe alguma associação entre complicações perinatais e transtorno de déficit de atenção/hiperatividade – subtipo desatento em crianças e adolescentes?

Resumo
Objetivo: O objetivo desse estudo é investigar a associação entre complicações perinatais (complicações ocorridas nos períodos pré, peri e pós-natal imediato - CPPs) e transtorno de déficit de atenção/hiperatividade (TDAH) do subtipo desatento (TDAH-D). *Método:* Em um estudo de casos e controles, foram avaliadas 124 crianças e adolescentes (6-17 anos) com TDAH-D e 124 controles sem a doença, provenientes tanto de uma amostra populacional (n = 200), quanto de uma amostra clínica (n = 48). Casos e controles, pareados por gênero e idade, foram sistematicamente avaliados através de entrevistas diagnósticas estruturadas. Informações sobre as complicações ocorridas durante os períodos pré, peri e pós-natal imediato (CPPs), assim como sobre potencias confundidores, foram obtidas através de entrevistas realizadas diretamente com as mães biológicas. *Resultados:* A análise de regressão logística condicional mostrou que para as crianças e adolescentes cujas mães apresentaram maior número de CPPs, o risco de TDAH-D foi significativamente mais elevado (p = 0.005; OR = 1.25; IC 95%: 1.1-1.5). *Conclusões:* Em um estudo de caso-controle, foi possível expandir, para o TDAH predominantemente desatento, os achados prévios que sugeriam a associação entre complicações perinatais e TDAH sem um subtipo específico. Em virtude da possibilidade de prevenção de algumas dessas complicações, nossos resultados podem exercer impacto sobre políticas públicas de saúde.

Introduction

Although the etiology of ADHD is not entirely clear, studies have shown the contribution of genetic and environmental factors.[1] Results from twin and adoption studies have shown that ADHD heritability is high, accounting for more than 75% of the phenotypic heterogeneity of the disorder.[2,3] It is important to notice that a high heritability indicates that genetic factors account for a large amount of the variation in the susceptibility for showing a particular characteristic in a specific population at a certain point in time. A modification of the heritability is to be expected if there are changes in genetic or environmental conditions.[3] Therefore, environmental factors such as prenatal, delivery and early postnatal complications (PDPC) may increase the risk of ADHD or contribute to its expression.[4-6]

A large body of literature documents the association of complications in pregnancy, delivery, and early neonatal period with an increased risk of neurological and psychiatric disorders in childhood and adult life.[7,8] The central nervous system (CNS) is vulnerable to different injuries throughout fetal, neonatal and infancy periods. Most frequently, injuries to the developing CNS do not result in malformations but rather in functional abnormalities detectable only later in life (see Huizink & Mulder, 2006, for a review).[9]

Case-control studies indicate that pregnancy, labor/delivery and early neonatal complications are environmental factors found more often in children diagnosed with ADHD compared with non-affected controls.[5,6,10] Milberger et al.[11] evaluated the role of pregnancy, delivery, and infancy complications (PDIC) in boys with ADHD (n = 140) compared with normal controls (n = 120) and with their first-degree biological relatives. A positive association between ADHD and PDIC was found in this study. Specific complications reflecting chronic exposure - such as family problems, maternal bleeding and/or smoking, and illicit drug use during pregnancy - accounted for this result.[11] On the other hand, some studies did not find significant differences in the occurrence of perinatal complications comparing ADHD cases and non-affected controls.[12,13]

Methodological limitations in studies may explain part of the contradictory findings. Limitations such as different diagnostic criteria to identify affected subjects; use of different instruments to measure PDPC; insufficient adjustment for confounding factors - including assessment of familial ADHD - and assessment of samples with extreme phenotypic variability are some examples.

Reducing phenotypic heterogeneity through the assessment of a more homogeneous group of patients might be an interesting strategy for studies assessing the role of either genetic or environmental risk factors in ADHD. Several Investigators suggest significant clinical differences among ADHD types.[14] While the combined type (ADHD-C) is the most common subtype of ADHD in clinical referred samples, the inattentive type (ADHD-I) seems to be more prevalent in population-based samples. A recent review showed that the predominantly inattentive type was the most common ADHD type (45%), followed by ADHD-C (34%) and ADHD-HI (21%) in non-referred samples.[15] Despite the extensive body of literature documenting differences among ADHD types, we could not find many studies addressing the role of perinatal complications on specific ADHD subtypes.[16,17] For instance, Langley et al.,[16] in a clinical sample of children with ADHD and associated antisocial behavior, observed that maternal smoking during pregnancy and social class independently predict severity of hyperactive-impulsive symptoms and conduct disorder. Conversely, the indicators of environmental risk studied (low birth weight, maternal smoking in pregnancy and social class) did not predict total number of inattentive symptoms. One limitation of this study was the modest number of individuals with DSM-IV ADHD predominantly inattentive type: 19 subjects.[16]

Since we are not aware of previous studies investigating perinatal risk factors in this specific and highly prevalent population of inattentive children, the objective of the present study was to examine the role of PDPC in ADHD-I, comparing a sample of affected children and adolescents with a sample of unaffected controls. Our hypothesis is that a higher prevalence of complications during pregnancy, delivery, and immediate postnatal period would be found in mothers of patients with ADHD-I.

Method

Subjects

The sample for this study was derived from two different sources: a) a population-based case-control study [49]; and b) the ADHD outpatient program at our University Hospital.

The inclusion criteria for both samples were (1) age 6 to 17 years; (2) contact with the biological mother; and (3) met full DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, 4th edition) diagnostic criteria for ADHD-I. Each positive case selected was matched with a control (same gender and age). The exclusion criteria for cases and controls were an estimated IQ < 70 and the diagnosis of psychosis.

The detailed description of the sampling process for subjects enrolled from the population case-control study is found elsewhere.[18] Briefly, the sample of 100 ADHD-I cases and 100 non-affected controls, matched by age and gender, was ascertained from 12 public schools in Porto Alegre, Brazil. All subjects went through an extensive clinical evaluation in our ADHD outpatient clinic.

Regarding the clinical sample, we first selected all ADHD-I cases assessed from January 2001 to November 2007 in our program that fulfilled the inclusion/exclusion criteria mentioned above. Those who could be matched for gender and age to a non-ADHD control either assessed in our outpatient program or in our general pediatric clinic were invited to take part of the study. We identified 51 ADHD-I cases and 41 potential controls aged 6-17 years old at the time of ascertainment. Four patients with mental retardation (3 cases and 1 control) and three cases that did not have contact with their biological mothers were excluded. We could not find five of the ADHD-I patients and eight of the potential controls. From the remaining 72 subjects, 24 ADHD-I cases and 24 non-ADHD controls matched for gender and age and were included in the study.

The project was approved by the Ethical Committee of our university hospital (approved as an institutional review board by the Office for Human Research Protections, United States of America, IRB 00000921). Written informed consent was obtained from parents for the assessment of children. Children or adolescents provided verbal assent to participate in the study.

Diagnostic Process

The diagnoses of ADHD-I and its comorbidities were performed in our outpatient clinic through a three-stage process described extensively in previous investigations.[14,19] First, all subjects passed through an initial assessment made with a semi-structured interview (Schedule for Affective Disorders and Schizophrenia for School-Age Children, Epidemiological Version – K-SADS-E)[20] modified to assess DSM-IV criteria and administered to the parents by trained research assistants. This interview had been previously translated into Portuguese and the inter-rater reliability for the ADHD diagnosis was previously assessed (kappa coefficient = 0.94; $p < 0.001$).[21] Second, each diagnosis derived from the K-SADS-E was discussed in a clinical committee chaired by an experienced child and adolescent psychiatrist (L.A.R). At the third stage, a clinical evaluation of ADHD-I and comorbid conditions were performed according to DSM-IV criteria by a child and adolescent psychiatrist who previously had access to K-SADS-E results. All diagnostic interviews were conducted with the parents and the child or adolescent. When a diagnostic disagreement occurred in the three-stage process, priority was given to diagnoses derived from clinical interviews.[19] The same diagnostic procedures were applied for the sample derived from the case-control study (for details see Schmitz et al.[18]). However, to rest assured that we were dealing with a relatively pure ADHD-inattentive type, we only included cases fulfilling DSM-IV criteria for ADHD-inattentive type but presenting at most three symptoms of hyperactivity/impulsivity after this extensive evaluation in the non-referred sample. In the clinical sample, only cases fulfilling DSM-IV criteria for ADHD-I while presenting a maximum final score of one/three (range: 0-3) in the hyperactivity/impulsivity subscale of the 4th revision of the Swanson, Nolan, and Pelham Questionnaire (SNAP-IV) were included in the study.[22]

The estimated IQ score was obtained from the Vocabulary and Block Design subtests of the Wechsler Intelligence Scale-Third Edition (WISC III) administered by trained psychologists in both samples.[23]

Assessment of Demographic Variables, Pre-, Peri-, and Early Postnatal Complications, and Potential Confounding Factors

Demographic variables (age, gender, ethnicity, and schooling) were assessed with parents. A socioeconomic scale developed by the Brazilian Association of Market Research Institutes was used to define the families' socioeconomic status (SES).[24] Children's and adolescents' comorbidities were investigated through the diagnostic procedures described above. Maternal ADHD diagnoses were evaluated by a psychiatrist using the ADHD module from the K-SADS-E modified to assess DSM-IV criteria as extensively described by other authors.[25] This investigation was performed by direct clinical interviews in the sample from the community and by phone interviews in the clinical sample.

We assessed PDPC using a list of potential problems based in an extensive review of the available scales used in previous studies. First, prenatal, obstetric and neonatal risk factors were transformed in dichotomous variables (yes/no) based in the cut-points set in these scales.[26-30] Second, to increase power, we obtained a continuous score based on the sum of the complications investigated. This procedure assured us a comprehensive inclusion of potential risk variables. Pre-, peri-, and early postnatal complications and possible confounding factors were assessed by direct interview with biological mothers and supplemented with medical records when possible. For the clinical sample, mothers were interviewed by telephone.

Since the role of smoking during pregnancy as a risk factor for ADHD is already well documented in the literature[5,16] and we previously extended this association for ADHD-I,[17] we are here interested to assess impact of other PDPC. For this reason, smoking during pregnancy was treated as a potential confounding variable in the present study and was not integrated into our total score of PDPC.

Data Analyses

First, we compared patients with ADHD-I to their non-ADHD controls regarding age, gender, ethnicity, schooling, SES, IQ, maternal ADHD, tobacco use during pregnancy, and comorbidities. Second, we defined potential confounding factors. They were defined based on conceptual analyses of the literature and/or using a broad statistical definition (association with both the study factor and outcome for a $p \leq 0.20$). This approach ensured conservative analyses.

Because each set of a case and a control were matched by age and gender, we assessed differences between cases and controls for PDPC adjusting for potential confounders using conditional logistic regression analysis.[31] Analyses were performed using the Statistical Package for the Social Sciences for Windows, version 13.0 (SPSS). The a level for statistical significance was set at $p \leq 0.05$.

Results

First, we compared our clinical and non-referred samples regarding the following variables: age, gender, ethnicity, schooling, SES, estimate IQ, maternal ADHD diagnosis, smoking during pregnancy and comorbidities. Since no significant difference emerged from all comparisons, findings from both samples were distributed in two categories – ADHD-I and controls – for all further analyses. Demographic and clinical characteristics of the 124 ADHD-I subjects and the 124 non-ADHD controls are shown in Table 1. Compared with the control group, the ADHD-I group presented more maternal ADHD diagnoses ($p < 0.001$), lower estimated IQ ($p = 0.001$), higher number of cigarettes smoked per day during pregnancy ($p = 0.017$), and greater social phobia ($p < 0.001$) and oppositional defiant disorder ($p < 0.001$).

Pre-, peri-, and postnatal variables assessed are described in Table 2, along with the prevalence of each variable for cases and controls. A significant difference was found in the average number of complications ($p = 0.002$). Regarding specific variables, differences were detected in the number of previous pregnancies ($p = 0.008$), and previous abortions ($p = 0.009$). Mothers of ADHD-I children also presented more illnesses ($p = 0.003$) and used more prescribed drugs ($p = 0.003$) during pregnancy, compared with mothers of non-affected controls.

Table 1 Demographic and clinical characteristics of ADHD-I cases and non-affected controls

Characteristic	ADHD-I (n = 124)	Controls (n = 124)	p-value
Average age, months (SD)	141.7 (38)	140 (37)	0.7
Gender: n (%) male	86 (69.4)	86 (69.4)	1
Ethnicity: n (%) white	83 (67)	91 (73)	0.33
Average schooling, years (SD)	4.4 (2.7)	4.6 (3)	0.6
SES: middle class (%)	70 (58)	72 (59)	0.89
Average estimate IQ (SD)	93.5 (12.4)	98.8 (11.5)	0.001
Maternal ADHD: no. (%)	29 (23.6)	5 (4)	< 0.001
Average of cigarettes/day: median (range)	0 (0 to 40)	0 (0 to 20)	0.017
Children and adolescents comorbidities:			
Mood disorders			
Major depression	5 (4)	3 (2.4)	0.72
Dysthymia	5 (4)	1 (.8)	0.21
Anxiety disorders			
Simple phobia	24 (19.4)	25 (20.2)	1
GAD	15 (12)	6 (4.8)	0.06
SAD	9 (7.3)	7 (5.6)	0.8
Social phobia	23 (18.5)	5 (4)	< 0.001
Agoraphobia	13 (10.5)	6 (4.8)	0.15
Disruptive behavior disorders			
ODD	45 (36.3)	19 (15.3)	< 0.001
CD	3 (2.4)	1 (.8)	0.62

ADHD-I: attention deficit/hyperactivity disorder - inattentive type; SD: standard deviation; SES: socioeconomic status; GAD: generalized anxiety disorder; SAD: separation anxiety disorder; ODD: oppositional defiant disorder; CD: conduct disorder.

Table 2 Odds ratio (OR) for ADHD-I according to perinatal complications, adjusted for potential confounders

Complications	SE	Wald	p-value	Adjusted OR	95%CI
Prenatal					
Maternal age during pregnancy < 16 or > 34 years-old	0.4	0.1	0.7	1.1a	0.5-2
More than 4 previous pregnancies	1.3	1	0.3	3.7b	0.3-49
Previous abortion	0.4	1.5	0.2	1.6c	0.7-3
Bleeding during pregnancy	0.5	0.8	0.4	1.5d	0.6-4
Rhesus incompatibility	0.6	0.5	0.5	0.6e	0.2-2
Maternal illness during pregnancy	0.4	7	0.01	2.7f	1.3-6
Use of prescribed drugs	0.5	8.5	0.003	4.6g	1.6-13
Alcohol use during pregnancy	0.7	3	0.1	3.2h	0.8-12.6
Drug use during pregnancy	2	0.6	0.4	0.3i	0.01-8
Perinatal					
Caesarian delivery	0.3	1	0.3	1.3j	0.8-2
Bad fetal position (breech or transverse)	1	1.5	0.2	0.4k	0.1-2
Anesthesia	0.3	0.04	0.8	1l	0.6-2
Preeclampsia / eclampsia	0.4	0.7	0.4	1.5m	0.6-3.5
Placental abnormalities	1	2	0.1	4n	0.6-21
Early Postnatal					
Low birth weight (< 2,500 g)	0.6	0.1	0.7	1o	0.3-3
Prematurity	0.4	1	0.3	1.5p	0.7-3.5
Neonatal jaundice	0.4	0.005	1	1q	0.4-2
Cord around neck	1	0.01	1	1r	0.1-5.5
Acute postnatal complications	0.6	0.2	0.7	1s	0.4-4.5

ADHD-I: attention deficit/hyperactivity disorder – predominantly inattentive subtype;
CI: confidence interval; CDP: cigarettes/day during pregnancy; GAD: generalized anxiety disorder; ODD: oppositional defiant disorder; SE: standard error; SP: social phobia; y.o: years old; **a**: adjusted for IQ, maternal ADHD and CDP; **b**: adjusted for IQ, maternal ADHD and CDP; **c**: adjusted for SP, agoraphobia, ODD, maternal ADHD and CDP; **d**: adjusted for IQ, SP, agoraphobia, maternal ADHD and CDP; **e**: adjusted for maternal ADHD and CDP; **f**: adjusted for agoraphobia, ODD, maternal ADHD and CDP; **g**: adjusted for GAD, ODD, maternal ADHD and CDP; **h**: adjusted for IQ, SP, ODD, maternal ADHD and CDP; **i**: adjusted for maternal ADHD and CDP; **j**: adjusted for IQ, maternal ADHD and CDP; **k**:adjusted for maternal ADHD and CDP; **l**: adjusted for SP, agoraphobia, maternal ADHD and CDP; **m**: adjusted for agoraphobia, maternal ADHD and CDP; **n**: adjusted for agoraphobia, maternal ADHD and CDP; **o**: adjusted for GAD, agoraphobia, ODD, maternal ADHD and CDP; **p**: adjusted for GAD, agoraphobia, ODD, maternal ADHD and CDP; **q**: adjusted GAD, maternal ADHD and CDP; **r**: adjusted for IQ, GAD, maternal ADHD and CDP; **s**: adjusted for IQ, GAD, agoraphobia, maternal ADHD and CDP.

The diagnoses of oppositional defiant disorder (ODD), generalized anxiety disorder (GAD), and agoraphobia were considered potential confounding factors (associations for both the study factor and the outcome measure with $p \leq 0.2$). We decided to conservatively keep in the model maternal ADHD and number of cigarettes smoked per day during pregnancy based on conceptual analyses of literature.

The conditional logistic regression analysis (adjusted for these five confounding factors) demonstrated that children and adolescents whose mothers presented more PDPC had a significant higher risk for ADHD-I ($p = 0.005$; OR = 1.25; CI 95% 1.1-1.5) (Table 3).

Discussion

We investigated the association between pre-, peri-, and early postnatal complications and the diagnosis of ADHD-I in a sample with 248 children and adolescents. We were able to find significant differences between cases and controls regarding to the presence of these complications. An increase in the number of PDPC determined a higher OR for ADHD-I.

The strength of the association found between PDPC and ADHD-I may have been small and more significant in the clinical sample. This is expected since population and clinical samples can have different abilities to detect association with causal factors. This can be a limitation of our study.

These findings suggest that biological risk factors, such as PDPC, may play an important role in the pathogenesis of ADHD-I regardless the presence of comorbid disorders in probands, ADHD diagnosis in mothers, and tobacco exposure during pregnancy. The combination of multiple environmental factors as risk factors for ADHD is an interesting direction for future investigation of the dopamine deficit hypothesis of ADHD. In animal models, the dopaminergic system appears to be particularly vulnerable to a wide range of perinatal insults, resulting in persistent alterations in function of mesolimbic and mesostriatal pathways (see Boksa & El-Khodor, 2003, for a review).[7] In a recent study, adult rats that were exposed to repeated hypoxia during the equivalent of extreme prematurity were hyperactive in response to delayed reward.[32]

Table 3 Odds ratio (OR) for ADHD-I according to perinatal complications, adjusted for potential confounders in ADHD-I cases and controls

	SE	Wald	p value	Unadjusted OR	Adjusted OR	95%CI
Perinatal complications	0.08	7.6	0.005	1.23	1.25	1.1-1.5
GAD	0.63	0	0.9	2.5	1	0.3-3.5
Agoraphobia	0.6	2.6	0.1	2.16	2.6	0.8-8.6
ODD	0.36	3.8	0.05	2.85	2	1.0-4.2
Maternal ADHD	0.6	11	0.001	7	11	2.2-23.2
Cigarettes/day during pregnancy	0.03	1.7	0.2	1.06	1	0.9-1.1

ADHD-I: attention deficit/hyperactivity disorder – predominantly inattentive subtype; CI: confidence interval; GAD: generalized anxiety disorder; ODD: oppositional defiant disorder; SE: standard error.

There is no doubt that severe perinatal adversity can damage the CNS development. This will apply, for instance, to cerebral palsy, intraventricular hemorrhage, or when birth weight is less than 1,500 g or the gestational age is less than 29 weeks. Milder levels of perinatal stress are much more common, and may be significant if they occur in combination.[8] In fact, a large number of epidemiological studies confirmed that obstetric complications associated with fetal or neonatal hypoxia increase the risk for schizophrenia.[33,34] Also, Kinney et al.[27] found association between obstetric complications and bipolar disorders.[27]

The association between PDPC and ADHD-I suggested in our study concurs with those found in the existing literature for ADHD in general. There is an increasing interest on the study of the association of pregnancy and delivery complications and ADHD in the last few years, with most of the studies showing positive results for this association.[2,35] For example, Amor et al.[35] found greater number of neonatal complications in their sample of 50 ADHD children compared with their 50 unaffected siblings. No differences between cases and controls related to low birth and to maternal alcohol and tobacco consumption during pregnancy were found.[35] In another study, disruptive behavior disorders were significantly associated with maternal physical problems during pregnancy and delivery, especially acute anoxia/hypoxia.[26] However, there is a scarcity of studies addressing the association between inattentive scores and perinatal risk factors. Previous investigations have suggested that both environmental and genetic factors contribute to the phenotypic heterogeneity of ADHD characterized by the type and severity of the symptoms (ADHD subtypes).[16]

Our findings must be understood in the context of some limitations. First, our measurement of exposure was susceptible to error since retrospective case-control studies rely on self-report interviews. However, to check the reliability of our estimates of association, we compared mothers' information to hospital registers in 38% of our sample. For example, the mean difference between mother's information and hospital registers in birth weight was 7 g ($p = 0.8$). No other significant difference emerged from these comparisons. Second, mothers can underreport perinatal complications which might have affected our results in a conservative way.[36,37] Cantor-Graae et al.[38] found no significant differences between patient and control mothers in error type or recall facility for selected events. However, patients had significantly more obstetric events than controls only when hospital record information was utilized.[38]

As we know, the contribution of genetic factors in ADHD heritability is very high: around 75%.[2,3] So, we expected to find a significant association between diagnosis of maternal ADHD and ADHD-I in the probands (Table 3). This also can be a limitation of our study that we tried to reduce including maternal ADHD as a confounding factor (for both cases and controls) in our analyses.

A recent study about the association between smoking in pregnancy and ADHD showed evidence that this association could be confounded by genetic variants. The authors evaluated the association between antenatal smoking and ADHD behavior in the offspring in mothers genetically related (normal in vitro fertilization) and genetically unrelated (in vitro fertilization with egg donation). Association between smoking during pregnancy and lower birth weight was found in unrelated and related mother-offspring pairs. However, for ADHD symptoms, the magnitude of association was significantly higher in the related pairs ($p < 0.02$) than in the unrelated pairs ($p > 0.10$), suggesting inherited effects. One major problem was the small sample size of the unrelated group genetic who smoked ($n = 9$).[39] Other recent studies have been showing the association between intrauterine tobacco exposure and low birth weight, prematurity and intrauterine growth restriction.[40-42] Even though we chose to include the number of cigarettes/day during pregnancy as a potential confounding factor in the analyses because this variable was associated with ADHD-I in the study by Schmitz et al that used a similar sample.[17]

Finally, we assessed some variables from direct interviews in the community sample and from phone interviews in the clinical sample. Although this might create noise in analyses, we were not able to identify any significant difference between clinical and community samples in these variables.

Our strategy for measuring PDPC was not based in the application of any individual scale. Most of the studies have been using scales created in the early seventies to identify pre- and perinatal complications in mothers of schizophrenic patients. The scales generate scores considering different weights for complications based on levels of severity. Since we were not able to identify any study testing the validity of these scores, we implemented a more comprehensive

strategy of including the entire list of variables from different scales.[5,11,26-30,35] Despite the lack of studies on the validity of these scales, we decided to check our results entering data to generate scores in the extensively used scale developed by Kinney et al.[27] Using this analytic strategy, the conditional logistic regression analysis (adjusted for the same five confounding factors) showed very similar results (p = 0.007; OR = 1.2; CI 95% 1.05-1.35).

A recent revision paper considered prenatal, perinatal and postnatal factors together as acquired risk factors in the etiology of ADHD. The author suggested that environmental factors, including prematurity, alcohol and tobacco exposure during pregnancy, cerebral hypoxic ischemia, viral infection and endocrine disorders may contribute as secondary causes for ADHD. He also emphasized that the early prenatal recognition, prevention, and treatment of environmental causes may provide more effective management and reduces the reliance on symptom modification with medication. Furthermore, advice regarding hazards of nicotine and alcohol exposure and monitoring of blood count and thyroid function during pregnancy could be particularly important for patients with a family history of ADHD.[43]

Conclusion

There is an extensive debate in the literature on the validity of ADHD subtypes in the DSM-V era.[44] Moreover, it is not clear if "real" ADHD predominantly inattentive type (not only subthreshold ADHD combined) is a different nosological construct than the well established ADHD-combined construct. Our findings corroborate for this discussion showed that similar environmental factors may act as environmental triggers in both conditions. Another interesting strategy for future studies is to evaluate the role of perinatal factors between ADHD-I and ADHD-combined samples.

In a recent review of community-based interventions for improving perinatal and neonatal health outcomes in developing countries, authors emphasized the lack of studies addressing the impact of "standardized" antenatal care programs on maternal health and pregnancy outcomes.[45] Even in this context, our results can have a clear impact in public mental health policies due to the preventable nature of some of these PDPC.

In sum, our results suggest that there is an association between ADHD-I and perinatal complications. As far as we are aware, this study is the first to focus on a sample of extensively assessed subjects with ADHD – predominantly inattentive type. Our results expanded to ADHD-I previous findings suggesting the association between perinatal factors and broadly defined ADHD in clinical samples. Future prospective studies are necessary to establish a causal association.

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