Preterm Birth and Poor Fetal Growth as Risk Factors of Attention-Deficit/ Hyperactivity Disorder

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abstract

BACKGROUND: Previous studies have shown an association between prematurity and attention-deficit/hyperactivity disorder (ADHD). Results concerning late preterm infants are controversial, and studies examining fetal growth represented by weight for gestational age are scarce. Our objective was to examine the association between gestational age by each week of fetal maturity, weight for gestational age, and ADHD.

METHODS: In this population-based study, 10 321 patients with ADHD, diagnosed according to the *International Classification of Diseases* and 38 355 controls individually matched for gender, date and place of birth, were identified from Finnish nationwide registers. Perinatal data were obtained from the Finnish Medical Birth Register. Conditional logistic regression was used to examine the association between gestational age, weight for gestational age, and ADHD after controlling for confounding factors.

RESULTS: The risk of ADHD increased by each declining week of gestation. The associations were robust after adjusting for confounders. An elevated risk also was seen among late preterm and early term infants. As for fetal growth, the odds ratio showed a U-shaped curve with an increased risk seen when the weight for gestational age was 1 SD below and 2 SD above the mean.

CONCLUSIONS: Our findings suggest that each gestational week has significance for child's subsequent neurodevelopment and risk for ADHD. We also showed that poor fetal growth increased the risk of ADHD. This highlights the importance of taking into account both prematurity and poor fetal growth when planning the timing of birth as well as later follow-up and support policies.

WHAT'S KNOWN ON THIS SUBJECT: Infants born very prematurely or with a very low birth weight are known to have an increased risk of attention-deficit/hyperactivity disorder (ADHD). Results concerning late preterm children are controversial and studies examining fetal growth represented by weight for gestational age are scarce.

WHAT THIS STUDY ADDS: We demonstrate that each declining week of gestation increases the risk of ADHD. Also, late preterm infants have an increased risk. Furthermore, as weight for gestational age becomes smaller than 1 SD below the mean, the risk of ADHD increases.

Attention-deficit/hyperactivity disorder (ADHD) is a common neurodevelopmental disorder characterized by symptoms of inattention, hyperactivity, and impulsivity. It is estimated to have a worldwide prevalence of approximately 3.4% to 7.2%.[1–3] The disabling symptoms often persist beyond childhood.[4,5] The development of the disorder is thought to have a strong heritable component.[6] However, environmental factors and gene-environment interaction play a notable role in the etiology of ADHD as well. Identified environmental risk factors include young maternal age, low socioeconomic status (SES), and prenatal exposure to smoking and alcohol.[7–9] Premature birth and low birth weight have been shown to increase the risk of ADHD in a number of studies.[10–13]

Most studies concerning preterm birth and ADHD have focused on extremely preterm infants, whereas the vast majority of children born prematurely are born at a later gestational age.[14] Studies concerning the ADHD risk of late preterm infants are significantly fewer and have yielded somewhat contradictory results.[4,15–18]

Poor fetal growth or being small for gestational age (SGA) also has been associated with neurodevelopmental problems and ADHD.[4,13,19,20] Most studies have analyzed the association between low birth weight and ADHD.[13] There are, however, limited population-based studies focusing on fetal growth represented by birth weight for gestational age. Cohort studies have concluded that rather than prematurity or very low birth weight per se, the SGA status increases the risk of ADHD.[21–23]

The risk of ADHD has not been previously studied by each week of fetal maturity. Four previous population-based studies reporting the association between gestational age and ADHD have shared the limitation of not adjusting the results with parental psychiatric history and maternal substance abuse.[4,9,15,18] A strong correlation between psychosocial adversities and intrauterine growth restriction is acknowledged as well.[24,25] However, there is a lack of studies analyzing the association of antenatal growth and ADHD while taking into account the major confounders related to fetal growth.

We sought to examine the associations of prematurity and fetal growth in relation to ADHD in a nationwide, nested, case-control study in Finland. Our first aim was to examine the association between gestational age and ADHD by each gestational week. Our second aim was to study the association of weight for gestational age and ADHD. Our hypothesis was that both premature birth and suboptimal fetal growth are risk factors for ADHD and that there is a linear association between a declining gestational age and the risk for ADHD.

METHODS

The Finnish Health Care System

Finland has universal health coverage; the public health care system includes primary health care (maternity and child welfare clinics, school health care services, and health care centers), and specialized health care provided as inpatient and outpatient care. The visits to child and school health care services are free of charge, and virtually all children in Finland use these services. Children suspected of having ADHD are referred from primary health care to specialized outpatient clinics to be assessed by a child psychiatrist or neurologist.

The Nationwide Registries

The data for this study were collected from 3 nationwide registries: the Finnish Hospital Discharge Register (FHDR), the Finnish Medical Birth Register (FMBR), and the Finnish Central Population Register (FCPR). All residents in Finland receive a unique personal identification code at birth or migration. This number enables linkage of information from several sources. The FHDR is maintained by the National Institutes of Health and Welfare and includes all inpatient diagnoses since 1967 and outpatient diagnoses from specialized services since 1998. In Finland, diagnostic classification is based on the *International Classification of Diseases* (ICD); the 10th Revision has been used since 1996.[26] From 1987 to 1995 the diagnoses were coded according to ICD-9.[27] The validity of the ADHD diagnosis in the FHDR has been evaluated in a previous study showing that 88% of subjects examined met the *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* diagnostic criteria for ADHD.[28]

The FMBR, established in 1987, contains comprehensive data on all newborns in Finland, maternal health-related behaviors, demographic characteristics, and perinatal events. The FCPR contains basic information regarding citizens and permanent residents of Finland, such as family relations, and date of birth and death. Approval for the utilization and linkage of register data for this research was obtained from the Data Protection Ombudsman. Ethical approval for the study was provided by the Ethics Committee of the Hospital District of Southwest Finland.

The Study Design

This study followed all singleton newborns born in Finland between January 1, 1991, and December 31, 2005 (*n* = 900 603), for ADHD diagnoses until December 31, 2011 (diagnostic codes F90 in ICD-10 or 314 in ICD-9). Children who had received an ADHD diagnosis before the age of 2 years, but not after that, were excluded (*n* = 16). Children diagnosed with severe or profound

mental retardation (ICD-10: F72–F73, ICD-9: 318) also were excluded (n = 13). Children for whom information on gestational age or birth weight was not available (n = 87) or clearly inaccurate (n = 1) were excluded. A total of 10 321 children with ADHD were thus included in the study. The most recently registered diagnosis was used for identification. All children were diagnosed with an ICD-10 code.

Each patient was matched with 4 controls on the date of birth (±30 days), gender, and the place of birth. The controls were identified through linkage between the FHDR and the FCPR. The controls were to be alive and residing in Finland at the time of the patient's diagnosis and were not to have a diagnosis of ADHD, conduct disorder (ICD-10: F91-F92) or severe or profound mental retardation. Controls with lacking (n = 452) or clearly incorrect (n = 1) information on gestational age or birth weight, and controls of excluded cases (n = 317) were excluded, resulting in 38 355 controls.

Gestational Age and Birth Weight for Gestational Age Information

Data on gestational age and birth weight were obtained from the FMBR. The first exposure, gestational age, was analyzed by each completed gestational week, using week 40 as the reference. Because of a limited number of infants born in week 23, we combined them with week 24. Gestational age was calculated mainly based on information of the last menstrual period, but it has been verified, and corrected if needed, with a first trimester ultrasound since the late 1980s.[29] The second exposure, weight for gestational age, was calculated according to national gender-specific birth weight distribution standards at a given gestational age for singletons. The references are derived from all newborns in Finland born between 1996 and 2008.[30] We divided the weight for gestational age into 9

categories by a change of 0.5 SDs. The categories were thereby < –2.00 SD, –2.00 to –1.51 SD, –1.50 to –1.01 SD, –1.00 to –0.51 SD, –0.50 to +0.50 SD (reference), 0.51 to 1.00 SD, 1.01 to 1.50 SD, 1.51 to 2.00 SD, and >2.00 SD. We also analyzed gestational age and weight for gestational age as continuous variables.

Additional analyses were made by gender and these are available as supplementary material. Because of a limited number of extremely preterm girls, the gestational age was categorized as ≤28, 29 to 31, 32 to 33, 34 to 36, 37 to 38, 39 to 40 (reference), and ≥42 weeks for these analyses.

Confounding Factors

A number of potential confounding factors suggested as having an association with prematurity and/or fetal growth and ADHD were considered for inclusion in the analyses. These factors included smoking during pregnancy,[17,31] parental age,[32,33] number of previous births,[34,35] parental psychiatric history[36,37] and immigration background,[38–40] maternal alcohol or substance abuse,[7,8,41] SES based on maternal occupation,[42,43] marital status,[41,42] and the urbanity of the child's birth place.[44,45] Data on these variables were obtained from the FMBR and the FHDR. Parental age was classified into 4 categories: <20, 20 to 29, 30 to 39, and ≥40 years. Smoking during pregnancy was classified as a binary variable (yes/no). The number of previous births was categorized as 0 or ≥1. Maternal marital status was classified as a binary variable (married/in a relationship or single). A parent was defined as having psychiatric history if he or she had any psychiatric diagnoses registered in the FHDR during his or her lifetime: F10–F99 (mental and behavioral disorders) based on the ICD-10 (corresponding diagnoses based on the ICD-9 [291–316] and the ICD-8[46] [291–309]). The association with

maternal disorders due to alcohol or substance abuse was tested separately (diagnoses of ICD-10: F10–19; ICD-9: 291–292, 303–305; and ICD-8: 291, 303, and 304). Parental psychiatric history and maternal substance abuse were classified as binary variables (yes/no). Maternal SES categories were based on national classifications used in the FMBR: upper white collar, lower white collar, blue collar workers, and others (eg, students and housewives) or missing (if unavailable). The urbanity of the birth place was categorized into rural, semi-urban, or urban. The immigrant status of each parent was categorized as binary variable (yes/no). The data on paternal characteristics were missing if the paternity of the child was unknown.

Statistical Methods

Potential confounders were tested using the Pearson χ^2 test for the association with both exposures (gestational age and weight for gestational age) among controls. Conditional logistic regression was then used to test for the association between potential confounders and ADHD. Confounders were included in the regression models if they were associated with either one of the exposures and the outcome at $P < .10$.

Conditional logistic regression models for matched pairs were used to examine the associated exposures between the patients and controls. In the first stage, we estimated unadjusted odds ratios (ORs) and 95% confidence intervals (CIs) for the gestational age by each week and weight for gestational age in the previously mentioned categories. In the final model, adjustment was made for all the confounders.

For the analysis of gestational age and weight for gestational age as continuous variables, linear and quadratic models were fitted. The quadratic model was selected based

on the Akaike information criterion. A similar adjustment was made as for the categorical analysis. A 2-sided $P < .05$ was considered statistically significant. Statistical analyses were performed with SAS statistical software (SAS version 9.4; SAS Institute, Inc, Cary, NC).

RESULTS

The mean age at ADHD diagnosis was 7.6 years (SD 2.9 years, range: 3–19 years). In total, 84% of the children with ADHD were boys and 16% were girls.

Bivariate testing for potential confounding factors demonstrated that maternal age, substance abuse and smoking during pregnancy, number of previous births, marital status, paternal age, and the urbanity of the child's birthplace had an association with gestational age, weight for gestational age, and ADHD. Maternal psychiatric history was associated with gestational age and ADHD. Maternal SES and paternal psychiatric history and immigrant status were associated with weight for gestational age and ADHD. All of

these factors were included as confounders in the final analyses. Among the tested, potential confounders, maternal immigrant status did not have a correlation with the gestational age or weight for gestational age (Supplemental Table 3).

Table 1 shows the results of the analysis for gestational age by each week of maturity and ADHD. After adjustment for confounders, premature birth remained as a risk factor for ADHD. The risk showed a dose effect with each declining week of gestation increasing the risk of ADHD when compared with week 40. An elevated risk was seen in late-preterm and early-term infants as well, with the exception of week 34 lacking statistical significance. At week 25, the adjusted OR was 5.77 (95% CI 1.68–19.83); week 30, 3.55 (95% CI 2.02–6.23); and week 35, 1.41 (95% CI 1.12–1.78). The risk remained moderately elevated until early-term birth (week 37 OR 1.31, 95% CI 1.16–1.47; week 38 OR 1.12, 95% CI 1.03–1.22). Figure 1 shows the results of the adjusted association for the weekly increase in gestational

age and of the continuous model. Figure 2 shows these results focused to present the findings in the late preterm group.

Table 2 shows the results of the analysis for weight for gestational age and ADHD. Infants born SGA (<−2 SD) had more than twofold increased risk for ADHD in the univariate analysis, and after adjustment for confounders, the OR was 1.80 (95% CI 1.58–2.05). A significantly increased risk also was seen in the groups of weight for gestational age from −2.0 to −1.5 SD and from −1.5 to −1.0 SD, resulting in adjusted ORs of 1.36 (95% CI 1.21–1.52) and 1.14 (95% CI 1.04–1.24), respectively. Infants born large for gestational age (LGA) (>2 SD) had a 1.21-fold (95% CI 1.05–1.40) increased risk according to the adjusted model. Figure 3 presents the results of the adjusted analysis examining the association of continuous weight for gestational age and ADHD. The ORs showed a U-shaped curve with the highest risk for ADHD in the infants with the lowest weight for gestational age, and the risk for ADHD rising again for LGA infants. The results of

TABLE 1 Frequencies of ADHD Cases and Controls and ORs with 95% CI for Associations Between Gestational Age in Weeks and ADHD

Gestational Age, wk	Patients, %	Controls, %	Unadjusted OR	95% CI	P	Adjusted OR[a]	95% CI	P
	n = 10 321	n = 38 355						
23–24	14 (0.1)	4 (0.01)	14.59	4.79–44.47	<.001	11.96	3.60–39.72	<.001
25	11 (0.1)	6 (0.01)	7.05	2.60–19.13	<.001	5.77	1.68–19.83	.005
26	17 (0.2)	6 (0.02)	11.19	4.39–28.48	<.001	5.85	1.87–18.25	.002
27	19 (0.2)	18 (0.1)	4.35	2.27–8.31	<.001	3.69	1.65–8.23	.001
28	23 (0.2)	20 (0.1)	4.73	2.59–8.62	<.001	3.34	1.67–6.69	<.001
29	30 (0.3)	25 (0.1)	4.77	2.80–8.14	<.001	3.34	1.80–6.18	<.001
30	36 (0.4)	43 (0.1)	3.46	2.22–5.41	<.001	3.55	2.02–6.23	<.001
31	45 (0.4)	47 (0.1)	3.95	2.61–5.98	<.001	2.87	1.77–4.64	<.001
32	41 (0.4)	84 (0.2)	1.98	1.36–2.88	<.001	1.96	1.25–3.07	.004
33	72 (0.7)	111 (0.3)	2.61	1.93–3.53	<.001	2.61	1.80–3.78	<.001
34	62 (0.6)	202 (0.5)	1.26	0.95–1.69	.11	1.01	0.70–1.46	.94
35	145 (1.4)	372 (1.0)	1.61	1.32–1.97	<.001	1.41	1.12–1.78	.004
36	297 (2.9)	788 (2.1)	1.54	1.34–1.78	<.001	1.48	1.25–1.74	<.001
37	593 (5.8)	1765 (4.6)	1.38	1.24–1.52	<.001	1.31	1.16–1.47	<.001
38	1431 (13.9)	5050 (13.2)	1.16	1.08–1.25	<.001	1.12	1.03–1.22	.008
39	2515 (24.4)	9725 (25.4)	1.06	0.998–1.13	.058	1.08	1.003–1.15	.042
40	2706 (26.2)	11 112 (29.0)	Reference			Reference		
41	1799 (17.4)	7248 (18.9)	1.01	0.95–1.08	.70	1.02	0.95–1.10	.60
42	451 (4.4)	1676 (4.4)	1.10	0.98–1.23	.11	1.08	0.95–1.24	.23
43	14 (0.1)	53 (0.1)	1.08	0.60–1.95	.80	0.99	0.48–2.02	.97

[a] Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, number of previous births, urbanity of child's birth place and paternal immigrant status.
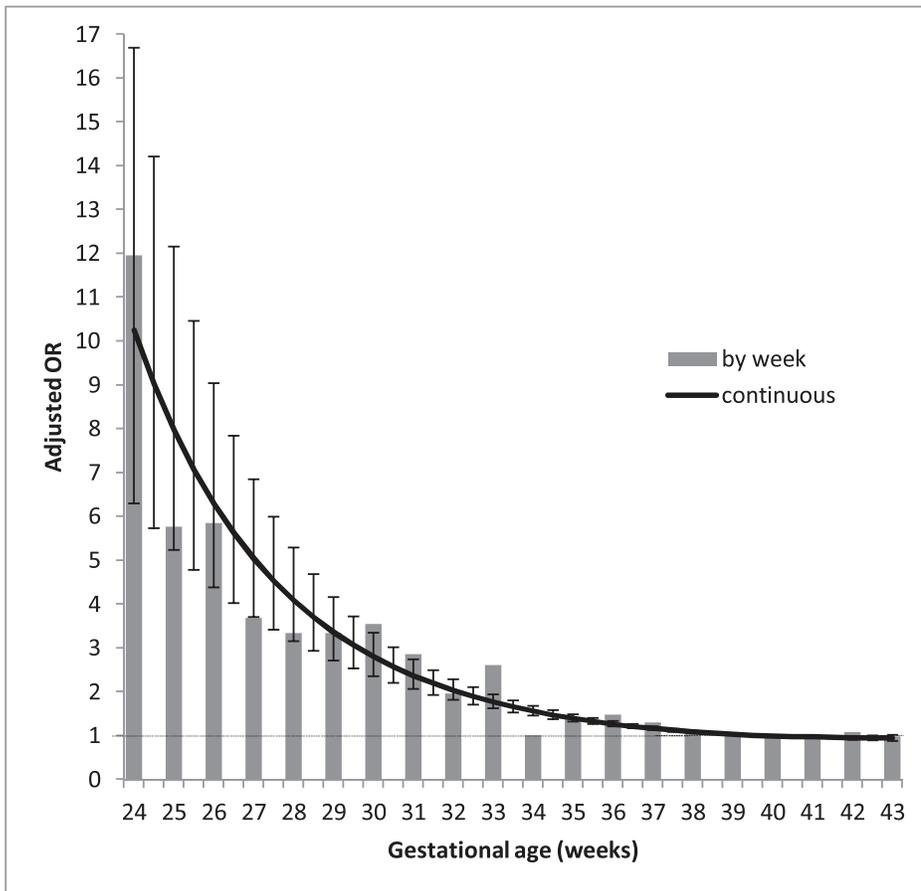
FIGURE 1
Associations of ADHD and gestational age by each gestational week and by fitting a continuous quadratic model (with 95% CIs).

the additional analyses by gender can be found in Supplementary Tables 4 and 5.

DISCUSSION

This population-based study demonstrated that premature birth is a risk factor for ADHD, with each declining week of gestation increasing the risk of ADHD. Interestingly, the risk of ADHD remained moderately elevated even in late-preterm and early-term infants. Second, we demonstrated an increased risk for ADHD with a decreasing weight for gestational age. The risk already increased when the birth weight was 1 SD below the mean. Therefore, our study showed that an elevated risk was evident before the cutoff limit of −2 SD used in many studies. The additional analyses by gender showed similar results in the risks as seen in the overall group.

Four Nordic population-based studies,[4,16,17,47] consistent with our results, have shown an increased risk of ADHD related to preterm birth. Late-preterm children in these studies had a moderate, but consistently increased risk of ADHD, similar to our findings. Our results demonstrated also a slightly increased risk related to early-term birth, which is in line with studies from Denmark,[17] Sweden,[16] and Australia.[18] Few other studies, however, have not shown similar findings. A study from the United States with 1509 children with ADHD or learning difficulties found no increased incidence of ADHD in late-preterm children.[15] An Australian study concluded that reduced gestational age did not remain as a risk factor after adjustment for confounders.[18] To the best of our knowledge, no previous study has reported the risk for ADHD by each week of fetal maturity.

There are few population-based studies on the association between weight for gestational age and ADHD. Our results showing an increasing risk for ADHD with a decreasing weight for gestational age is in line with a Norwegian study,[4] which also used weight for gestational age as an indicator of fetal growth. Our results are, however, in contrast with 2 studies from Australia. A large cohort study[48] found an association between SGA status and attention problems only among term-born girls. Another study did not find an increased risk of ADHD among SGA children in the adjusted model.[18] However, a recent twin study showed that among monozygotic twin pairs, a difference in birth weight was related to ADHD symptoms. These results indicate that restricted fetal growth is likely to act in the causal pathway of ADHD through impaired in utero nourishment, leading to disturbed brain development and subsequently neurodevelopmental problems.[49]

Gestational overgrowth has been associated with several subsequent morbidities[50] and in our data this also was seen as an increased risk of ADHD among LGA children. This was in line with a study from Norway,[4] but in contrast with a study from Australia.[18] LGA is typically associated with maternal diabetes or overweight and it has previously been shown that there is an association between maternal overweight and offspring ADHD symptoms.[51]

A large Swedish study showed that the association between gestational age and ADHD was largely independent of familial confounding factors.[47] This is also consistent with our results showing only a minor impact after adjustment for a number of confounders. In Finland, the socioeconomic differences in perinatal health and preterm births are low.[52] Therefore, the association between prematurity and ADHD is unlikely to be attributed to potentially uncontrolled social
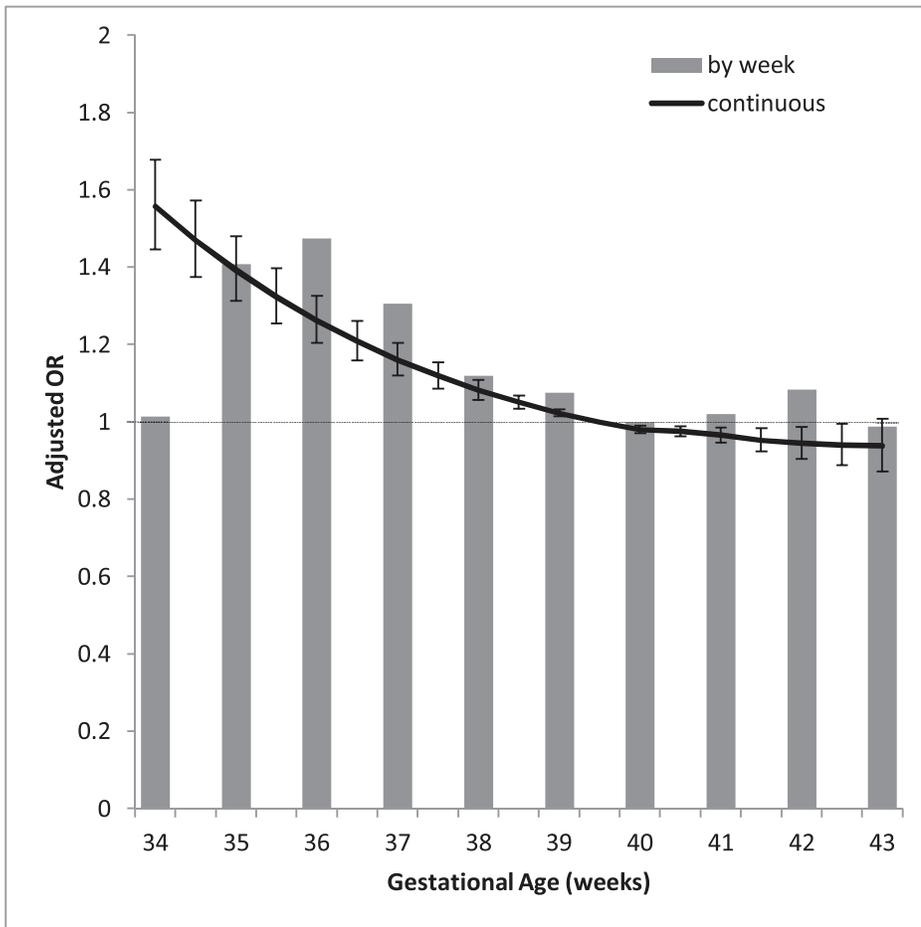
FIGURE 2

Associations of ADHD and gestational age by weekly categories and by fitting a continuous quadratic model (with 95% CIs) among late preterm and term infants. For weeks 34, 41, 42, and 43, P > .05.

background factors. Furthermore, the Finnish health care system, which follows all children, is likely to detect most children with ADHD. The settings in other Nordic countries are similar, which may explain consistent results from Nordic studies compared with studies from Australia and the United States.

During fetal development, neurogenesis and neuronal migration to form the neocortex continue until the end of the second trimester. Synaptogenesis, brain folding, and myelination are still in progress after very premature birth and thus prone to disruptions in cortical connectivity, cell death, and

myelination disorders.[53,54] This may provide explanations for the etiology of ADHD in very preterm infants. In addition, possible mechanisms may lie in the etiology of the preterm birth and the processes behind it. Preterm labor is thought to be initiated by multiple mechanisms, including infection or inflammation, utero-placental ischemia or hemorrhage, stress, and other immunologically mediated processes.[55] These may account for the cascade leading to the development of ADHD, especially in an individual genetically susceptible to the disorder.

As the vast majority of preterm infants today survive without major neurodevelopmental disabilities,[56,57] there is concern about the risk of later inattention/hyperactivity and learning difficulties by school age and during adolescence.[58] Becoming aware of the long-term outcomes of children born late preterm is noteworthy, because ~72% of infants born prematurely are born during that period (34–36 weeks).[59] Thus, even a modest increase in the ADHD risk observed in this group, as seen in our data, results in a substantial number of ADHD cases at the population level. The same applies to a slightly increased ADHD risk among early term (37–38 weeks) infants, which calls for attention especially when planning iatrogenic timing of birth.

TABLE 2 Frequencies of ADHD Cases and Controls and ORs With 95% CI for Association Between ADHD and Weight for Gestational Age

Weight for Gestational Age SD[a]	Patients, %	Controls, %	Unadjusted OR	95% CI	P	Adjusted OR[b]	95% CI	P
	n = 10 321	n = 38 355						
<(−2.00)	583 (5.7)	1069 (2.8)	2.20	1.97–2.45	<.001	1.80	1.58–2.05	<.001
(−2.00)−(−1.51)	673 (6.5)	1707 (4.5)	1.59	1.44–1.75	<.001	1.36	1.21–1.52	<.001
(−1.50)−(−1.01)	1187 (11.5)	3777 (9.9)	1.27	1.18–1.37	<.001	1.13	1.04–1.24	.005
(−1.00)−(−0.51)	1652 (16.0)	5956 (15.5)	1.12	1.05–1.20	<.001	1.02	0.95–1.11	.54
(−0.50)−(+0.50)	3551 (34.4)	14 350 (37.4)	Reference			Reference		
0.51–1.00	1219 (11.8)	5362 (14.0)	0.92	0.85–0.99	.018	0.99	0.91–1.08	.85
1.01–1.50	729 (7.1)	3195 (8.3)	0.92	0.84–1.01	.075	0.97	0.88–1.08	.62
1.51–2.00	385 (3.7)	1625 (4.2)	0.96	0.85–1.08	.47	1.09	0.95–1.24	.22
>2.00	342 (3.3)	1311 (3.4)	1.05	0.93–1.19	.43	1.21	1.05–1.40	.009

[a] SD according to national references derived from all singleton newborns in Finland born in 1996–2008.[30]

[b] Adjusted for maternal and paternal age and psychiatric history, maternal SES, marital status, smoking during pregnancy and substance abuse, no. of previous births, urbanity of child's birth place, and paternal immigrant status.
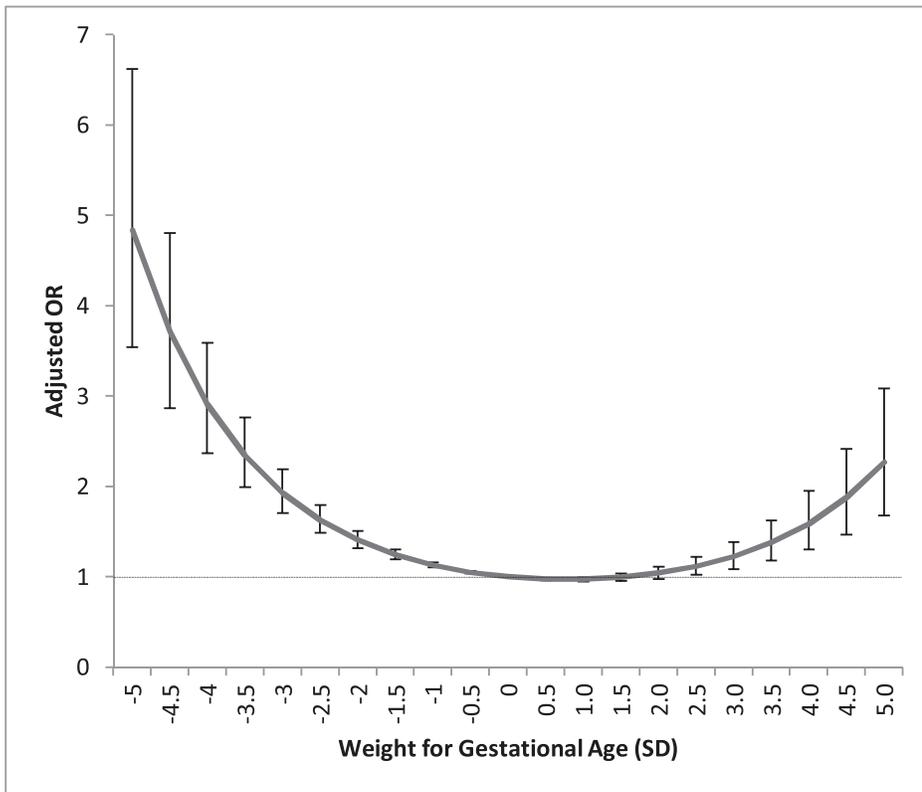
FIGURE 3
Association of ADHD and weight for gestational age by fitting a continuous model with 95% CIs. SDs according to national birth-size references[30]

There are limitations that have to be considered when interpreting our findings. First, the ADHD diagnoses used in this study were derived from hospital discharge registers, including outpatient visits and inpatient admissions. Therefore, we have included only children with ADHD diagnosed or followed in specialized health care. Some ADHD diagnoses could have been made in the community health care and these children may have ended up in the control group. In addition, some children with ADHD problems may have been missed altogether, remaining without a diagnosis and thus end up as controls. These flaws would, however, decrease the observed difference between the patients and controls, and thus our current finding would rather underestimate the association. Second, the ADHD diagnoses in the registers were made based on clinical routines, which might include variations. We acknowledge that we did not make the diagnoses by using standardized interviews. In Finland, a child typically receives an ADHD diagnosis in specialized health care after having undergone psychological testing and a diagnostic interview by a child psychiatrist or child neurologist combined with information gathered from questionnaires to parents and school or day care personnel. However, the accuracy of the diagnoses in the FHDR has been found to be good for the diagnosis of mental disorders.[60] Furthermore, a previous validation study showed good validity (88%) of the ADHD diagnoses in the FHDR.[28] Third, children born very prematurely generally receive more specified follow-up in their first years of life compared with term controls. This may potentially lead to a higher alertness to neurodevelopmental problems and thus a lead to a higher rate or sooner occurrence of ADHD diagnoses to some extent. Fourth, we used weight for gestational age as our measure of fetal growth, as we could not directly observe intrauterine growth trends.[61] However, by using new birth-size references from a nationwide validation of growth curves, we assume that our references reflect optimal and healthy growth of the newborn.[30]

CONCLUSIONS

We demonstrated that each declining week of gestation increased the risk of ADHD. This emphasizes the significance of each gestational week for later neurodevelopment. However, we also showed that poor fetal growth increased the risk of ADHD. This makes it challenging to balance between nonoptimal fetal growth and the risks of prematurity from the perspective of the long-term outcome while planning the optimal timing of birth. In addition, this highlights the importance of taking into account both prematurity and poor fetal growth when planning follow-up and support policies.

ACKNOWLEDGMENTS

ABBREVIATIONS

ADHD: attention-deficit/ hyperactivity disorder
CI: confidence interval
FCPR: Finnish Central Population Register
FHDR: Finnish Hospital Discharge Register
FMBR: Finnish Medical Birth Register
ICD: International Classification of Diseases
LGA: large for gestational age
OR: odds ratio
SES: socioeconomic status
SGA: small for gestational age

REFERENCES

1. Polanczyk G, de Lima MS, Horta BL, Biederman J, Rohde LA. The worldwide prevalence of ADHD: a systematic review and metaregression analysis. *Am J Psychiatry.* 2007;164(6):942–948

2. Thomas R, Sanders S, Doust J, Beller E, Glasziou P. Prevalence of attention-deficit/hyperactivity disorder: a systematic review and meta-analysis. *Pediatrics.* 2015;135(4). Available at: www.pediatrics.org/cgi/content/full/135/4/e994

3. Polanczyk GV, Salum GA, Sugaya LS, Caye A, Rohde LA. Annual research review: a meta-analysis of the worldwide prevalence of mental disorders in children and adolescents. *J Child Psychol Psychiatry.* 2015;56(3):345–365

4. Halmøy A, Klungsøyr K, Skjærven R, Haavik J. Pre- and perinatal risk factors in adults with attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2012;71(5):474–481

5. Simon V, Czobor P, Bálint S, Mészáros A, Bitter I. Prevalence and correlates of adult attention-deficit hyperactivity disorder: meta-analysis. *Br J Psychiatry.* 2009;194(3):204–211

6. Faraone SV, Perlis RH, Doyle AE, et al. Molecular genetics of attention-deficit/hyperactivity disorder. *Biol Psychiatry.* 2005;57(11):1313–1323

7. Thapar A, Cooper M, Jefferies R, Stergiakouli E. What causes attention deficit hyperactivity disorder? *Arch Dis Child.* 2012;97(3):260–265

8. Banerjee TD, Middleton F, Faraone SV. Environmental risk factors for attention-deficit hyperactivity disorder. *Acta Paediatr.* 2007;96(9):1269–1274

9. Gustafsson P, Källén K. Perinatal, maternal, and fetal characteristics of children diagnosed with attention-deficit-hyperactivity disorder: results from a population-based study utilizing the Swedish Medical Birth Register. *Dev Med Child Neurol.* 2011;53(3):263–268

10. Aarnoudse-Moens CS, Weisglas-Kuperus N, van Goudoever JB, Oosterlaan J. Meta-analysis of neurobehavioral outcomes in very preterm and/or very low birth weight children. *Pediatrics.* 2009;124(2):717–728

11. Bhutta AT, Cleves MA, Casey PH, Cradock MM, Anand KJ. Cognitive and behavioral outcomes of school-aged children who were born preterm: a meta-analysis. *JAMA.* 2002;288(6):728–737

12. Botting N, Powls A, Cooke RW, Marlow N. Attention deficit hyperactivity disorders and other psychiatric outcomes in very low birthweight children at 12 years. *J Child Psychol Psychiatry.* 1997;38(8):931–941

13. Class QA, Rickert ME, Larsson H, Lichtenstein P, D'Onofrio BM. Fetal growth and psychiatric and socioeconomic problems: population-based sibling comparison. *Br J Psychiatry.* 2014;205(5):355–361

14. de Jong M, Verhoeven M, van Baar AL. School outcome, cognitive functioning, and behaviour problems in moderate and late preterm children and adults: a review. *Semin Fetal Neonatal Med.* 2012;17(3):163–169

15. Harris MN, Voigt RG, Barbaresi WJ, et al. ADHD and learning disabilities in former late preterm infants: a population-based birth cohort. *Pediatrics.* 2013;132(3). Available at: www.pediatrics.org/cgi/content/full/132/3/e630

16. Lindström K, Lindblad F, Hjern A. Preterm birth and attention-deficit/hyperactivity disorder in schoolchildren. *Pediatrics.* 2011;127(5):858–865

17. Linnet KM, Wisborg K, Agerbo E, Secher NJ, Thomsen PH, Henriksen TB. Gestational age, birth weight, and the risk of hyperkinetic disorder. *Arch Dis Child.* 2006;91(8):655–660

18. Silva D, Colvin L, Hagemann E, Bower C. Environmental risk factors by gender associated with attention-deficit/hyperactivity disorder. *Pediatrics.* 2014;133(1). Available at: www.pediatrics.org/cgi/content/full/133/1/e14

19. Hultman CM, Torrång A, Tuvblad C, Cnattingius S, Larsson JO, Lichtenstein P. Birth weight and attention-deficit/hyperactivity symptoms in childhood and early adolescence: a prospective Swedish twin study. *J Am Acad Child Adolesc Psychiatry.* 2007;46(3):370–377

20. Monset-Couchard M, de Bethmann O, Relier JP. Long term outcome of small versus appropriate size for gestational age co-twins/triplets. *Arch Dis Child Fetal Neonatal Ed.* 2004;89(4):F310–F314

21. Heinonen K, Raikkonen K, Pesonen AK, et al. Behavioural symptoms of attention deficit/hyperactivity disorder in preterm and term children born small and appropriate for gestational age: a longitudinal study. *BMC Pediatr.* 2010;10:91

22. Strang-Karlsson S, Räikkönen K, Pesonen AK, et al. Very low birth weight and behavioral symptoms of attention deficit hyperactivity disorder in young adulthood: the Helsinki study of very-low-birth-weight adults. *Am J Psychiatry.* 2008;165(10):1345–1353

23. Guellec I, Lapillonne A, Renolleau S, et al; EPIPAGE Study Group. Neurologic outcomes at school age in very preterm infants born with severe or mild growth restriction. *Pediatrics.* 2011;127(4). Available at: www.pediatrics.org/cgi/content/full/127/4/e883

24. Indredavik MS, Vik T, Evensen KA, Skranes J, Taraldsen G, Brubakk AM. Perinatal risk and psychiatric outcome in adolescents born preterm with very

low birth weight or term small for gestational age. *J Dev Behav Pediatr*. 2010;31(4):286–294

25. Glinianaia SV, Ghosh R, Rankin J, Pearce MS, Parker L, Pless-Mulloli T. No improvement in socioeconomic inequalities in birthweight and preterm birth over four decades: a population-based cohort study. *BMC Public Health*. 2013;13:345

26. World Health Organization. *International Classification of Diseases, Tenth Revision (ICD-10)*. Geneva, Switzerland: World Health Organization; 1992

27. World Health Organization. *International Classification of Diseases, Ninth Revision (ICD-9)*. Geneva, Switzerland: World Health Organization; 1977

28. Joelsson P, Chudal R, Gyllenberg D, et al. Demographic characteristics and psychiatric comorbidity of children and adolescents diagnosed with ADHD in specialized healthcare. Unpublished manuscript

29. Pihkala J, Hakala T, Voutilainen P, Raivio K. Uudet suomalaiset sikiön kasvukäyrät [Characteristic of recent fetal growth curves in Finland]. *Duodecim*. 1989; 105(18):1540–1546

30. Sankilampi U, Hannila ML, Saari A, Gissler M, Dunkel L. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Ann Med*. 2013;45(5–6): 446–454

31. Wen SW, Goldenberg RL, Cutter GR, et al. Smoking, maternal age, fetal growth, and gestational age at delivery. *Am J Obstet Gynecol*. 1990;162(1):53–58

32. Chang Z, Lichtenstein P, D'Onofrio BM, et al. Maternal age at childbirth and risk for ADHD in offspring: a population-based cohort study. *Int J Epidemiol*. 2014;43(6):1815–1824

33. Restrepo-Méndez MC, Lawlor DA, Horta BL, et al. The association of maternal age with birthweight and gestational age: a cross-cohort comparison. *Paediatr Perinat Epidemiol*. 2015;29(1): 31–40

34. Carballo JJ, García-Nieto R, Alvarez-García R, et al. Sibship size, birth order, family structure and childhood mental disorders. *Soc Psychiatry Psychiatr Epidemiol*. 2013;48(8):1327–1333

35. Conde-Agudelo A, Rosas-Bermúdez A, Kafury-Goeta AC. Birth spacing and risk of adverse perinatal outcomes: a meta-analysis. *JAMA*. 2006;295(15):1809–1823

36. Sengupta SM, Fortier ME, Thakur GA, Bhat V, Grizenko N, Joober R. Parental psychopathology in families of children with attention-deficit/hyperactivity disorder and exposed to maternal smoking during pregnancy. *J Child Psychol Psychiatry*. 2015;56(2):122–129

37. Lobel M, Dunkel-Schetter C, Scrimshaw SC. Prenatal maternal stress and prematurity: a prospective study of socioeconomically disadvantaged women. *Health Psychol*. 1992;11(1):32–40

38. Malin M, Gissler M. Maternal care and birth outcomes among ethnic minority women in Finland. *BMC Public Health*. 2009;9:84

39. Zwirs BW, Burger H, Schulpen TW, Wiznitzer M, Fedder H, Buitelaar JK. Prevalence of psychiatric disorders among children of different ethnic origin. *J Abnorm Child Psychol*. 2007; 35(4):556–566

40. Pedersen GS, Mortensen LH, Gerster M, Rich-Edwards J, Andersen AM. Preterm birth and birthweight-for-gestational age among immigrant women in Denmark 1978–2007: a nationwide registry study. *Paediatr Perinat Epidemiol*. 2012;26(6): 534–542

41. Copper RL, Goldenberg RL, Das A, et al; National Institute of Child Health and Human Development Maternal-Fetal Medicine Units Network. The preterm prediction study: maternal stress is associated with spontaneous preterm birth at less than thirty-five weeks' gestation. *Am J Obstet Gynecol*. 1996; 175(5):1286–1292

42. Russell G, Ford T, Rosenberg R, Kelly S. The association of attention deficit hyperactivity disorder with socioeconomic disadvantage: alternative explanations and evidence. *J Child Psychol Psychiatry*. 2014;55(5):436–445

43. Mortensen LH, Diderichsen F, Arntzen A, et al. Social inequality in fetal growth: a comparative study of Denmark, Finland, Norway and Sweden in the period 1981–2000. *J Epidemiol Community Health*. 2008;62(4):325–331

44. Kent ST, McClure LA, Zaitchik BF, Gohlke JM. Area-level risk factors for adverse birth outcomes: trends in urban and rural settings. *BMC Pregnancy Childbirth*. 2013;13:129

45. Zahner GE, Jacobs JH, Freeman DH Jr, Trainor KF. Rural-urban child psychopathology in a Northeastern US state: 1986–1989. *J Am Acad Child Adolesc Psychiatry*. 1993;32(2):378–387

46. World Health Organization. *International Classification of Diseases, Eighth Revision (ICD-8)*. Geneva, Switzerland: World Health Organization; 1967

47. D'Onofrio BM, Class QA, Rickert ME, Larsson H, Långström N, Lichtenstein P. Preterm birth and mortality and morbidity: a population-based quasi-experimental study. *JAMA Psychiatry*. 2013;70(11):1231–1240

48. O'Keeffe MJ, O'Callaghan M, Williams GM, Najman JM, Bor W. Learning, cognitive, and attentional problems in adolescents born small for gestational age. *Pediatrics*. 2003;112(2):301–307

49. Pettersson E, Sjolander A, Almqvist C, et al. Birth weight as an independent predictor of ADHD symptoms: a within-twin pair analysis. *J Child Psychol Psychiatry*. 2015;56(4):453–459

50. Grissom NM, Reyes TM. Gestational overgrowth and undergrowth affect neurodevelopment: similarities and differences from behavior to epigenetics. *Int J Dev Neurosci*. 2013;31(6):406–414

51. Rodriguez A, Miettunen J, Henriksen TB, et al. Maternal adiposity prior to pregnancy is associated with ADHD symptoms in offspring: evidence from three prospective pregnancy cohorts. *Int J Obes (Lond)*. 2008;32(3):550–557

52. Gissler M, Rahkonen O, Arntzen A, Cnattingius S, Andersen AM, Hemminki E. Trends in socioeconomic differences in Finnish perinatal health 1991–2006. *J Epidemiol Community Health*. 2009;63(6): 420–425

53. Kallankari H, Kaukola T, Olsén P, Ojaniemi M, Hallman M. Very preterm birth and foetal growth restriction are associated with specific cognitive deficits in children attending mainstream school. *Acta Paediatr*. 2015;104(1):84–90

54. Ment LR, Hirtz D, Hüppi PS. Imaging biomarkers of outcome in the developing preterm brain. *Lancet Neurol*. 2009;8(11): 1042–1055

55. Goldenberg RL, Culhane JF, Iams JD, Romero R. Epidemiology and causes of

preterm birth. *Lancet.* 2008;371(9606): 75–84

56. Korvenranta E, Lehtonen L, Rautava L, et al; PERFECT Preterm Infant Study Group. Impact of very preterm birth on health care costs at five years of age. *Pediatrics.* 2010;125(5). Available at: www.pediatrics. org/cgi/content/full/125/5/e1109

57. Setänen S, Haataja L, Parkkola R, Lind A, Lehtonen L. Predictive value of neonatal brain MRI on the neurodevelopmental outcome of preterm infants by 5 years of age. *Acta Paediatr.* 2013;102(5): 492–497

58. Johnson S, Wolke D. Behavioural outcomes and psychopathology during adolescence. *Early Hum Dev.* 2013;89(4): 199–207

59. Shapiro-Mendoza CK, Lackritz EM. Epidemiology of late and moderate preterm birth. *Semin Fetal Neonatal Med.* 2012;17(3):120–125

60. Keskimäki I, Aro S. Accuracy of data on diagnoses, procedures and accidents in the Finnish hospital discharge register. *Int J Health Sci.* 1991;2(1): 15–21

61. Levine TA, Grunau RE, McAuliffe FM, Pinnamaneni R, Foran A, Alderdice FA. Early childhood neurodevelopment after intrauterine growth restriction: a systematic review. *Pediatrics.* 2015; 135(1):126–141

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