Environmental Risk Factors by Gender Associated With Attention-Deficit/Hyperactivity Disorder

WHAT'S KNOWN ON THIS SUBJECT: Attention-deficit/hyperactivity disorder (ADHD) is the most common mental health condition diagnosed in childhood, is highly heritable, and more common in boys. Although studies have identified perinatal risk factors, no one has investigated perinatal risk factors separately in boys and girls.

WHAT THIS STUDY ADDS: Contrary to other studies, low birth weight, postterm pregnancy, low Apgar scores, and fetal distress were not risk factors for ADHD irrespective of gender. Early term deliveries increased the risk of ADHD, and oxytocin augmentation in girls may be protective.

abstract

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BACKGROUND: Early environmental risk factors associated with attention-deficit/hyperactivity disorder (ADHD) have been increasingly suggested. Our study investigates the maternal, pregnancy, and newborn risk factors by gender for children prescribed stimulant medication for treatment of ADHD in Western Australia.

METHODS: This is a population-based, record linkage case–control study. The records of all non-Aboriginal children and adolescents born in Western Australia and aged <25 years who were diagnosed with ADHD and prescribed stimulant medication (cases = 12 991) were linked to the Midwives Notification System (MNS) to obtain maternal, pregnancy, and birth information. The control population of 30 071 children was randomly selected from the MNS.

RESULTS: Mothers of children with ADHD were significantly more likely to be younger, be single, have smoked in pregnancy, have labor induced, and experience threatened preterm labor, preeclampsia, urinary tract infection in pregnancy, or early term delivery irrespective of the gender of the child, compared with the control group. In the fully adjusted model, a novel finding was of a possible protective effect of oxytocin augmentation in girls. Low birth weight, postterm pregnancy, small for gestational age infant, fetal distress, and low Apgar scores were not identified as risk factors.

CONCLUSIONS: Smoking in pregnancy, maternal urinary tract infection, being induced, and experiencing threatened preterm labor increase the risk of ADHD, with little gender difference, although oxytocin augmentation of labor appears protective for girls. Early term deliveries marginally increased the risk of ADHD. Studies designed to disentangle possible mechanisms, confounders, or moderators of these risk factors are warranted. *Pediatrics* 2014;133:e14–e22

AUTHORS: Desiree Silva, MB, BS, FRACP, MPH,[a,b] Lyn Colvin, MPH, PhD,[a] Erika Hagemann, BAppSc (Hon), PhD,[c] and Carol Bower, MBBS, MSc, PhD, FAFPHM[a,b]

[a]Telethon Institute for Child Health Research, Centre for Child Health Research, and [b]School of Paediatrics and Child Health, University of Western Australia, Perth, Australia; and [c]Fremantle Speech Pathology Services, Fremantle, Australia

KEY WORDS

ADHD, risk factors, gestational age, birth weight, smoking in pregnancy

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
AGA—appropriate for gestational age
CI—confidence interval
GA—gestational age
LGA—large for gestational age
MODDS—Monitoring of Drugs of Dependence System
MNS—Midwives Notification System
OR—odds ratio
SEIFA—Socio-Economic Indexes for Areas
SGA—small for gestational age
SM—stimulant medication
UTI—urinary tract infection
WA—Western Australia

Professor Silva conceptualized and designed the study, assisted with the analyses, drafted the manuscript, and revised it critically; Dr Colvin assisted with the study design, carried out the analyses, and reviewed the manuscript; Dr Hagemann assisted with, conceptualized, and designed the study and reviewed and revised the manuscript; Professor Bower conceptualized and designed the study, assisted with the analyses, and assisted with the manuscript; and all authors approved the final manuscript as submitted.

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Address correspondence to Desiree Silva, MB, BS, FRACP, MPH, Telethon Institute for Child Health Research, PO Box 855, West Perth, Western Australia 6872. E-mail: desirees@ichr.uwa.edu.au

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Attention-deficit/hyperactivity disorder (ADHD) is the most common mental health disorder in childhood, with a global prevalence of 5.2%.[1] The key features of ADHD are inattention with or without hyperactivity and impulsivity, which can result in a lifelong disorder with significant social and economic burden.[2] Strong inheritance of ADHD is not disputed,[3] with mean heritability estimated at ~79% and male predominance.[4] However, environmental factors are important.[5] Environmental influences may correlate with, interact with, or mediate genetic influences and the outcome of ADHD and its symptoms.[5–10] For example, genetic effects may be conditional on exposure to certain environmental risks. A recent literature review that focused on the genetic and environmental causes of ADHD suggested that after genetic factors, the strongest evidence of environmental factors relating to ADHD were the rare adversities that include extreme prematurity, very low birth weight, fetal alcohol syndrome, and behaviors associated with early institutionalized deprivation.[10] Others have suggested that the strong genetic risk for ADHD can be moderated or mediated by prenatal (eg, exposure to maternal stress, alcohol, nicotine, lead, preeclampsia, and maternal urinary tract infection [UTI]), perinatal (prematurity, low birth weight, anoxic–ischemic encephalopathy, meningitis, encephalitis), and postnatal (viral meningitis, encephalitis, cerebral trauma) factors.[6,8,9,11,12] However, population studies have shown varying results, from no elevated risk or low risk for ADHD due to perinatal factors[13,14] to an elevated risk associated with prematurity and postterm babies.[15,16] Recently there has been a focus on early term births (37–38 weeks' gestation), which may also increase the risk of ADHD.[17] Being first born has shown mixed results, from no increased risk[18] to nearly twice the risk of ADHD being reported.[19] An elevated risk of ADHD subsequent to administration of perinatal oxytocin has also been reported recently.[20]

Biederman et al[21] suggested that boys may be more susceptible to environmental risk factors than girls. These authors questioned whether the important environmental risk factors may differ between boys and girls, and they identified this as an important subject for additional research. Although most studies have adjusted for some potential confounders, no study to date has considered a comprehensive set of environmental predictors by child's gender. Furthermore, as outlined by Froehlich and colleagues,[22] who reviewed the literature on environmental risk factors and ADHD symptoms, most such studies have limitations, including small sample size, insufficient power, the use of questionnaire reports, parent or caregiver diagnosis of ADHD, recall or social desirability bias, symptoms in toddlers and preschoolers that may not correlate to later diagnostic status, and inconsistencies in diagnosis of ADHD.

To overcome some of these limitations, the population-based, nested case–control study reported here examines a comprehensive set of possible environmental factors, related to the mother, the pregnancy and delivery of the infant, and the newborn, in association with subsequent diagnosis and treatment with stimulant medication (SM) for ADHD. Extending previous research, it explores whether the risk factors differ between boys and girls.

METHODS

In August 2003 the Stimulant Regulatory Scheme commenced in Western Australia (WA), where specific guidelines were set for prescribing SM by an authorized prescriber for people with ADHD diagnosed using either the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* or *International Classification of Diseases, 10th Revision* criteria.[23] Notification to the Monitoring of Drugs of Dependence System (MODDS) of any person commenced on SM is mandatory.

Case Population

For this study, data were extracted from the MODDS on all children and young adults born since January 1, 1980 and <25 years of age who were dispensed SM between August 2003 and December 2007 in WA. A total of 15 733 non-Aboriginal cases were identified. Records of children identified from MODDS were linked to the Midwives Notification System (MNS), a statutory collection of pregnancy, birth, and neonatal information completed by midwives for all births ≥20 weeks' gestation in WA since 1980.[24] We limited our analysis to non-Aboriginal cases born between 1981 and 2003. A total of 12 991 non-Aboriginal cases of ADHD were successfully linked to the MNS. Aboriginal children were not included in this study because ethnic minority groups are less likely to be diagnosed and treated for ADHD.[25] Most nonlinked cases were children born outside WA. The study design is illustrated in Fig 1.

Reference (Control) Population

A random sample of records not linked to MODDS was selected from the MNS. They were frequency matched by year of birth, gender, and socioeconomic status to the case group (2:1); 30 071 controls with pregnancy, birth, and neonatal information were selected. Socioeconomic status was assessed by using the Socio-Economic Indexes for Areas (SEIFA), which provides a measure of relative socioeconomic status about the area in which a person lives.[26]

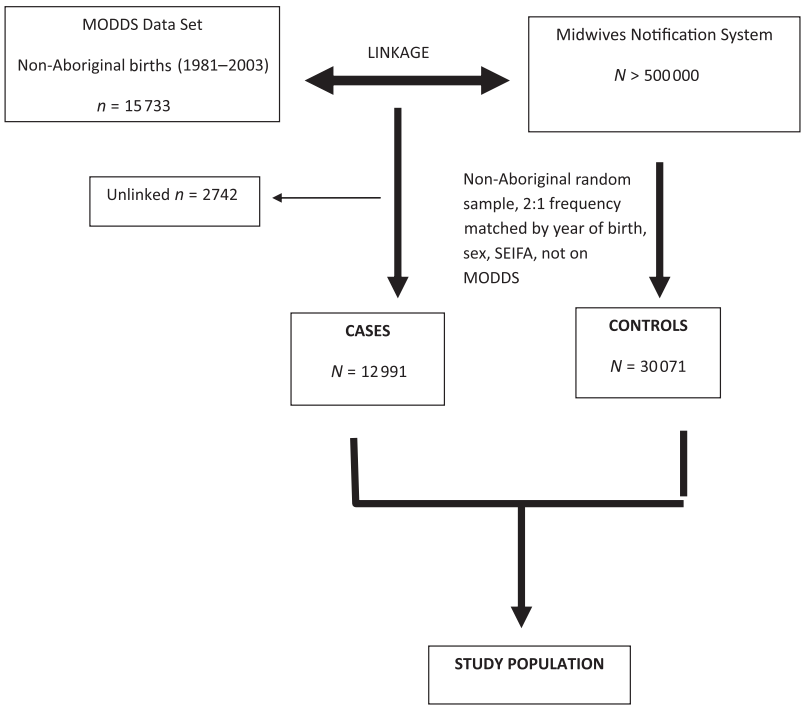

FIGURE 1
Study method flowchart.

Data linkage and extraction were performed by staff of the WA Data Linkage Branch. Once linked, the information was deidentified and provided to the researchers.

Risk and Protective Factors

The maternal, pregnancy, and newborn factors listed in Tables 2, 3, and 4 were available from the MNS for data analysis (for births from 1980 unless otherwise stated).

Maternal factors were maternal age (6 categories), marital status (single), birth order (first born), and postcode of residence at delivery. Smoking in pregnancy was available for birth records since 1997.

Pregnancy, labor, and delivery factors were threatened abortion before 20 weeks' gestation; maternal UTI; preeclampsia; premature rupture of membranes; onset of labor (spontaneous, induced, no labor); complications of labor, which include precipitous delivery, fetal distress, cord prolapse, and cord tight around neck; delivery presentations (vertex, breech, other); and mode of delivery (spontaneous vaginal, vacuum, forceps, emergency cesarean, and elective cesarean). From 1997, information was available on threatened preterm labor (<37 weeks) and oxytocin for both augmentation and induction of labor.

Newborn factors were gender, gestational age (GA), birth weight, and Apgar at 5 minutes. We calculated GA by using the algorithm described by Blair et al,[27] who included both antenatal and neonatal indicators of gestational duration to obtain a more accurate population measure. We also calculated appropriate for gestational age (AGA), small for gestational age (SGA), and large for gestational age (LGA) to provide a better measure of fetal growth and development.

Ethics approval for this study was obtained from the WA Department of Health Human Research Ethics Committee and the Human Ethics Committee of the University of Western Australia.

Statistical Analysis

By using conditional logistic regression to calculate odds ratios (OR) with 95% confidence intervals (CIs), we initially described the associations between each potential risk factor and the diagnosis of ADHD treated with SM, adjusted only for the matching variables year of birth and SEIFA, examined separately for male and female births (partially adjusted model). For our fully adjusted model we simultaneously included all risk factors from the partially adjusted model of clinical significance and relevance. Two multivariable models were constructed using our limited data set from 1997 to 2002 (Model A) and our complete data set from 1981 to 2002 (Model B), which excluded smoking in pregnancy, preterm labor, and oxytocin use. The data analysis for this paper was generated by using SAS/STAT software, version 9.3 of the SAS System for Windows (SAS Institute, Inc, Cary, NC).[28]

RESULTS

The 2 study groups were well matched by gender, year of birth, and SEIFA (Table 1). Seventy-seven percent were male, and a marginally larger proportion of children with ADHD were in the lower SEIFA group.

Partially Adjusted Model: Factors Related to the Mother, Pregnancy, Labor, and Delivery

As shown in Table 2, compared with control mothers, mothers of children with ADHD were more likely to be younger, single, and smokers during pregnancy, irrespective of the gender of the child. There was no elevated risk for first-born boys or girls being diagnosed with ADHD. Mothers of children with ADHD were more than twice as likely to have had threatened preterm labor before 37 weeks compared with the control sample (OR = 2.46, 95% CI, 1.73–3.51 for boys; OR = 2.09, 95% CI, 0.90–4.85 for girls).

TABLE 1 Distribution of Frequency Matching Variables in ADHD Cases and Controls

Matched Variables	Cases		Controls	
	N = 12 991	%	*N* = 30 071	%
Male	10 065	77	23 156	77
Female	2926	23	6915	23
SEIFA, %				
<25	3486	27	7363	25
25–50	2921	22	7494	25
50–75	2673	21	6747	22
>75	2621	20	6735	22
Missing	1290	10	1732	6
Year of birth				
1981–1988	4092	32	9849	33
1989–1996	7211	55	16 373	54
1997–2003	1688	13	3849	13

Threatened abortion before 20 weeks' gestation was also more likely among mothers of cases. There was an elevated risk of ADHD in both boys and girls when mothers had a UTI during pregnancy (OR = 1.37, 95% CI, 1.21–1.55 for boys; OR = 1.51, 95% CI, 1.21–1.90 for girls), or preeclampsia (OR = 1.32, 95% CI, 1.21–1.44 for boys; OR = 1.44, 95% CI, 1.22–1.70 for girls). Induction of labor or no labor and both elective and emergency cesarean deliveries carried a higher risk of subsequently being diagnosed and treated for ADHD. Only

TABLE 2 Partially Adjusted[a] OR and 95% CI of Maternal, Pregnancy, and Labor Risk and Protective Factors Associated With ADHD

Risk and Protective Factors	Male			Female		
	Cases, *N* = 10 065	Controls, *N* = 23 156	OR (95% CI)	Cases, *N* = 2926	Controls, *N* = 6915	OR (95% CI)
Maternal Factors						
Maternal age, y						
<20	687	1029	1.57 (1.40–1.76)	198	325	1.57 (1.28–1.93)
20–24	2302	4765	1.17 (1.09–1.25)	703	1407	1.26 (1.12–1.43)
25–29	3432	8454	1	1001	2578	1
30–34	2538	6426	1.00 (0.94–1.07)	727	1852	1.00 (0.89–1.13)
35–39	975	2143	1.17 (1.06–1.28)	256	659	1.01 (0.85–1.21)
40+	131	339	0.98 (0.79–1.22)	41	94	1.04 (0.70–1.55)
Marital status, single	1288	2057	1.50 (1.39–1.63)	407	664	1.55 (1.35–1.78)
First pregnancy	2978	6711	1.02 (0.97–1.08)	837	1996	1.00 (0.90–1.10)
Smoking in pregnancy[b]	369	510	2.06 (1.74–2.44)	78	113	1.73 (1.21–2.48)
Pregnancy Factors						
Threatened abortion	629	1275	1.15 (1.04–1.27)	183	348	1.28 (1.06–1.55)
Threatened preterm[b]	70	67	2.46 (1.73–3.51)	12	14	2.09 (0.90–4.85)
Maternal UTI	483	820	1.37 (1.21–1.55)	144	227	1.51 (1.21–1.90)
Preeclampsia	891	1587	1.32 (1.21–1.44)	262	443	1.44 (1.22–1.70)
Premature rupture of membrane	427	925	1.04 (0.92–1.18)	104	246	1.02 (0.80–1.30)
Onset of labor						
Spontaneous	5621	14 182	1	1594	4245	1
Induced	3099	6202	1.25 (1.18–1.32)	932	1833	1.33 (1.20–1.48)
No labor	1345	2772	1.17 (1.08–1.26)	400	837	1.15 (1.01–1.31)
Oxytocin use						
Oxytocin augmentation[b]	99	249	0.93 (0.72–1.21)	21	81	0.58 (0.34–0.98)
Oxytocin induction[b]	261	503	1.18 (0.99–1.41)	63	133	1.07 (0.74–1.55)
Complications of labor						
Precipitate delivery	487	1163	0.94 (0.84–1.06)	166	363	1.10 (0.90–1.34)
Fetal distress	1488	3161	1.09 (1.02–1.17)	394	848	1.11 (0.97–1.27)
Cord prolapse	30	59	1.13 (0.71–1.81)	12	16	2.50 (1.08–5.77)
Cord tight around neck	695	1610	0.99 (0.90–1.08)	193	420	1.11 (0.93–1.33)
Presentation						
Vertex	9512	22065	1	2769	6536	1
Breech	471	952	1.17 (1.04–1.31)	133	337	0.98 (0.79–1.21)
Other	79	127	1.29 (0.97–1.73)	23	40	1.47 (0.87–2.46)
Mode of delivery						
Spontaneous vaginal	5921	14 021	1	1800	4337	1
Vacuum	1071	2546	1.01 (0.93–1.10)	283	648	1.09 (0.93–1.27)
Forceps	1025	2249	1.08 (0.99–1.17)	263	665	1.01 (0.86–1.19)
Elective caesarean	1144	2428	1.15 (1.06–1.25)	347	726	1.17 (1.01–1.36)
Emergency caesarean	1063	2294	1.10 (1.01–1.19)	265	596	1.03 (0.88–1.22)

[a] Partially adjusted by year of birth and SEIFA.

[b] Restricted data set: data available from 1997–2002.

oxytocin augmentation and not oxytocin induction of labor appeared to have an effect, protective in female births (OR = 0.58, 95% CI, 0.34–0.98). For fetal distress there was a small (~10%) elevated risk for both boys and girls. Cord prolapse carried a 2.5 times significant increased risk for ADHD in female births, based on small numbers (OR = 2.50, 95% CI, 1.08–5.77). Breech presentation in boys but not girls was associated with a 17% elevated risk of ADHD (OR = 1.17, 95% CI, 1.04–1.31). There was no elevated risk associated with forceps or vacuum delivery, irrespective of gender.

Partially Adjusted Model: Factors Related to the Newborn

Reducing GA carried elevated risk of ADHD for both boys and girls, reaching significance for male births early preterm (<32 weeks), late preterm (33–36 weeks), and early term (37–38 weeks). For early term births, boys had a 12% elevated risk (OR = 1.12, 95% CI, 1.06–1.18), and girls had a 14% elevated risk (OR = 1.14, 95% CI, 1.03–1.27) of ADHD compared with controls (Table 3). There was no increase in risk for postterm deliveries, irrespective of gender. Very low birth weight (<1500 g) carried a small but not significant risk for ADHD, similar for boys and girls. Low birth weights (1500–2499 g) carried an elevated risk for ADHD in boys (OR = 1.16, 95% CI, 1.03–1.30). SGA carried an elevated risk for ADHD for both boys and girls; however, there was no effect for LGA. Low Apgar scores at 5 minutes did not carry an elevated risk for ADHD irrespective of gender.

Fully Adjusted Model

The fully adjusted models looked at all relevant study risk factors associated with ADHD (Table 4). The OR associated with single mothers, maternal UTI, preeclampsia, and induced onset of labor remained elevated irrespective of gender. Threatened preterm labor for boys carried a significant risk (OR = 1.83, 95% CI, 1.22–2.75). The OR for smoking in pregnancy remained elevated, with CI excluding unity for both boys (OR = 1.86, 95% CI, 1.53–2.27) and girls (OR = 1.67, 95% CI, 1.07–2.61). Oxytocin used to augment deliveries was protective for girls, although the CI included unity (OR = 0.58; 95% CI, 0.32–1.06). There was a threefold elevated OR for cord prolapse for females only (OR = 2.83; 95% CI, 1.13–7.12). Reducing GA in boys increased the risk of ADHD where CI excluded unity only for early term deliveries. SGA did not remain associated with ADHD in the fully adjusted model.

DISCUSSION

This is the first population study of Australian children with ADHD and one of the largest internationally, looking at potential early risk and protective factors related to the mother, pregnancy, delivery, and the newborn.

This study clearly identifies an elevated risk of being diagnosed with ADHD and treated with SM among the offspring of young and single mothers, mothers who smoked in pregnancy, and those who had threatened preterm labor, preeclampsia, UTI, and induction of labor, irrespective of the gender of the child. Lower GA and low birth weight for boys were significantly related to ADHD only in our partially adjusted model, although early term deliveries remained significant in our fully adjusted model. Similar to most larger

TABLE 3 Partially Adjusted[a] OR and 95% CI of Newborn Risk and Protective Factors Associated With ADHD

Newborn Factor	Male			Female		
	Cases, *N* = 10 065	Controls, *N* = 23 156	OR (95% CI)	Cases, *N* = 2926	Controls, *N* = 6915	OR (95% CI)
Gestation, wk						
<29	60	108	1.25 (0.89–1.75)	16	30	1.20 (0.62–2.32)
29–32	139	122	1.54 (1.23–1.92)	31	58	1.34 (0.85–2.10)
33–36	688	1421	1.16 (1.05–1.28)	179	382	1.18 (0.97–1.43)
37–38	2734	5931	1.12 (1.06–1.18)	757	1625	1.14 (1.03–1.27)
39–41	6211	14 883	1	1866	4620	1
>41	219	553	0.94 (0.79–1.11)	69	178	1.00 (0.74–1.35)
Birth wt, g						
<1500	120	208	1.23 (0.97–1.56)	34	66	1.22 (0.79–1.88)
1500–2499	507	994	1.16 (1.03–1.30)	166	364	1.07 (0.88–1.31)
2500–3999	8086	18 715	1	2499	5920	1
≥4000	1352	3239	0.95 (0.88–1.02)	227	565	0.91 (0.76–1.08)
AGA	8030	18 583	0.97 (0.92–1.04)	2319	5511	0.97 (0.87–1.09)
SGA	1009	2071	1.13 (1.05–1.24)	309	656	1.16 (1.00–1.34)
LGA	1011	2468	0.94 (0.86–1.01)	290	728	0.91 (0.78–1.05)
Apgar 5 min						
0–4	49	112	0.93 (0.65–1.34)	9	33	0.62 (0.28–1.34)
5–7	405	833	1.08 (0.95–1.23)	99	208	1.14 (0.88–1.47)
8–10	9601	22 183	1	2815	6669	1

[a] Partially adjusted by year of birth and SEIFA.

TABLE 4 Fully Adjusted Risk and Protective Factors Associated With ADHD by Gender

Risk and Protective Factor	Male		Female	
	Model A,[a] OR (95% CI)	Model B,[b] OR (95% CI)	Model A, OR (95% CI)	Model B, OR (95% CI)
Maternal characteristics				
Marital status, single	1.44 (1.10–1.88)	1.41 (1.29–1.54)	2.79 (1.54–5.06)	1.48 (1.27–1.73)
First pregnancy	1.14 (0.93–1.40)	0.96 (0.91–1.02)	0.73 (0.47–1.13)	0.90 (0.80–1.01)
Smoked in pregnancy	1.86 (1.53–2.27)		1.67 (1.07–2.61)	
Complications of pregnancy				
Threatened abortion	0.99 (0.69–1.42)	1.11 (0.99–1.24)	1.25 (0.59–2.64)	1.23 (1.00–1.52)
Threatened preterm labor	1.83 (1.22–2.75)		1.21 (0.36–4.06)	
Maternal UTI	1.17 (0.79–1.76)	1.26 (1.11–1.44)	0.83 (0.25–2.70)	1.33 (1.04–1.70)
Preeclampsia	1.19 (0.84–1.67)	1.15 (1.03–1.27)	1.49 (0.75–2.99)	1.28 (1.05–1.56)
Onset of labor				
Induced	1.26 (0.95–1.68)	1.23 (1.16–1.31)	0.93 (0.49–1.78)	1.30 (1.17–1.44)
Augmentation of labor				
Oxytocin augmentation	1.09 (0.82–1.45)		0.58 (0.32–1.06)	
Oxytocin induction	1.02 (0.75–1.37)		1.15 (0.59–2.24)	
Complications of labor				
Fetal distress	1.01 (0.79–1.28)	1.07 (1.00–1.15)	1.05 (0.60–1.82)	1.09 (0.95–1.26)
Cord prolapse	3.96 (0.67–23.31)	1.04 (0.63–1.73)	8.36 (0.55–126.31)	2.83 (1.13–7.12)
Type of delivery				
Caesarean	1.02 (0.78–1.32)	0.99 (0.90–1.08)	1.02 (0.57–1.82)	0.96 (0.81–1.15)
Child characteristics				
GA, wk				
<29		1.70 (0.88–3.29)		0.74 (0.18–3.13)
29–32	2.54 (0.77–8.42)	1.28 (0.90–1.82)		1.22 (0.58–2.55)
33–36	1.32 (0.89–1.96)	1.12 (0.99–1.27)	1.03 (0.41–2.61)	1.06 (0.83–1.37)
37–38	1.12 (0.91–1.37)	1.07 (1.00–1.14)	0.79 (0.50–1.25)	1.08 (0.95–1.22)
39–41	1	1	1	1
>41	0.47 (0.16–1.42)	0.86 (0.72–1.02)	6.44 (0.63–65.65)	0.94 (0.70–1.28)
Birth wt, g				
<1500		0.89 (0.50–1.58)		1.40 (0.43–4.53)
1500–2499	0.72 (0.41–1.24)	1.01 (0.86–1.18)	0.88 (0.34–2.29)	1.02 (0.79–1.34)
2500–3999	1	1	1	1
≥4000	0.99 (0.76–1.29)	0.99 (0.91–1.07)	0.97 (0.53–1.75)	0.92 (0.77–1.11)
AGA	1.18 (0.94–1.47)	0.98 (0.92–1.05)	0.89 (0.58–1.37)	0.97 (0.86–1.10)
SGA	0.80 (0.56–1.16)	1.00 (0.89–1.11)	0.75 (0.36–1.59)	1.07 (0.87–1.31)
LGA	0.74 (0.49–1.11)	0.97 (0.86–1.11)	0.98 (0.42–2.27)	1.03 (0.81–1.30)

[a] Model A: Fully adjusted for all factors in the model including maternal age, Apgar at 5 min, year of birth, and SEIFA (data in model available from 1997–2003).

[b] Model B: Fully adjusted for all factors in the model (excluding smoking, preterm labor, and oxytocin induction) including maternal age, Apgar at 5 min, year of birth, and SEIFA (data in model available for full data set from 1981–2003).

studies in the literature that support the correlation of ADHD by degree of prematurity,[16,17,29,30] we also suggest the need to recognize the effect of prematurity even in early term deliveries on subsequent behavior problems including ADHD, and parents requesting early delivery with no obstetric complication should be discouraged.[17,31,32] Gustafsson et al[14] reported only a weak correlation with perinatal, maternal, and fetal characteristics of children diagnosed with ADHD, and their study lacked power because of a small sample size. Our study was able to expand on their findings using a larger population sample and examining the potential risk factors separately for male and female children. We acknowledge that adjusting for a large number of factors may reduce precision, and real associations may be blurred by the choice of variables included in our model. Although precision was reduced, as evident by wider CIs, we found little change in the estimates of ORs between the partially and fully adjusted models except for lower GA estimates in girls, possibly related to a smaller sample size.

The gender difference in ADHD is well documented, particularly among children. However, almost all potential risk factors examined were similar for boys and girls, although CI more often excluded unity for boys because of their larger sample size. The exceptions were threatened preterm labor for boys, where there was a twofold elevated risk, and oxytocin augmentation for girls, where there was a reduction in risk of being diagnosed and treated for ADHD.

Birth order is considered a key environmental factor in child development, shown to be associated with an elevated risk of psychiatric disorders such as ADHD.[19] In our fully adjusted model, being first born was not associated with ADHD.[18] We found that smoking in pregnancy remained elevated after adjustment for a number of maternal, pregnancy, and birth factors. Chronic exposure to smoking in pregnancy has been extensively studied, with the theoretical model predicting that nicotine receptors modulate dopaminergic activity and dysregulation, which can cause ADHD. Literature supports this consistent association,[14,33–37] although several studies question whether the smoking association is all caused by biological effects of tobacco smoke rather than being at least partly explained by confounding factors, which include genetic, socioeconomic, and household factors.[38–41] The mechanism of how tobacco smoke affects the fetal brain remains unclear,[6,33] but it has been hypothesized that perinatal events resulting in hypoxia may affect brain development and lead to ADHD.[11,42,43] Such risk factors include threatened abortion, threatened preterm labor, preeclampsia, prematurity, intrauterine growth retardation, low Apgar scores, and fetal distress.[35,44,45] Our study contradicts some of these

findings in that we found no association with acute events around delivery except for the rare event of cord prolapse in girls, also suggested in a recent study.[11] Maternal preeclampsia and genitourinary tract infections have been associated with other neurodevelopmental disorders, including ADHD,[12,46] where an inflammatory cascade affecting fetal brain development has been suggested. In our fully adjusted model, both preeclampsia and maternal genitourinary tract infections were associated with an elevated risk of ADHD irrespective of gender. Induction of labor has been associated with ADHD[16] and difficult behavior,[20] although no mechanism has been described. We confirmed this finding with an elevated risk irrespective of gender. In our limited data set (Model A) oxytocin augmentation (but not induction) of labor was protective for girls, but CI included unity, and we acknowledge that this may be a chance finding. Oxytocin has recently received more interest in the literature, especially its role in social behavior, although a number of unanswered questions about plausible mechanisms and actions remain.[47] Additional studies should investigate this association and provide some neurobiological explanation, including whether a reduced duration of labor is plausible, because it is surprising that such a late intervention as augmentation of labor may potentially have a neuroprotective effect for female births.

We acknowledge that there are some limitations to our study. First, we had no data on parental mental health; therefore, variables such as family history of ADHD could not be studied.[41] Second, our control population consisted of children who were randomly selected from all WA births not prescribed SM from 2003, when the register was first introduced. It is possible that some of the controls may have been on SM before commencement of the register or have ADHD but were not treated with SM at the time. However, because only 1.2% of children <18 years old are commenced on SM in WA, we believe that the number of children with ADHD in the control sample would have little effect on our results, and any effect would have biased the estimates toward the null. Third, data for smoking, threatened preterm labor, oxytocin induction, and oxytocin augmentation of labor were available for only 10% of cases and controls, limiting analyses for these variables. However, we noted little difference when comparing the fully adjusted complete data set (Model B) with the limited data set (Model A). Finally, our study looked at children diagnosed and treated with SM for ADHD, and therefore it is likely to reflect the more severe cases.

Strengths of this population-based study include the large sample size and the use of record linkage, which removes the possibility of participation and recall bias and loss to follow-up. Furthermore, all the cases met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* and *International Classification of Diseases, 10th Revision* criteria for ADHD and were diagnosed by a pediatrician or psychiatrist, requirements of the prescribing guidelines set out by government legislation in WA.

Our study is one of the largest population studies on antenatal risk factors published to date, using a robust, reliable data linkage system with only deidentified data, ensuring strict privacy. Importantly, we found that risk associations were generally similar for boys and girls with ADHD. We did not confirm an elevated risk for a number of previously published prenatal, pregnancy, and postnatal factors. However, the risk of ADHD remained elevated in children exposed to maternal smoking, preeclampsia, maternal UTIs, induced labor, and early term deliveries, irrespective of gender. For boys, threatened preterm labor was an elevated risk, and for girls the rare condition of cord prolapse nearly tripled the risk of ADHD. Some events related to the mother, pregnancy, delivery, and newborn contribute to the risk of subsequent ADHD, with few gender differences. Perhaps population studies designed to disentangle possible mechanisms, confounders, or moderators of these risk factors are warranted.

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