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Environmental (Perinatal) Risk Factors of ADHD in a Sibling Control Design Study

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Abstract

Background: ADHD is a common disorder affecting 5% of children worldwide. Many previous studies have examined associated risk factors of ADHD, but the aetiology of ADHD still remains multifactorial and inconclusive. Our study examined perinatal environmental risk factors of ADHD children in a sibling control study.

Method: We collected data of 130 ADHD-sibling pairs; ADHD children who met the DSM IV for ADHD and had been on stimulant medication for at least a year while their siblings closest in age without ADHD were selected for comparison. We utilized a sibling design to control for shared genetic and environmental factors.

Results: The ADHD subjects were similar to controls for birth weight, gestation, mean age and the occurrence of maternal post-natal depression; but significantly different in gender ratio. Adverse events in pregnancy were reported more commonly in the ADHD group than the sibling group. Smoking and alcohol use in pregnancy were similar in both groups. Siblings without ADHD were more likely to be delivered by spontaneous delivery ($p = 0.044$) and ADHD children more likely to require induction ($p = 0.014$).

Conclusion: Children with ADHD and their siblings were equally exposed to risk factors such as smoking and alcohol in utero, popularly thought to be implicated in ADHD aetiology. Risk factors previously thought to be associated with ADHD need to be re-examined through intra-familiar studies adequately controlling for confounding factors.

Keywords: ADHD; Environmental Risk Factors

Introduction

ADHD is a common neurodevelopmental disorder of childhood with a worldwide prevalence estimate of 5% [1], affecting boys more than girls in a 4:1 ratio [2-4]. The disease extends into adulthood in the majority of people; interferes with social, educational, financial and career development and future sustainability and independence [5-8]. ADHD carries an enormous health burden and a substantial socioeconomic cost [9]. It is characterized by inattention, hyperactivity and or impulsivity that is excessive for the developmental age and impairing functioning in several domains of life [10].

ADHD in the Australian paediatric practice is the most frequent diagnosis in general paediatric practice and accounts for 18-30%, [11] of presentations. More children with ADHD are seen through private paediatric service than

any other diagnosis in Australia [12]. Most of the children with ADHD are diagnosed by pediatricians [2,13].

ADHD has a high heritability rate of 75-79% [14,15] in twin and adoption studies depicting a large genetic/familial causative pathway. The exact aetiology remains inconclusive despite many studies on this complex disorder. The relationship between genetic and environmental factors and the expression of ADHD is complex, hence the true isolation of both factors is difficult to achieve in research studies [16,17]. The genes may increase susceptibility to developing ADHD and environmental factors may interfere with gene expression [18]. The current position suggests a multimodal genetic- environmental interactional mechanism as a causal pathway for ADHD development [18]. The gene or environment cannot be treated in isolation in the discovery of the causal factors for ADHD. As a result, intra-familial studies (prospective) are significantly useful and better designed to unravel such a complex multi-mechanism causal relationship [16,17,19]. Environmental factors such as: smoking, alcohol and substance use in pregnancy; low birth weight and prematurity; maternal stress, severe early deprivation, home environment and parenting factors; environmental toxins and dietary deficiencies/surpluses have been described in the literature to be associated with ADHD. These factors can be further categorized into perinatal, environmental toxins, dietary factors and psychosocial adversity [18,20]. Behavioural genetic research studies, categorized them into shared and non-shared environmental factors which respectively explain the similarity and differences specific to family members [21]. The role played by shared factors in differential behavioural/pathological outcome of siblings have been estimated to be minimal [21,22], however the non-shared factors may contribute more to the development of ADHD [16,21,22]. Severe early deprivation has been strongly linked to ADHD [18,23]. Maternal stress, alcohol, drug and tobacco use; low birth weight, prematurity and environmental toxins have been moderately linked to ADHD; while family adversity and low income, conflicting home environment and dietary factors have a weaker link to ADHD [18].

Our study examined children with ADHD and their siblings in an Australian city with an intra-familial study design focusing on perinatal environmental risk factors and their relationship with ADHD. This intra-familial study design has the advantage of controlling for 50% of shared genetic factors and some shared environmental factors such as socioeconomic factors, family environment, parenting factors and pre-pregnancy medical problems. However, we admit unshared factors will still exist depending on the degree of sibling ship and other uncontrollable environmental factors [19].

We hypothesized that the comparison of ADHD children to their siblings while examining risk factors such as smoking, alcohol and substance use in pregnancy, adversity in pregnancy, medical problems in pregnancy, birth weight, gestation at delivery and type of delivery while keeping genetic influences and shared environmental factors controlled (such as home environment, parenting style, pre-pregnancy medical and mental health, socioeconomic status) would expose the true relationship between these factors and the development of ADHD.

Method

We collected data as part of a larger study of 360 ADHD children and their families in Perth between November 2009 and July 2010. We were interested in comparing the environmental risk factors that distinguished the ADHD children from their sibling. This study is an intra-familial study that focused on known perinatal environmental risk factors. Ethics approval was sought from the Human Research Ethics Committee of the University of Western Australia. Children with ADHD and their siblings closest in age were recruited from private paediatric clinics across Perth. Children with ADHD were eligible if they met the DSM IV or ICD 10 diagnostic criteria for ADHD and had been on pharmacotherapeutic treatment for minimum of a year before enrolment in study. Siblings without ADHD diagnosis and closest in age to the ADHD children were selected. Their parents were invited to participate and consent was sought after the research process was explained. Consenting parents received questionnaires for both the ADHD child and siblings. The full questionnaires requested information related to parental and child demographic details, ADHD history and management, medical and mental comorbidities, perinatal history, growth and development in early years, school performance and allied health involvement [24]. The information obtained for this study include: child demographic details; smoking, alcohol and drug use in pregnancy, pregnancy-related adversity, medical complications of pregnancy and mode of delivery.

One hundred and thirty ADHD-sibling pairs were analysed in this study. All of the siblings are full siblings. The study had a response rate of 89% and exclusion of 30 subjects due to partial completion of questionnaire. The number of all notified ADHD children by stimulant prescription in WA remained stable over the period of data collection.

Statistical Analysis

Categorical data were described using frequencies and proportions, and continuous data using medians and ranges or inter quartile ranges. Differences in proportions

for pregnancy related adversity, smoking and alcohol use, medical conditions and delivery mode was assessed using chi square or fishers exact test (when cell counts were <5). T test was used to compare the mean age, birth weight and gestational age of the two groups.

Conditional logistic regression was used to determine odds ratios, their 95% confidence intervals and corresponding p values. This method was chosen over unconditional (standard) logistic regression to account for the matching of the children with ADHD with their sibling.

All data were assessed using Stata 14 (College Station, TX: StataCorp LP). Alpha was set as $p<0.05$.

Results

The ADHD and sibling groups were well matched for age, birth weight, gestation age and pregnancy associated postnatal depression. There were gender differences, with the ADHD group having more male children. This is illustrated in Table 1.

	ADHD n (%)	Sibling Control n (%)	p value
Gender of child			
male	104 (80.0)	56 (43.1)	<0.001
female	26 (20.0)	74 (56.9)	
Pregnancy planned			
no	33 (25.4)	30 (23.1)	0.664
yes	97 (74.6)	100 (76.9)	
Post Natal depression			
no	109 (83.9)	112 (86.8)	0.421
yes	12 (9.2)	13 (10.1)	
Suspected	9 (6.9)	4 (3.1)	
	ADHD mean (SD)	**Sibling Control mean (SD)**	**p value**
Age (years)	12.7 (3.4)	12.58 (5.2)	0.777
Birth weight (grams)	3256.2 (661.4)	3329.9 (565.1)	0.34
Gestational age (months)	38.5 (2.9)	39.0 (2.7)	0.233

Table 1: Distribution of selected demographic and maternal health parameters in the study population.

Parental reports of adversity in pregnancy (all trimesters combined) were more common among children with ADHD than their siblings as shown in Table 2. Mothers of children with ADHD recorded a higher proportion of pregnancy related problems, death of close relative and marital problems than the sibling group (OR 2.0, CI 0.9-4.45, p 0.09; OR 2.0, CI 0.6-6.64, p 0.258 and OR 2.5, CI 0.49-12.89, p 0.273 respectively). However, these differences did not show statistical significance. Reports of financial difficulties were significantly more common in the ADHD group than in the sibling group (OR 4.0; CI 1.3 -11.96; p 0.013). Mothers in the sibling group reported having problems (during pregnancy) with their other children compared to mothers in the ADHD group (9.2% versus 2.3% respectively). A relatively higher proportion of ADHD children (60%) compared to siblings (46.9%) were exposed to adverse events in pregnancy. The likelihood of being later diagnosed with ADHD increased with the number of adverse events in pregnancy as shown in Table 3.

Adverse Events During Pregnancy	ADHD n (%)	Sibling Control n (%)	OR (95% CI)	p value
Pregnancy related problems	35 (27.1)	26 (20.0)	2.00 (0.90, 4.45)	0.09
Death of a close relative	8 (6.2)	4 (3.1)	2.0 (0.60, 6.64)	0.258
Death of a close friend	6 (4.6)	5 (3.9)	1.25 (0.34, 4.65)	0.739
Violence/abuse	13 (10)	13 (10)	1.0 (0.20, 4.96)	1

Separation/divorce	2 (1.5)	3 (2.3)	0.67 (0.11, 3.99)	0.657
Marital problems	18 (13.8)	15 (11.5)	2.50 (0.49, 12.89)	0.273
Problems with other children	**3 (2.3)**	**12 (9.2)**	***0.25 (0.07, 0.89)****	***0.032****
Respondents' job loss	1 (0.8)	2 (1.5)	0.50 (0.05, 5.51)	0.571
Partners' job loss	6 (4.6)	4 (3.1)	1.50 (0.42, 5.32)	0.53
Financial problems	**29 (22.5)**	**17 (13.1)**	**4.0 (1.34, 11.96)**	**0.013***
Residential move	32 (24.6)	30 (23.1)	1.12 (0.57, 2.21)	0.732
Other	12 (9.2)	9 (6.9)	1.60 (0.52, 4.89)	0.41

Table 2: Adverse events reported during pregnancy in the ADHD-Sibling Group.

Events in pregnancy	ADHD n (%)	Sibling Control n (%)	OR (95%CI)	p Value
0	52(40.0)	69 (53.1)	Reference	
1-2	56 (43.1)	39 (30.0)	2.11 (1.14, 3.93)	***0.018****
3-4	17 (13.1)	13 (10.0)	2.14 (0.55, 8.26)	0.269
5 or more	5 (3.8)	9 (6.9)	0.64 (0.11, 3.73)	0.617

Table 3: Number of reported adverse events/problems in pregnancy of the ADHD-Sibling Group.

Parental reports of selected medical conditions experienced in pregnancy for both groups showed no significant difference as shown in Table 4. Hypertension had an OR of 1.67 and migrated to 3.39 after adjustment for gender, age, birth weight and gestation age, but still not did not meet statistical significance.

Medical Condition	ADHD n (%)	Sibling Control n (%)	OR (95%CI) Unadjusted[a]	OR (95%CI) Adjusted[ab]
Severe Vomiting	30 (23.1)	25 (19.4)	2.25 (0.69, 7.31)	0.79 (0.06, 10.76)
Hypertensive disorders of Pregnancy				
Pre-eclampsia	6 (4.6)	11 (8.5)	0.25 (0.05, 1.18)	NA
Hypertension	17 (13.1)	14 (10.9)	1.67 (0.61, 4.59)	3.39 (0.38, 30.07)
Threatened miscarriage				
Mild	9 (6.9)	11 (8.5)	0.86 (0.29, 2.55)	0.05 (0.00, 21.09)
Moderate -Severe (requiring bed rest)	9 (6.9)	10 (7.7)	0.8 (0.21, 2.98)	NA
Diabetes	7 (5.4)	7 (5.4)	1.5 (0.25, 8.98)	NA
Iron Deficiency	28 (21.5)	25 (19.2)	1.6 (0.52, 4.89)	NA

NA-fail to converge. Substantial number of observations dropped due to all positive or negative outcomes **(a)** OR for yes vs. no (unsure excluded); **(b)** Adjusted for gender, age, birth weight and gestation age.

Table 4: Medical conditions reported during pregnancy for the ADHD-Sibling Group.

For both groups, there was no significant difference for smoking or drinking before or during pregnancy as shown in Table 5. Alcohol consumption rates in both groups were similar, 33% vs. 31.8% in the sibling group compared to the ADHD group respectively. Similar smoking rates were seen in both groups before and during pregnancy.

Smoking & Alcohol	ADHD n (%)	Sibling Control n (%)	OR (95%CI)	p value
Alcohol Use				
Ever	106 (81.5)	109 (83.8)	0.25 (0.03,2.37)	0.215
Use within 3 months prior to pregnancy	75 (68.2)	78 (62.4)	1.67 (0.61,4.58)	0.323
Continued use during pregnancy	41 (31.8)	36 (33.0)	1.67 (0.61,4.48)	0.323
Continued but reduced use during pregnancy	39 (95.1)	31 (88.6)	NA	NA
Smoking				
Ever	61 (46.9)	62 (47.7)	1.05 (0.87,1.27)	0.604
Within 3 months prior to pregnancy	42 (32.3)	38 (29.5)	1.60 (0.52,4.89)	0.41
Continued during pregnancy	29 (22.3)	29 (22.3)	1.00(0.29,3.45)	1
Continued to smoke but reduced quantity during pregnancy	23 (79.3)	20 (69.0)	NA	NA

NA-fail to converge. Substantial number of observations dropped due to all positive or negative outcomes

Table 5: Maternal smoking and alcohol use reported during pregnancy for the ADHD-Sibling Group.

Siblings of ADHD children were more likely to be delivered by spontaneous delivery while ADHD children were more likely to be induced or delivered via assisted vaginal delivery as shown in Table 6.

Type of Delivery	ADHD n (%)	Sibling Control n (%)	OR (95%CI) Unadjusted	p value	OR (95%CI) Adjusted[a]	p value
Spontaneous	56 (43.4)	69 (53.9)	0.48 (0.23,0.98)	0.044	0.67 (0.25, 1.77)	0.418
Induced	41 (31.8)	24 (18.8)	2.33 (1.19, 4.59)	0.014	2.98 (1.24,7.14)	0.015
Forceps	10 (7.8)	5 (3.9)	2.25 (0.69, 7.31)	0.177	NA	NA
Vacuum	13 (10.1)	8 (6.3)	1.71 (0.67, 4.35)	0.257	13.27 (0.21,844.52)	0.222
Emergency CS	14 (10.9)	21 (16.4)	0.42 (0.15, 1.18)	0.1	NA	NA
Elective CS	13 (10.1)	11 (8.6)	1.13 (0.43,2.92)	0.808	NA	NA

Table 6: Mode of Delivery.

Discussion

Environmental factors and their relationship to ADHD have been extensively studied and discussed. It is unclear in most studies whether these factors are correlates, risk factors or causal risk factors. Our purpose in this study is to further clarify this relationship. Our main findings suggest that ADHD children share similar smoking and alcohol risks as their unaffected siblings. We show that ADHD children have a greater exposure to adversity in pregnancy and are more likely to need assistance at delivery than their non-affected siblings.

Smoking in pregnancy is a widely studied risk factor which has been associated with increased risk of ADHD [25-29]. These studies have mostly adjusted for important environmental confounders and have examined this risk in comparison with healthy unrelated controls such that a large genetic confounding exists as well as other factors that may/may not interfere with ADHD development. The associated risk of ADHD with maternal smoking was significantly reduced when the same exposure was analysed in an intra-familial study population, distinguishing the confounding roles of genetic and sociodemographic factors [30]. The possibility that families of ADHD children have a higher incidence of smoking, alcohol and psychiatric disorder remains [31,32]. Hence a higher proportion of maternal smoking, alcohol use and other psychiatric comorbidities in pregnancy may not be far-fetched [31,33]. This association may be a secondary effect or due to genetic expression [19,31,34]. A study of smoking and ADHD in siblings with discordant maternal smoking practices in pregnancy showed smoking in pregnancy may cause the hyperactivity type ADHD if Conner's rating (a more sensitive assessment) is used; however no causality is shown for inattentive or combined ADHD type or if CBCL is used [35]. The more recent studies on smoking have also established a similar result to our study suggesting smoking in pregnancy to be a confounding factor and not a causal

factor of ADHD [36-38]. Lastly, smoking during pregnancy is also associated with LBW and preterm birth which is known to influence brain development. This is further discussed in a later paragraph.

Similarly, studies of prenatal alcohol use have portrayed an increased risk of ADHD [39,40]. Prenatal alcohol exposure is associated with ADHD-like symptoms (attention deficits, hyperactivity, distractibility, impulsivity) in such children [41-44]. Problems with executive dysfunction and adaptive functioning are both common to FASD and ADHD children [45-47]. However using the four-factor model of attention, there are differences in symptoms and treatment response between typical ADHD and ADHD in FASD [46]. The description of ADHD found in FASD as a different phenotype negates alcohol as a causative factor for ADHD while the similarity in symptomology of ADHD and FASD and lack of clinical separability leads to the suggestion that alcohol maybe a possible variable causal factor for ADHD [48]. The prevalence of ADHD in children with heavy alcohol exposure is higher than that in the general population [40,41,49]; and in fact, ADHD is the most common mental health disorder diagnosed in children with prenatal exposure to alcohol [40,41]. Correspondingly the proportion of FASD kids diagnosed with ADHD increases with the level of alcohol exposure [40]. Depending on the level of alcohol consumption, timing and duration, different manifestation of symptoms will be seen for both FASD and ADHD [41,50]. At all levels of alcohol consumption, there is some level of inattention seen [50]. However, despite this high co-morbidity of ADHD in FASD children [39,45], there are ADHD children exposed to alcohol with no FASD, ADHD children not exposed to alcohol and alcohol exposed children with no ADHD symptoms [26,45]. The lack of clarity and measurability of the quantity of alcohol ingested and the timing of ingestion that translates to ADHD development persists. Moreover, the relationship between alcohol in pregnancy and ADHD development may be described by gene expression, a causative factor or a confounding factor. The twins design study demonstrated that the relationship between prenatal maternal alcohol use disorder and offspring ADHD was primarily related to the effect of genetic inheritance of ADHD rather than the effect of alcohol use [31]. However certain factors such as adversity, traumatic brain injury and other perinatal causes were not controlled for in this study. A recent prospective study reports a small causal factor for alcohol and the association stronger if the numerous confounding factors are not accounted for [51]. They showed a positive association between maternal alcohol use in pregnancy and ADHD symptoms in children but no association with ADHD diagnosis.

Maternal stress during pregnancy is a risk factor linked to offspring ADHD. Our study confirms the ADHD group was reportedly exposed to adversity in pregnancy more than the siblings. Similar results were described in an intrafamilial study [52] in which ADHD children were shown to have been exposed to a higher level of stress in pregnancy compared to their unaffected siblings when family history of ADHD and environmental factors such as parenting style, smoking and alcohol in pregnancy, home environment were controlled for. Prenatal stress, specifically bereavement of a spouse or child is associated with a greater risk of ADHD in male children [53]. Furthermore, a prospective study that examined smoking and maternal stress in pregnancy showed an independent strong association of maternal stress with ADHD, especially in boys [54]. An association was found between combined and inattentive type ADHD and maternal stress during pregnancy, post-partum depression and changes in primary caretaker [55]. The exact mechanism for stress/adverse event in ADHD causation is poorly understood. The effect of adverse effects in pregnancy can cause psychological or physical disturbances in the mother and direct or indirect effects on the offspring. There is good evidence both in animal and human studies that prenatal maternal stress has significant effects on growth and development, specifically brain development [56-58]. The underlying mechanism is unclear. In addition, adverse events/stress in pregnancy can result in maternal anxiety, with increase in cortisol levels which is known to affect fetal programming and interfere with neuronal development and the developing HPA axis of the fetus [59,60]. This has been described to have an effect on behavioural development in children.

Furthermore adversity as a risk factor may be considered from a prenatal onset and continuing through childhood in children with ADHD. It is known that families with ADHD are characterized by a high conflict environment which affects the parents, siblings and the ADHD child as compared to non-affected control counter families [61-63]. The mother-child relationship in ADHD children and their affected siblings compared to unaffected siblings and a youth population control is characterized by less affection, more authoritarian control, impaired interactions with mothers and more problems at home [64]. Studies that have examined adversity in childhood have shown it increases the risk of ADHD. An exponential effect was observed as the number of adversity factors increased [23,65-68]. Adversity such as severe marital discord, low social class, large family size, paternal criminality, maternal mental disorder and placement in foster care increased the risk of ADHD when maternal smoking, parental ADHD and gender were adjusted for [65]. There is an inconsistency in reports on how this stressful environment relates to the development of ADHD. The need to further explore the interacting influences between the family environment and the genetic predisposition towards the development of ADHD is vital [69]. A parental ADHD diagnosis also interferes with the family environment and so does an environment of conflict and stress increase the

impairment in children with ADHD [63]. A less supportive home environment has been associated with a higher teacher-rated hyperactivity/impulsivity and a greater risk of oppositionality in combined ADHD and a higher parent-rated hyperactivity/impulsivity and oppositionality in non-ADHD siblings when measured confounding factors are controlled. A home environment of stress and conflict is associated with hyperactive/impulsive symptoms but not with inattention symptoms [62]. Other less adverse factors such as the parenting style, socioeconomic status and their contributory role towards ADHD are complex; and not further discussed as some of these factors are shared across the ADHD-Sibling pair.

Both groups in our study were well matched for their birth weight and gestational age. Birth weight has been linked to ADHD when other confounding factors are controlled for in case control studies [70-72]. Birth weight and gestational age commonly coupled together have been associated with ADHD [73-76]. A study of both monozygotic and dizygotic twins showed that LBW is associated with development of ADHD symptoms when the usual genetic and environmental confounders were controlled for [77]. A population-based sibling control study showed fetal growth predicted an increased risk of ADHD when premature births were accounted for and also when familial confounding factors, both genetic and environmental were controlled for. Broadly speaking, gestational age versus intellectual and physical abilities (developmental disabilities) have been described to have an inverse relationship [78-82]; ADHD has also been specifically linked to prematurity [74,78,83,84]. Moreover, substance use such as smoking and certain medical conditions in pregnancy can result in a low birth weight child. Other factors that affect LBW also need to be considered in the interpretation of studies examining smoking in pregnancy and LBW in the development of ADHD for an adjustment of confounders.

The role of medical conditions in pregnancy and the development of ADHD is a broad field. A case- control study on pregnancy-related maternal risk factors of ADHD showed that somatic and psychiatric disorders in pregnancy are risk factors for ADHD [85]. Research in this area describes varying association of ADHD with multiple medical conditions including hypertensive disorders, diabetes, hyperthyroidism, iron deficiency, etc.. The effect of maternal mental health conditions in pregnancy on ADHD development has been discussed in a sister paper [86]. The selected medical conditions examined in our study showed no significant difference between the two groups. However an increased risk of ADHD has been described in pregnancies with hypertensive disorders with no change in association when individual potential confounders were tested for [87,88]. 2.2% of a prospective cohort of adolescents exposed to diabetes in utero reported ADHD medication use when compared to healthy controls. However when the cohort was subjected to Conner's continuous performance 2 testing, there was no significant difference in attention symptoms [89].

Lower serum ferritin levels were found in children with ADHD compared to their healthy control in a systematic review [90]. They suggested that the true relationship between Ferritin, iron stores in the brain, ADHD symptomology and the effect of ADHD medication on iron needs further research. Our study examined iron deficiency in pregnancy but our findings did not show a significant difference between the ADHD and control group.

Lastly, perinatal complications such as ischemic hypoxic conditions are common in ADHD children than their non-ADHD controls [91]. Our study finding that term children with ADHD are more likely to be delivered by induction compared to their siblings is supported by a recent study [92], which showed births delivered by induction of labor and caesarean section had higher inattention and ADHD scores at the child-follow-up survey after adjusting for parity, sociodemography and maternal mental health both during pregnancy and at the time of the survey. It is interesting to note that a study of augmentation of labor with oxytocin and risk of ADHD Henriksen et al. showed no association between both. The described association between obstetric mode of delivery and a higher risk of ADHD may be due to confounding factors not identified [33,93]. A study of ADHD cases and their controls showed no difference in elective C-section and induction [94].

Our study was designed to further expose the association between ADHD expression and perinatal environmental factors if other important determinants were controlled. The strength of our study is the intra-familial study design which controls for genetic and environmental factors that have confounded many studies examining the effect of environmental factors on the expression of ADHD. Siblings raised together are matched for pre-existing maternal medical and psychiatric disease, home environment, family lifestyle, parenting behaviour and socioeconomic status. The matching of the groups for gestational age is to our benefit as both parameters would have been confounders/ unmeasured variables. The exposure of both study groups equally to smoking and alcohol enables us to control for this factor in relation to other environmental factors.

Parent recall bias represents the main limitation of our study. Another limitation is the sample size of the study. Our small numbers may explain the lack of significant difference seen in both study groups for medical conditions and perhaps for smoking and alcohol. It is possible that there are unshared

environmental factors in the ADHD-sibling group that were not examined in our study that may represent unmeasured cofounders. A third comparison group of siblings with ADHD may be useful to further delineate the linkage between the expression of ADHD and unique environmental factors.

Conclusion

In conclusion, children with ADHD and their siblings were equally exposed to risk factors such as smoking and alcohol in utero, popularly thought to be implicated in ADHD aetiology. Adverse events in pregnancy were reportedly more common in the ADHD group than the sibling. Risk factors previously thought to be associated with ADHD need to be re-examined through intra-familiar studies adequately controlling for confounding factors. ADHD, genetics and environmental factors represent a group of intricately woven factors and their effect cannot be truly established unless carefully designed studies controlling for the possible genetic and environmental factors are performed. We recommend larger-sized prospective, intra-familial studies in this field, with attention to adequate control of relevant risk factors and an in depth study into non-shared factors for future studies to confirm or dispute our findings.

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