Preterm Birth and Attention-Deficit/Hyperactivity Disorder in Schoolchildren

WHAT'S KNOWN ON THIS SUBJECT: Attention problems have been described in survivors of neonatal intensive units in school age.

WHAT THIS STUDY ADDS: This study demonstrates that not only extremely preterm birth, but also moderately preterm birth, increases the risk of ADHD by degree of immaturity at birth. Social adversity, as expressed by low maternal education, modifies the risk of ADHD in moderately preterm birth.

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KEY WORDS

preterm, ADHD, socioeconomic, inequity, child, behavior

ABBREVIATIONS

ADHD—attention-deficit/hyperactivity disorder
OR—odds ratio

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abstract

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OBJECTIVE: Previous studies have demonstrated an increased risk for attention-deficit/hyperactivity disorder (ADHD) in follow-up studies of preterm survivors from NICUs. In this study we analyzed the effect of moderate as well as extreme preterm birth on the risk for ADHD in school age, taking into account genetic, perinatal, and socioeconomic confounders.

METHODS: Register study in a Swedish national cohort of 1 180 616 children born between 1987 and 2000, followed up for ADHD medication in 2006 at the age of 6 to 19 years. Logistic regression was used to test hypotheses. A within-mother-between-pregnancy design was used to estimate the importance of genetic confounding in a subpopulation of offspring ($N = 34\,334$) of mothers who had given birth to preterm ($\leq$34 weeks) as well as term infants.

RESULTS: There was a stepwise increase in odds ratios for ADHD medication with increasing degree of immaturity at birth; from 2.1 (1.4–2.7) for 23 to 28 weeks' gestation, to 1.6 (1.4–1.7) for 29 to 32 weeks', 1.4 (1.2–1.7) for 33 to 34 weeks', 1.3 (1.1–1.4) for 35 to 36 weeks', and 1.1 (1.1–1.2) for 37 to 38 weeks' gestation compared with infants born at 39 to 41 weeks' gestation in the fully adjusted model. The odds ratios for the within-mother-between-pregnancy analysis were very similar. Low maternal education increased the effect of moderate, but not extreme, preterm birth on the risk for ADHD.

CONCLUSION: Preterm and early term birth increases the risk of ADHD by degree of immaturity. This main effect is not explained by genetic, perinatal, or socioeconomic confounding, but socioeconomic context modifies the risk of ADHD in moderately preterm births. *Pediatrics* 2011;127:858–865

Increasing numbers of infants born preterm are reaching adulthood as a consequence of advances in perinatal care. A negative effect of preterm birth on the neurologic and psychological development of children and youth is well documented.[1–3] Severe neurologic impairment has been reported in 10% to 12% of school-aged children born very preterm.[4,5] Much higher rates have been reported for more subtle neurocognitive impairment with reports of lower IQ and poor academic achievement.[2,3,6–9]

Attention-deficit/hyperactivity disorder (ADHD) is the most common neurodevelopmental disorder in Western countries,[10] with a prevalence of 3% to 5% in Swedish school children.[11] Several studies have indicated that attention problems are more common in children born preterm. In previous Swedish studies, Farooqi et al[12] found that 11-year-old children born after 23 to 25 gestational weeks had 3 to 4 times as many attention problems compared with term infants, while Stjernqvist and Svenningsen,[9] in their study of Swedish 10-year-old children born after <29 weeks, found a more modest twofold increase. A recent French study of 1102 5-year-old children, born after 22 to 32 gestational weeks, demonstrated a twofold risk for hyperactivity/inattention problems compared with term controls.[13]

Follow-up studies of ADHD in children born preterm have, with very few exceptions, focused on children born extremely preterm and cared for in NICUs.[2] However, studies that include the moderately preterm have indicated that this much larger group of infants also is at risk for negative outcomes in school age and young adulthood,[14–16] including ADHD.[3]

There is agreement about the importance of genetic factors for ADHD even if specific genes have not been identified.[17] A variety of environmental factors are also influential. Exposure, especially fetal exposure, to toxic substances such as lead, alcohol, and PCB have been reported to increase the risk of ADHD (for a review, see Refs 18 and 19). The psychosocial environment, manifested as maltreatment[20] or unfavorable socioeconomic conditions,[21,22] also is associated with an increased risk of ADHD.

Several perinatal complications have been associated with an increased risk for short and long-term neurologic sequeale. A link between intrauterine growth retardation and ADHD has been suggested, even if results are not conclusive.[18,23,24] Perinatal asphyxia may cause hypoxic-ischemic encephalopathy in the neonate with widespread brain injuries as a consequence, and periventricular hemorrhage is a well known risk factor for cerebral palsy in preterm infants.[25–27] However, these perinatal risk factors have not been investigated much in relation to ADHD.

The interplay between potential etiologic factors is intricate, and confounding may obscure seemingly well established associations. For instance, genetic confounding, was found to explain most of the well established association between fetal exposure to nicotine and ADHD in a recent Swedish study.[28] Thus, in studies on preterm birth and ADHD, contributions of other potentially influential factors need to be estimated.[2,29] Swedish national registers offers good prerequisites for studies of this kind. They include comprehensive coverage of the whole population with good quality data about perinatal and socioeconomic risk factors for children born at all gestational ages. Large study groups can be created, which makes it possible to control for genetic influence by comparing offspring from 2 pregnancies of the same mother and father, when only 1 child has been exposed to preterm birth.[28,30] Thus, the aim of this study was to study the effect of different levels of preterm birth on ADHD, taking genetic, environmental and perinatal risk factors into consideration.

METHODS

This study was based on Swedish national registers held by the National Board of Health and Welfare and Statistics Sweden. All Swedish residents are assigned a unique 10-digit identification number at birth or immigration. This identification number was used to link information from different register sources.

Study Population

The study population was created from the 1,242,459 children with a Swedish-born mother in the birth cohorts of 1987 to 2000 who survived infancy, according to the Swedish Medical Birth Register. From this total population, we identified 1,227,096 (98.8%) who were still residents in Sweden on December 31, 2005, according to the Register of the Total Population. We excluded 35 404 children because of at least 1 significant malformation at birth diagnosed by the attending pediatrician and 11 076 because of a registered birth weight above 3 SD or less than −6 SD, according to the growth chart developed by Marsal et al,[31] which indicated a probable coding error.[32] The remaining 1,180,616 were included in the study population and followed up during 2006 at the age of 6 to 19 years.

Perinatal and Socioeconomic Indicators

Perinatal variables were collected from the Swedish Medical Birth Register, a register that contains information about all births in Sweden (Table 1). Gestational age was categorized according to national Swedish perinatal statistics as extremely preterm (23–28 weeks), very preterm (29–32 weeks),

TABLE 1 Register Variables in the Study

Variables	National Register	Definitions
Outcome of ADHD medication	Swedish Prescribed Drug Register	At least 1 purchase of prescription during 2006 of drugs with ATC-codes N06BA01-N06BA04 or N06BA01
Perinatal		
Gestational age	Swedish Medical Birth Register	According to ultrasound measures in early pregnancy (10–18 weeks) in 70.1% and maternal report of last menstrual period in the remaining
Small for gestational age	Swedish Medical Birth Register	Less than −2 SD according to the scale created by Marsal et al (Ref 31) on the basis of intrauterine ultrasound measures
Multiple birth	Swedish Medical Birth Register	Categorized as no if singleton, all others as yes
Low Apgar	Swedish Medical Birth Register	Apgar <7 at 5 min
Maternal smoking	Swedish Medical Birth Register	Information routinely collected by midwife at the first visit to the maternity health clinic after 8–12 weeks' gestation. Categorized into no, 1–9 cigarettes per day, 10 or more cigarettes per day, and missing
Significant malformation	Swedish Medical Birth Register	All (Q00-Q99 ICD-10) except undescended testicle, preauricular appendage, congenital nevus, and hip dislocation
Cerebral palsy	Swedish Hospital Discharge Register 1987–2005	At least 1 hospital admission after 2 years of age with a diagnosis of G80-G80.9 (ICD-10) at discharge
Sociodemographic		
Maternal education	Swedish National Education Register	Highest formal education attained by each individual up to 2005. If mother no longer was a Swedish resident we replaced with paternal education if possible. Categorized by years of education: ≤9; 10–12; 13–14; 15 or more
Maternal age	Swedish Medical Birth Register	Categorized by years: 12–19; 20–24; 25–29; 30–34; 35 or more
County of residence	Total Enumeration Income survey of 2005	See METHODS
Single-parent household	Total Enumeration Income survey of 2005	Household with only 1 adult
Social assistance	Total Enumeration Income survey of 2005	Cash income allowance from local social authorities after a thorough means investigation with the purpose to guarantee the applicant a minimum standard of living
Parental morbidity		
Psychiatric disorder	Swedish Hospital Discharge Register 1973–2005 and National Cause of Death Register 1986–2005	At least 1 hospital discharge diagnosis or cause of death of suicide death/attempt, (X60-X84 or Y10-34 in ICD-10), psychotic disorder (F20-F29 in ICD 10), or affective disorder (F30-F39 in ICD-10)
Addictive disorder	Swedish Hospital Discharge Register 1973–2005 and National Cause of Death Register 1986–2005	At least 1 hospital discharge diagnosis or cause of death of alcohol abuse or illicit drug abuse (F10-F19 in ICD-10)

and moderately preterm (33–36 weeks). The latter group was divided in 2 (33–34 and 35–36 weeks) when the numbers allowed us to do this. Term was divided into 2 groups: early term (37–38 weeks) and term (39–41 weeks).

Sociodemographic and parental morbidity variables were obtained through linkage via the Multigeneration Register to the biological mother and father (see Table 1). Information on inpatient care in the Patient Discharge Register was used to create the parental morbidity variables, and information on inpatient and outpatient care from the Patient Discharge Register was used to create the cerebral palsy variable (Table 1). Evaluations of the Swedish Medical Birth Register and the Patient Discharge Register demonstrate coverage of 98% to 99% of all hospital admissions and births in Sweden in public as well as private care. Evaluations of the register have found the quality of the main variables to be generally high.[34–36]

ADHD

National guidelines for medication of ADHD, issued by the National Board of Health and Welfare in 2002, stated that medication should be reserved for cases in which other supportive interventions have failed, thus reserving medication for the more severe cases. The right to prescribe stimulants for ADHD in Sweden is restricted to specialists with particular familiarity with treatment of this disorder.

The Swedish Prescribed Drug Register contains data with unique patient identifiers for all drugs prescribed and dispensed to the whole population of Sweden (more than 9 million inhabitants) since July 2005.[20] In this study we used the purchase of at least 1 prescription of a stimulant (see Table 1 for definition) during the calendar year 2006 as our outcome variable. There were considerable regional differences in the consumption of ADHD medication. Because these differences did not follow any obvious demographical or geographical pattern, we assumed that they mirrored varying prescription patterns in different counties rather

than variations in the prevalence of ADHD. The counties were classified in 4 categories according to the proportion of children having purchased ADHD medication during 2006: high prescription rates (>0.8%); high average prescription rates (0.7–0.8%); low average prescription rates (0.5–0.6%); and low prescription rates (<0.5%).

Statistical Analysis

Logistic regression was used to calculate odds ratios (OR) with 95% confidence intervals as estimates of effects, with ADHD medication (see Table 1) as the outcome variable.

We used 3 models to investigate the effects of preterm birth on ADHD medication. Model 1 included gender, a 3-category variable for age (6–9, 10–15, 16–19), and county of residence in 4 categories according to level of ADHD medication. In model 2 we added birth order, maternal age, maternal education, single parenthood, public welfare, maternal smoking, and maternal and paternal psychiatric/addictive disorder (see Table 1 for definitions) as possible confounders. In the final model 3 we added low Apgar score and being small for gestational age as possible perinatal mediators/confounders of preterm birth.

To adjust the analysis for potential influence of genetic confounding, we analyzed the within-subjects variation in the subpopulation ($N = 34\,334$) of offspring of mothers who had given birth to preterm as well as term infants. A generalized linear model with the binomial distribution was used to create a conditional logistic regression in which the effects were compared between pregnancies in the same mother. This within-mother-between-pregnancy model, apart from maternal identification, was adjusted for gender and birth order of each child included, age of the mother at the birth of each child included, and age of each child included in 2006.

Interaction analyses were made in a logistic regression model with adjustment for age, gender, and county only. In this analysis we investigated possible effect modifications of cerebral palsy and preterm birth, small for gestational age and preterm birth, low Apgar score and preterm birth to ADHD as potential pathways for the effects of preterm birth on ADHD. Low education was investigated as a marker of social adversity. In these analyses, a simplified categorization of gestational age was applied ([39–41] vs preterm birth [22–36 weeks] or moderately preterm birth [33–36 weeks])because of the comparatively small numbers.

All statistical analyses were performed using SPSS 18.0 (SPSS Inc, Chicago, IL) for Windows.

RESULTS

In all, 7 506 children in the study population had a record of ADHD medication in the register, corresponding to 1.05% of the boys and 0.29% of the girls. The most commonly purchased drug was methylphenidate (87.8%), followed by atomoxetine (9.2%) and amphetamine (3%).

In Table 2, sociodemographic indicators, parental psychiatric morbidity, and perinatal variables by gestational age and ADHD medication are presented. Such medication was more common in the presence of the following variables: teenage mother; single parent; public welfare; low maternal education; maternal as well as paternal addictive/ psychiatric disorder; low gestational age; small for gestational age; low Apgar score; maternal smoking during pregnancy; and cerebral palsy.

In Table 3, the multivariate analysis of ADHD medication is presented. In the analysis of ADHD medication in model 1, that was adjusted for age, gender, and county of residence, the odds ratios (ORs) for ADHD medication were 2.5 for 23 to 28 weeks' gestation, 1.9 for 29 to 32 weeks, 1.6 for 33 to 34 weeks, 1.4 for 35 to 36 weeks and 1.2 for 37 to 38 weeks' gestation compared with being born at term (39–41 weeks). The ORs decreased slightly to 2.1, 1.6, 1.4, 1.3, and 1.1 in the fully adjusted model. Infants born postterm did not have any increased risk for ADHD.

In Table 4, 2 different regression analyses of 34 344 children who are offspring of mothers who had given birth preterm (≤34 weeks) as well as term (39–41 weeks) within our study population, are presented. The first analysis repeats model 1 in Table 3 with similar results. In a second analysis, we compared different offspring of the same mother in a within-mother-between-pregnancy analysis, with ORs of 2.1 for being born at 23 to 28 weeks' gestation, 1.7 at 29 to 32 weeks and 1.4 at 33 to 34 weeks, compared with term births (39–41 weeks), thus similar to those in the fully adjusted model of Table 3.

In an interaction analysis, the effect of moderate (week 33–36) preterm birth on ADHD medication was higher ($P < .01$) in mothers with a low education (see Fig 1). The effects of gestational age on ADHD medication were similar in boys and girls.

A low Apgar score had a marginal effect on the risk of ADHD medication and did not modify the effect of preterm birth on ADHD medication. Being small for gestational age in children born term increased the OR for ADHD medication by 1.4 (1.2–1.6) after adjustment for sociodemographic variables. Being small for gestational age did not modify the effect of gestational age on ADHD medication.

Having an indication of cerebral palsy increased the OR of ADHD medication by 2.5 (1.8–3.3) in the whole study population. This effect was lower in all

TABLE 2 ADHD Medication by Sociodemographic, Parental Morbidity, and Perinatal Indicators With Stratification by Gestational Age, Week

	Week 23–28 ADHD		Week 29–32 ADHD		Week 33–36 ADHD		Week 37–38 ADHD		Week 39–41 ADHD		Week 42–45 ADHD	
	% Yes ($N = 36$)	% No ($N = 2\,257$)	% Yes ($N = 109$)	% No ($N = 8401$)	% Yes ($N = 537$)	% No ($N = 56\,113$)	% Yes ($N = 1\,683$)	% No ($N = 212\,792$)	% Yes ($N = 5\,195$)	% No ($N = 808\,411$)	% Yes ($N = 591$)	% No ($N = 84\,491$)
Gender												
Boys	83.3	51.4	81.7	54.2	81.6	53.5	79.4	50.7	79.5	50.7	80.5	55.4
Girls	16.7	48.6	18.3	45.8	18.4	46.5	20.6	49.3	20.5	49.3	19.5	44.7
County												
Category 1	41.7	28.2	24.8	27.5	33.5	27.7	38.9	28.4	38.4	27.6	34.2	27.3
Category 2	36.1	33.0	48.6	33.5	37.2	32.6	32.1	32.8	32.3	33.3	38.4	36.4
Category 3	16.7	22.7	17.4	22.8	18.1	23.5	20.3	22.9	20.6	23.5	20.3	22.3
Category 4	5.6	16.1	9.2	16.2	11.2	16.2	8.7	15.9	8.8	15.6	7.1	14.0
Maternal age												
12–19	5.6	3.7	7.3	2.8	6.5	2.7	5.3	2.3	5.2	2.1	6.3	2.3
20–24	19.4	16.5	31.2	19.6	33.1	20.5	27.2	19.1	28.3	19.6	30.5	19.1
25–29	30.6	34.1	28.4	33.5	31.3	35.3	32.7	36.2	35.8	38.1	33.5	37.2
30–34	25.0	27.6	22.9	28.4	20.3	26.9	21.4	28.1	21.5	28.2	20.1	28.7
35 or older	19.4	18.1	10.1	15.8	8.8	14.6	13.3	14.4	9.2	11.9	9.6	12.8
Single parent	52.8	27.7	49.5	28.0	38.5	26.5	42.1	25.7	38.9	24.4	41.6	25.3
Social assistance	16.7	5.5	18.3	5.0	16.8	5.3	14.5	4.7	9.9	3.8	12.0	4.0
Maternal education												
≤9 y	19.4	12.0	18.3	10.5	22.7	10.3	17.0	9.6	15.3	8.3	15.6	8.4
10–12 y	50.0	34.4	38.5	36.4	39.5	35.8	43.3	35.0	41.7	33.6	37.2	33.3
13–14 y	13.9	25.3	26.6	23.4	23.1	23.2	19.5	23.4	21.4	24.3	21.2	24.1
15 y or more	16.7	27.3	16.5	28.5	14.2	29.8	18.5	31.3	20.7	33.3	24.2	33.5
Missing	0.0	1.0	0.0	1.3	0.6	0.9	1.7	0.7	0.8	0.5	1.9	0.6
Maternal psychiatric or addictive disorder	16.7	6.9	11.9	6.3	13.8	5.7	14.4	5.1	11.2	4.0	11.0	4.1
Paternal psychiatric or addictive disorder	22.2	6.3	11.0	5.9	14.9	5.3	12.4	4.9	11.0	4.3	11.2	4.6
Small for gestational age	19.4	20.2	28.4	21.5	12.8	8.9	5.1	3.2	2.9	1.9	7.1	3.7
Multiple births	19.4	24.8	22.9	26.8	14.2	18.5	4.0	5.4	0.8	0.7	0.0	0.1
Low Apgar score (≤7 at 5 min)	36.1	18.7	6.4	7.5	3.2	2.1	1.1	0.7	0.9	0.7	1.9	1.2
Maternal smoking												
No	44.4	60.9	55.0	65.3	50.1	69.7	53.2	72.4	59.1	75.5	57.7	75.2
1–9 cigarettes	25.0	13.2	17.4	14.2	22.7	13.5	22.3	13.2	20.2	12.1	22.0	12.4
10 or more cigarettes	16.7	8.4	14.7	9.7	20.3	8.9	18.4	8.2	15.1	6.9	14.6	6.8
Missing	13.9	17.5	12.8	10.8	6.9	7.9	6.1	6.2	5.5	5.6	5.8	5.6
Has cerebral palsy	11.1	9.3	4.6	4.0	0.4	0.5	0.6	0.2	0.4	0.1	0.0	0.2

TABLE 3 Logistic Regression of ADHD Medication and Gestational Age

Gestational Age, wk	Model 1, OR (95% CI)	Model 2, OR (95% CI)	Model 3, OR (95% CI)
23–28	2.5 (1.8–3.5)	2.2 (1.6–3.2)	2.1 (1.4–2.7)
29–32	1.9 (1.5–2.3)	1.7 (1.4–2.1)	1.6 (1.4–1.7)
33–34	1.6 (1.3–1.9)	1.4 (1.2–1.7)	1.4 (1.2–1.7)
35–36	1.4 (1.2–1.5)	1.3 (1.1–1.4)	1.3 (1.1–1.4)
37–38	1.2 (1.1–1.3)	1.2 (1.1–1.3)	1.1 (1.1–1.2)
39–41	1	1	1
42 or more	1.0 (0.9–1.1)	1.0 (0.9–1.1)	1.0 (0.9–1.1)

Model 1 is adjusted for year of birth, gender, and county of residence. Model 2 is adjusted for year of birth, gender, county of residence, birth order, maternal age, maternal education, single parenthood, public welfare, maternal smoking, and maternal/paternal psychiatric/addictive disorders. Model 3 is adjusted for year of birth, gender, county of residence, birth order, maternal age, maternal education, single parenthood, public welfare, maternal smoking, and maternal/paternal psychiatric/addictive disorders, low Apgar score and small for gestational age. CI indicates confidence interval.

TABLE 4 Logistic Regression of Gestational Age and ADHD in Offspring of Mothers Who Had Given Birth to Term as Well as Preterm (≤34 Weeks) Infants ($N = 34\,334$)

Gestational Age, wk	Group Effects, OR (95% CI)	Within-Mother Effects, OR (95% CI)
23–28	3.3 (1.0–10.5)	2.1 (0.9–3.2)
29–32	2.0 (0.8–4.9)	1.7 (0.8–2.6)
33–34	1.5 (0.7–3.4)	1.4 (0.6–2.2)
39–41	1	1
42 or more	1.0 (0.6–1.6)	1.1 (0.6–1.6)

CI indicates confidence interval.

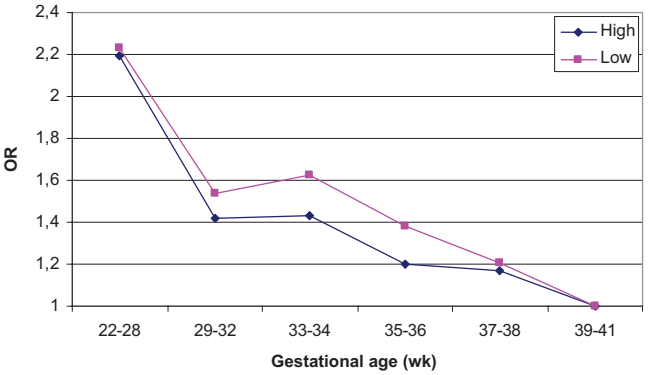

FIGURE 1
ADHD medication by maternal education and gestational age.

classes of preterm birth compared with term birth (ORs of 0.3–0.4 in interaction analyses, with $P < .05$ for a dichotomized variable of 22–36 weeks).

DISCUSSION

In this register study of whole national cohorts of more than 1 million school children, the degree of immaturity at birth, as measured by gestational age, was associated with risk of ADHD medication in school age. This effect was largely independent of socioeconomic and perinatal confounders, and, as confirmed by the within-mother-between-pregnancy analysis, also independent of genetic confounding. However, social adversity, as defined by low maternal education, increased the effect of moderately preterm birth on the risk of ADHD.

The risk for ADHD was doubled for children born at 23 to 28 weeks' gestation in the fully adjusted models, which is on the same level as in the meta-analysis of Bhutta et al.[2] The gradual risk increase for ADHD by increasing degree of immaturity, and the lack of a connection with cerebral palsy and growth restriction mentioned above, seems to point to the role of brain development for explaining the main mechanisms linking preterm birth with ADHD. The refinement of cortical connection peaks at gestational weeks 24 to 28 and the number of neurons around week 28.[36] There is evidence of a maturational lag in children with ADHD.[37] This lag has also been neuroanatomically verified by using neuroimaging techniques[38]; children with ADHD attained peak cortical thinness 3 years later than healthy controls (10.5 vs 7.5 years). It has been hypothesized that the effects of perinatal factors unfold across development.[39] It seems reasonable to hypothesize that such factors are involved in the development of ADHD symptoms in children born preterm. The risk decreased gradually in more mature preterm children but was still 30% higher in children born at 35 to 36 weeks of gestation. This is congruent with a hypothesis of disturbed maturation processes, diminishing over time.

Our results confirm the previous follow-up studies from NICUs that have demonstrated an association between extremely preterm birth and ADHD, using more precise measures of ADHD than in this study.[13,40,41] They also support findings from 1 study that indicated a link between moderately preterm birth and behavioral and attention problems.[42]

Cerebral palsy increased the risk for ADHD medication in term infants, but did not increase the risk for ADHD medication in preterm infants,[27] which indicates that the leukomalaciae caused by periventricular hemorrhage, which is so closely associated with the cerebral palsy of children born preterm, is not a common causal mechanism for ADHD associated with preterm birth. It is also noteworthy that growth retardation, as expressed by being small for gestational age, did not modify the risk

of preterm birth, which indicates that these 2 perinatal risk factors for ADHD are more or less independent of each other.

The importance of childhood socioeconomic factors in studies on psychological outcomes of children born prematurely has been demonstrated in previous Swedish follow-up studies of preterm infants. In these studies, low socioeconomic status modified the incremental association of cognitive competence with gestational level at all levels of preterm birth,[14] and low socioeconomic status increased the risk of psychiatric hospitalization associated with degree of preterm birth.[15] In this study, low maternal education is most probably a marker for a complex web of risk factors associated with social adversity, such as relative poverty, living in low status housing areas and family discord.[14,15] Thus, it is not surprising that the risk for ADHD caused by moderately preterm birth was modified by the socioeconomic context of the family in which the child had been brought up.

There are limitations to this study. ADHD is a difficult concept to define in a reliable way in epidemiologic studies because of the subjective and context-bound nature of the impairment criteria built into existing diagnostic classifications,[43] although successful attempts to operationalize diagnostics have been made.[44] We believe, however, that ADHD medication is a quite valid indicator of the more severe cases of ADHD in a Swedish context, considering the national guidelines and the restriction to prescribe stimulants described above.

The Swedish health care system offers child psychiatric and pediatric care free of charge to all Swedish residents. However, there are significant differences in access to ADHD medication between counties in Sweden, as demonstrated in this study. Counties are free to make their own priorities in health care and have different potential in attracting qualified pediatricians and child psychiatrists. However, this variation was adjusted for to a certain extent in the analysis, and moreover it seems quite improbable that such bias would be a major problem in the within-mother-between-pregnancy analysis, which confirmed the association between preterm birth and ADHD in this study. A more important source of bias in this study is probably the special access to care in follow-up programs for the most vulnerable patients from NICUs. It seems likely that this may lead to a better access to qualified care for ADHD-symptoms for the most preterm, but probably not the moderately preterm, compared with the general population.

The crude indicators of parental psychiatric morbidity in this study cannot be expected to be very efficient as indicators of genetic ADHD trait. This was the rationale behind adding a within-mother-between-pregnancy analysis (Table 4). This analysis gave no indication that genetic factors are major confounders in the association between preterm birth and ADHD, although the number of individuals in this analysis was too small to completely exclude this possibility.

CONCLUSION

In this study it is demonstrated that the association of preterm birth to ADHD is graded by degree of immaturity with significant increased risks also for children born moderately preterm. This study adds to the growing body of evidence that indicates that more attention is needed toward the advancement of care and follow-up for infants born moderately preterm.

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