[Original article: 2 tables, 1 figure]

Preterm postnatal complications and risk of attention-deficit/hyperactivity disorder

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ABBREVIATIONS

IVH intraventricular haemorrhage

ROP retinopathy of prematurity

[abstract]

AIMS To investigate the association between the risk of attention-deficit/hyperactivity disorder (ADHD) and preterm birth and determine how postnatal complications in children born preterm is associated with the risk of ADHD.

METHOD This population-based cohort study used data from the Hong Kong electronic medical records. We followed 359 614 children (48% female; 6-17 years old, mean = 11.58, SD =3.16) born in public hospitals in Hong Kong from 1st January 2004 to 31st December 2014 and collected medical records and demographic details for mothers and children until 11th November 2020.

RESULTS The risk of ADHD was 4.0% in children born at term and 5.1% in children born preterm. The odds ratio for ADHD was 2.08 (95% confidence interval [CI] 1.64–2.64) for children born extremely preterm, 1.64 (95% CI 1.46–1.85) for children born very preterm, and 1.15 (95% CI 1.08–1.23) for children born late preterm. Among preterm postnatal complications, only early respiratory disease, retinopathy of prematurity (ROP), and intraventricular haemorrhage were significant predictors of ADHD after controlling for preterm birth, other risk factors, and sociodemographic variables. The excess risk of ADHD among children born very preterm or late preterm could be partly explained by respiratory disease. ROP partially mediated the risk of ADHD in children born very preterm.

INTERPRETATION Children born preterm in all subcategories, from extremely preterm to late preterm, have increased risk of ADHD. Early respiratory infection partially mediates the risk of ADHD in children born preterm.

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What this paper adds

- A significant association was found between children born preterm in all subcategories and a diagnosis of attention-deficit/hyperactivity disorder (ADHD).
- Early respiratory diseases and retinopathy of prematurity (ROP) were associated with a higher risk of ADHD in children born preterm.
- Children born preterm with early respiratory diseases and ROP should be monitored for symptoms of ADHD.

[main text]

An estimated 15 million infants are born preterm annually worldwide.[1] Despite advances in antenatal and neonatal care, preterm birth is a leading cause of disability in childhood. Infants born preterm, particularly those delivered at the earliest gestational ages, have a higher risk of executive function deficits, impaired receptive and expressive language skills, and are associated with higher rates of co-occurring attention-deficit/hyperactivity disorder (ADHD) and other emotional and behavioural difficulties.[2]

ADHD is one of the most common neurodevelopmental disorders and is characterized by inattention, hyperactivity, and impulsivity.[2] A recent meta-analysis concluded that children born very preterm (28–32 weeks) with very low birthweight (1000–1500g) are about three times more likely to develop ADHD compared with children born at term, and that ADHD

symptoms are associated with gestational age.[2] Another large-scale research study analysing 546 894 pairs of full siblings born in Sweden found a significant association between fetal growth and later development of ADHD symptoms.[3] However, a systematic review analysing a large number of risk factors for ADHD concluded that the link between preterm birth and ADHD is still only 'suggestive'[4] and emphasized the need for further research. Furthermore, despite an association between an elevated risk for ADHD and very preterm birth, the relationship is less clear in children born late preterm, which is usually defined as the period between 34 and 36 weeks.[1]

Although most of these studies have also taken into account potential genetic, environmental, and perinatal confounding factors,[5,6] few studies have explored whether specific postnatal complications related to preterm birth contribute to or further increase the risk of ADHD later in life. With advances in neonatal medicine, more children born extremely preterm are surviving. However, they often suffer from multiple postnatal complications and are prone to developmental disabilities, such as ADHD, later on in life. The UK National Institute for Health and Care Excellence guidelines highlighted that children born preterm with specific risk factors should be referred for enhanced developmental surveillance. Nevertheless, risk factors only included existing developmental disorders in children born before 30 weeks or children born between 30 and 36 weeks with conditions affecting the central nervous system.[7] However, previous studies have demonstrated that a substantial proportion of infants born very preterm who survive without major impairments as shown from their first developmental assessment during the preschool period, exhibit more psychiatric disorders when they get to school age or adulthood.[8] Hence, it is essential that we gain a better understanding of how other preterm postnatal complications might affect the long-term risk of ADHD so that children at risk might benefit from longer developmental follow-up and receive earlier assessment and interventions.

To our knowledge, this is the first study that examines the association between common postnatal complications and ADHD in children from Hong Kong who were born preterm. We hypothesized that the risk of ADHD in children born preterm would be higher than that in children born at term, which is mediated by postnatal complications. With identification of specific postnatal complications as early risk factors for ADHD, this will facilitate timely interventions so as to maximize the developmental outcomes of children born preterm.

METHOD

Data source and study population

We conducted a population-based birth cohort study by analysing electronic medical records retrieved from the Clinical Data Analysis and Reporting System in Hong Kong. The Clinical Data Analysis and Reporting System is a medical database developed by the Hong Kong Hospital Authority; it is the only publicly funded health care provider in Hong Kong. The database has been used for several high-quality population-based studies and has been shown to have highly accurate coding.[9]

The current study retrieved all cases of births delivered in public hospitals between 1st January 2004 and 31st December 2014. The medical records from 1st January 2004 to 11th November 2020 and the demographic details for both mothers and children were collected. We excluded cases of abortion, perinatal or postnatal death, and those with missing essential birth-related information. To avoid potential bias, we also excluded children whose mothers were not Hong Kong residents because those children's medical records may be incomplete in Hong Kong. Thus, a total number of 359 164 deliveries were included in this study (Figure S1).

This research was approved by the institutional review board of the University of Hong Kong/Hospital Authority Hong Kong West Cluster: UW 20-568. Participant consent for data

sharing was not obtained because the data presented are anonymized and the risk of identification is very low.

Gestational age

Gestational age is defined as the length of pregnancy from the beginning of the mother's last menstrual period to the birth delivery date. Gestational age has been further categorized by the World Health Organization as extremely preterm (<28 weeks), very preterm (28–32 weeks), late preterm (33–36 weeks), term (37–41 weeks), and postterm (>41 weeks).

ADHD

In this study, children with a recorded diagnosis of ADHD (International Statistical Classification of Diseases and Related Health Problems, 9th Revision [ICD-9] 314) or prescribed with medications for ADHD (i.e. methylphenidate or atomoxetine) were considered to have ADHD. Methylphenidate or atomoxetine were the only available medications for ADHD in Hong Kong during the study period. ADHD is typically diagnosed clinically in Hong Kong in accordance with the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.[10] Using ADHD medications to estimate the prevalence of ADHD was successful in a previous study.[11]

Confounding covariates

As noted in the literature, there are several potential confounding variables associated with both gestational age/fetal growth and ADHD, including maternal age at delivery, sex of the child, birth year, birth order, socioeconomic status, mode of delivery, birth trauma, and maternal psychiatric history. The socioeconomic status of parents was estimated based on the median income in their residential region and the payment method. Maternal psychiatric history was defined as any diagnosis of psychiatric/mental disorder (ICD-9 290–319) before delivery.

Mediators and/or moderators: postnatal complications in children born preterm

Several postnatal complications were investigated as possible mediators and/moderators of the associations between preterm birth and ADHD. They included admission to the newborn intensive care unit (for longer than 24 hours), respiratory disease, patent ductus arteriosus, necrotizing enterocolitis, intraventricular haemorrhage (IVH), retinopathy of prematurity (ROP), and cerebral palsy. All variables were coded as binary variables. Respiratory diseases included all diagnosed infections of the respiratory system (ICD-9 460–519) on or before 2 years of age.

Statistical analysis

The odds ratios (ORs) of children born preterm with ADHD were calculated through logistic regression compared with children born at term. Three different models were used to evaluate the adjusted impact of preterm birth on ADHD. Model 1 included basic sociodemographic confounders: maternal age at delivery and socioeconomic status, sex of child, birth year, and birth order. Model 2 added maternal psychiatric condition, adjusting for potential genetic confounding and prenatal risk. Model 3 added potential postnatal mediating factors to estimate the associations of preterm birth on ADHD independent of those factors. To generate model 3, all of the identified postnatal risk factors were entered into a multiple logistic regression (with the outcome variable as ADHD) along with the sociodemographic variables in model 1. To retain statistical power and minimize multicollinearity, all non-significant risk factors ($p > 0.05$) were subsequently removed in the final model 3 and only potential mediators that reached statistical significance ($p < 0.05$) were included in the further mediation analysis. The potential mediators were regressed by preterm birth, other mediators, and sociodemographic factors in model 1 to establish the mediation model. The outcome model included all potential mediators, preterm birth, and sociodemographic factors in model 1 together with the outcome measure of ADHD. The selected postnatal mediating factors (as included in model 3) were regressed by preterm birth (different subcategories of preterm birth) and other covariates in multiple Poisson

models adjusting for each other and for sociodemographic factors (as included in model 1). The natural indirect effect and total effect were calculated by combining the outcome model and the mediation model based on a causal mediation framework.[12] The mediation proportion was calculated as the natural indirect effect over the total effect. Because there were slight variations in the follow-up duration between children, we also conducted a Cox proportional hazard model accounting for censoring in the sensitivity analysis (Appendix S1).

Statistical analyses were conducted using R 4.03 (R Foundation for Statistical Computing, Vienna, Austria) with the packages mgcv and mediation. For all comparisons, $p < 0.05$ was considered as statistically significant.

RESULTS

In the cohort of 359 614 children (48% female; 6-17 years old, mean = 11.58, SD =3.16), 330 087 (91.8%) children were born at term and 28 545 (7.9%) were born preterm. The mean age at ADHD diagnosis or medication use was 8 years 7 months (SD 1 year 10 months), which is consistent with a previous study showing that the mean age of intake to the child psychiatry service due to ADHD in Hong Kong was 7 years 8 months to 8 years (SD 1 year 7 months).[13] The mean age at diagnosis and ICD-9 code for conditions of interest are listed in Table S1.

Regarding ADHD diagnosis, 14 592 (4.1%) cases were either prescribed with medications for ADHD (i.e. methylphenidate or atomoxetine) or diagnosed with ADHD. Out of the 14 592 cases, 2023 (14%) had an ADHD diagnosis only, 3812 (26%) had prescriptions only, and 8757 (60%) were both diagnosed and prescribed with drugs. Out of 12 569 cases with drug prescriptions, 974 (7.7%) received just one prescription without ever having another refill. The risk of ADHD was 4.0% for children born at term and 5.1% for children born preterm. Among the cases with ADHD, 22.8% were female. Table 1 presents the relationship between gestational age, ADHD, and other variables of interest.

Table 2 presents the ORs of developing ADHD at different gestational ages compared with children delivered at term. Children born preterm in all subcategories had a higher risk of developing ADHD compared to children born at term. When controlling for sociodemographic variables in model 1, the OR for ADHD was 2.08 (95% CI 1.64–2.64) for children born extremely preterm, 1.64 (95% CI 1.46–1.85) for children born very preterm, and 1.15 (95% CI 1.08–1.23) for children born late preterm. The OR was 1.26 (95% CI 1.20–1.34) for all children born preterm. Figure S2 presents the OR of developing ADHD at each gestational age based on model 1. When adding all relevant postnatal risk factors (i.e. admission to the newborn intensive care unit, respiratory disease in the first 2 years of life, ROP, patent ductus arteriosus, necrotizing enterocolitis, IVH, and cerebral palsy) to model 1, only IVH, ROP, and respiratory disease were significant predictors of ADHD (Tables S2 and S3). Also, the excluded factors only had weak correlations ($\varphi < 0.2$) with the included factors (Table S4). The results estimated according to the Cox proportional models (Table S5) were generally consistent with the primary analysis, suggesting that censoring had no major impact on the conclusions.

Controlling for the sociodemographic variables in model 1, children born preterm had a significantly increased risk of respiratory disease (OR = 6.44, 95% CI 5.64–7.34), patent ductus arteriosus (OR = 1.38, 95% CI 1.34–1.41), necrotizing enterocolitis (OR = 87.71, 95% CI 69.71–110.35), IVH (OR = 98.55, 95% CI 83.56–116.24), and cerebral palsy (OR = 14.03, 95% CI 11.41–17.24) compared with those delivered at term. Among the preterm complications, only respiratory disease in the first 2 years of life (OR = 1.77, 95% CI 1.70–1.83, $p < 0.001$), ROP (OR = 1.64, 95% CI 1.29–2.09, $p < 0.001$), and IVH (OR = 1.28, 95% CI 1.02–1.61, $p = 0.033$) were significant predictors of ADHD after controlling for preterm birth, other risk factors, and sociodemographic variables in model 1. Thus, respiratory disease

in the first 2 years of life, ROP, and IVH are qualified potential mediators of the association between preterm birth and ADHD.

As shown in Table 3, respiratory disease in the first 2 years of life and IVH were significant mediators for late preterm birth. Respiratory disease and ROP were also significant mediators for very preterm birth. The mediation role was not significant in children born extremely preterm, which is likely due to the relatively small sample size in this subgroup. The numbers of postnatal complications (including respiratory disease, patent ductus arteriosus, necrotizing enterocolitis, IVH, ROP, and cerebral palsy) was significantly associated with the risk of ADHD (OR = 1.64, $p < 0.001$) adjusted for maternal age at delivery, sex, birth year, birth order, and socioeconomic status. (For the numbers of postnatal complications and the risk of ADHD in children born extremely preterm, see Table S6.)

Figure 1 presents the risk of ADHD at different gestational ages with or without certain risk factors. The OR of developing ADHD was higher in children with smaller gestational age and in children who had been affected by preterm complications (respiratory disease, ROP, and IVH). Children born at term with IVH had a significantly elevated risk for developing ADHD compared with children without IVH. Caesarean section increased the risk of ADHD in children born at term.

DISCUSSION

This population-based cohort study showed that children born preterm are at a higher risk of ADHD compared with children born at term. Children born extremely preterm had a nearly twofold increased risk of ADHD compared with children born at term. Consistent with recent findings showing that children born late preterm might be prone to poorer developmental outcomes,[14] we observed a small but significantly elevated risk of ADHD in children born late preterm. Therefore, elective caesarean section or purposeful early delivery due to social reasons

should be discouraged. Our study showed that early respiratory infections almost doubled the odds of ADHD in both children born at term and preterm. A longitudinal study should be conducted in the future to ascertain whether children born preterm with frequent early respiratory infections have a higher risk of ADHD. If the associations were later found to be causal, protecting children from early respiratory infections could be beneficial to their psychosocial well-being and neurodevelopment. Furthermore, infants born preterm with bronchopulmonary dysplasia are prone to serious complications from respiratory infections with high morbidity and mortality;[15,16] thus, preventive measures against viral infections, such as a yearly influenza vaccination, should be advocated.[17]

Several mechanisms have been proposed on how preterm postnatal complications mediate the associations between preterm birth and risk of ADHD. In the immediate postnatal period, the loss of autoregulation and systemic hypotension, which is commonly seen in infants born preterm, may result in cerebral hypoxia affecting the watershed regions of the brain including the striatum.[18] The cingulo-striato-thalamocortical loops are essential for optimizing higher cortical functions, such as attention and awareness, and have been implicated in ADHD. Repeated hypoxic-ischaemic events might damage the striatum and contribute to the pathogenesis of ADHD in children born preterm. Moreover, infants born preterm have immature respiratory systems that are prone to respiratory infections. An immature lung with frequent severe respiratory infections can affect the delivery of oxygen to the brain, leading to suboptimal neurodevelopment. Compared with children born at term, infants born preterm can have deficient immune systems, characterized by smaller pools of monocytes and neutrophils, and lower production of cytokines limiting T-cell activation,[19] which results in higher susceptibility to postnatal infections and inflammation. Thus, postnatal infections in infants born preterm could have causal associations with ADHD because they would introduce excessive inflammation and immune responses, which can interfere with neurodevelopment.[20]

IVH is common in infants born preterm and was shown to mediate ADHD risk in children born late preterm. Its mediating role was diminished in those born very preterm or extremely preterm, which might be related to the higher incidence of severe IVH in infants born very preterm or extremely preterm.[21] Severe IVH is related to significant mortality and neurodevelopmental impairment;[22] a diagnosis of ADHD might be underestimated in children with intellectual disabilities especially in those with severe or profound grade.[23] Notably, although IVH mainly occurs in children born preterm, we found that children born at term with IVH were at significantly higher risk of ADHD. Very few studies have investigated the association between ROP and ADHD risk in children born preterm.[24] Our study showed that ROP was associated with increased risk of ADHD in children born very preterm, although the exact mechanism of this association is unknown. Children with ROP have poorer executive function,[24] which is also seen in children with ADHD. Furthermore, children with a history of ROP show morphological and vascular structure changes of the fovea.[25] Changes to the foveal structure might affect visual attention and visual processing speed. Children with ADHD had significantly impaired sustained attention and visual processing speed.[26] In addition to a different foveal structure, children with ROP are also prone to refractive errors, amblyopia, and strabismus, which can also affect children's sustained attention and visual processing speed, eventually leading to possible attention-deficit disorders.

The current study has several limitations. First, children born preterm in Hong Kong receive more clinical follow-up compared to children born at term. This could increase the likelihood of alerting parents and clinicians to children's neurodevelopmental problems, thereby leading to an increased diagnosis rate in children born preterm. Second, preterm complications such as respiratory disease, ROP, or IVH could be simply co-occurring conditions with ADHD in children born preterm, rather than causal factors. Third, given that ADHD is highly heritable,[27] genetic factors may play a significant role in modifying the relationship between preterm birth

and ADHD. We cannot fully control its influence through adjusting for maternal psychiatric conditions. Fourth, our study could not exclude cases with diagnostic uncertainties because the diagnosis was based on diagnostic coding done by the clinicians during hospitalization and/or clinic visits. For children born preterm, we did not have ultrasound-derived estimates of gestational age. In addition, as motor function stabilizes later in life and some children no longer fit the case definition of cerebral palsy when they get older, there would be diagnostic uncertainties for the proportion of children who were diagnosed with cerebral palsy before the age of 4 years.[28] For children with ADHD, 7.7% received just one prescription without ever having another refill. We could not be certain whether this group of children discontinued their drug prescriptions due to intolerable side effects, continued their follow-up in the private sector, or discontinued their drug prescriptions due to diagnostic uncertainties. Fifth, children with mild ADHD might not seek help from health care professionals in the public sector but opt to use the private sector instead, which could undermine the incidence of ADHD as reported by the Clinical Data Analysis and Reporting System, although Hospital Authority hospitals and clinics account for most of the specialist care provision in Hong Kong.[29] Furthermore, the dichotomization of variables could cause imprecision in the findings; future studies with granular data should attempt to also include dose–response relationships. Lastly, similar to other observational studies, causality cannot be confirmed. The findings could be subject to collider bias, for example, by selection to the public health care system, and unmeasured confounding, for example, epigenetic factors.

In conclusion, a significant association was found between children born preterm in all subcategories and ADHD diagnosis. Respiratory infections in the first 2 years of life, ROP, and IVH can potentially influence the risk of ADHD in children born preterm. Children born preterm with a history of these postnatal complications should have enhanced developmental surveillance so they can be closely monitored for symptoms of ADHD. This will facilitate early

identification and timely interventions to improve the neurodevelopmental outcomes of children born preterm.

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Supporting information

The following additional material may be found online:

Table S1: List of International Classification of Diseases corresponding codes and age of diagnosis for diseases covered in this research

Table S2: Multinominal logistic regression for ADHD with the focal predictor of preterm birth and other potential mediators and confounding variables

Table S3: Multinominal logistic regression for ADHD with the focal predictor of preterm birth and other potential mediators and confounding variables

Table S4: Intercorrelation between risk factors related to preterm birth

Table S5: Hazard ratios for developing ADHD according to gestational age

Table S6: Number of cases with ADHD born extremely preterm with multiple postnatal complications

Figure S1: Flow chart of case inclusion.

Figure S2: Risk of ADHD in different preterm categories.

Appendix S1: Sensitivity analysis

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Table 1: Attention-deficit/hyperactivity disorder (ADHD) by sociodemographic characteristics, parental morbidity, perinatal and postnatal factors with stratification by gestational week

	Born extremely preterm (<28 weeks) *n* = 961 (0.3%)		Born very preterm (28–32 weeks) *n* = 4773 (1.3%)		Born late preterm (33–36 weeks) *n* = 22 811 (6.3%)		Born at term (37–41 weeks) *n* = 330 087 (91.8%)		Born postterm (42–44 weeks) *n* = 982 (0.3%)	
	ADHD *n* = 77 (8.0%)	Non-ADHD *n* = 884 (92.0%)	ADHD *n* = 311 (6.5%)	Non-ADHD *n* = 4462 (93.5%)	ADHD *n* = 1069 (4.7%)	Non-ADHD *n* = 21 742 (95.3%)	ADHD *n* = 13 087 (4.0%)	Non-ADHD *n* = 317 000 (96.0%)	ADHD *n* = 48 (4.9%)	Non-ADHD *n* = 934 (95.1%)
Follow-up (age at data collection), years:months, mean (SD)	12:7 (2:9)	11:7 (3:3)	12:9 (2:9)	11:6 (3:2)	12:8 (2:8)	11:6 (3:2)	12:9 (2:8)	11:6 (3:2)	14:6 (2:7)	14:0 (2:10)
Female	18 (23.4)	423 (47.9)	82 (26.5)	2008 (45.0)	237 (22.2)	9973 (45.9)	2978 (22.8)	15 7152 (49.6)	11 (22.9)	457 (48.9)
Normal spontaneous delivery[a]	40 (51.9)	376 (42.5)	117 (37.6)	1564 (35.1)	589 (55.1)	10 852 (49.9)	8619 (65.9)	21 4328 (67.6)	33 (68.8)	616 (66.0)
Birth order										
1	62 (80.5)	666 (75.3)	230 (74.0)	3228 (72.3)	835 (78.1)	16 191 (74.5)	11 026 (84.3)	248 381 (78.4)	42 (87.5)	800 (85.7)
2	14 (18.2)	186 (21.0)	68 (21.8)	1079 (24.2)	198 (18.5)	4904 (22.6)	1900 (14.5)	62 804 (19.8)	5 (10.4)	118 (12.6)
≥3	1 (1.3)	32 (3.6)	13 (4.2)	155 (3.5)	36 (3.4)	647 (3.0)	161 (1.2)	5815 (1.8)	1 (2.1)	16 (1.7)
Birthweight, g, mean (SD)	948 (474)	943 (436)	1484 (406)	1560 (422)	2445 (451)	2436 (448)	3182 (423)	3201 (406)	3247 (506)	3320 (467)
Birth trauma[b]	1 (1.3)	4 (0.5)	2 (0.6)	22 (0.5)	2 (0.2)	74 (0.3)	81 (0.6)	1421 (0.4)	0 (0)	8 (0.9)
Apgar score <7										
1 minute	53 (68.8)	586 (66.3)	112 (36.0)	1510 (33.8)	95 (8.9)	1675 (7.7)	307 (2.3)	6336 (2.0)	1 (2.1)	19 (2.0)
5 minutes	13 (16.9)	142 (16.1)	9 (2.9)	196 (4.4)	6 (0.6)	135 (0.6)	24 (0.2)	480 (0.2)	0 (0)	0 (0)
Respiratory diseases[c]	53 (68.8)	540 (61.1)	115 (49.8)	1643 (36.8)	417 (39.0)	5405 (24.9)	4174 (31.9)	64 123 (20.2)	14 (29.2)	182 (19.5)
Patent ductus arteriosus	47 (61.0)	520 (58.8)	60 (19.3)	817 (18.3)	25 (2.3)	403 (1.9)	65 (0.5)	1406 (0.4)	0 (0)	1 (0.2)
Necrotizing enterocolitis	8 (10.4)	134 (15.2)	20 (6.4)	330 (7.4)	10 (0.9)	150 (0.7)	6 (<0.1)	77 (<0.01)	0 (0)	0 (0)

Retinopathy of prematurity	45 (58.4)	459 (51.9)	52 (16.7)	447 (10.0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cerebral palsy	1 (1.3)	24 (2.7)	5 (1.6)	41 (0.9)	0 (0)	26 (0.1)	4 (<0.1)	77 (<0.1)	0 (0)	0 (0)
Intraventricular haemorrhage	34 (44.2)	356 (40.3)	51 (16.4)	722 (16.2)	12 (1.1)	190 (0.9)	13 (<0.01)	147 (<0.01)	0 (0)	0 (0)
Monthly income per capita (HK$), mean (SD)[d]	10 803 (2156)	10 890 (2208)	10 732 (2095)	10 755 (2129)	10 477 (1874)	10 490 (1907)	10 442 (1852)	10 451 (1882)	9907 (1442)	10 361 (1966)
Receiving public assistance	5 (6.5)	23 (2.6)	11 (3.5)	113 (2.5)	41 (3.8)	338 (1.6)	173 (1.3)	1714 (0.5)	1 (2.1)	14 (1.5)
Maternal age at delivery, years:months, mean (SD)	31:5 (6:7)	32:10 (5:4)	31:9 (5:5)	32:7 (5:4)	31:0 (5:6)	31:11 (5:3)	30:6 (5:3)	31:0 (5:0)	29:2 (5:2)	29:6 (5:10)
Maternal psychiatric history[e]	13 (16.9)	116 (13.1)	82 (26.4)	538 (12.1)	295 (27.6)	2740 (12.6)	3344 (25.6)	34 807 (11.0)	10 (20.8)	134 (4.3)

Values are *n* (%) unless stated otherwise.
[a]Normal spontaneous delivery is the delivery of the infant through the birth canal without any surgery.
[b]Birth trauma includes subaponeurotic haemorrhage, soft tissue trauma, nerve injury, visceral injury, cephalohaematoma, and fractures.
[c]Respiratory diseases indicate diagnosis of respiratory diseases (ICD-9 460–519) within 24 months after birth.
[d]Monthly income per capita was estimated through parents' residential region based on the regional median household income in Hong Kong.
[e]Maternal psychiatric history is defined as any psychiatric/mental diagnosis (ICD-9 290–319) before delivery.

Table 2: Odds ratio (OR) of developing attention-deficit/hyperactivity disorder (ADHD) by gestational age

	Gestational age, weeks	Unadjusted model		Model 1		Model 2		Model 3	
		OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*	OR (95% CI)	*p*
Born extremely preterm	<28	2.11*** (1.67–2.67)	<0.001	2.08*** (1.64–2.64)	<0.001	2.03*** (1.59–2.58)	<0.001	1.18 (0.80–1.76)	0.407
Born very preterm	28–32	1.69*** (1.50–1.90)	<0.001	1.64*** (1.46–1.85)	<0.001	1.63*** (1.45–1.83)	<0.001	1.34*** (1.17–1.53)	<0.001
Born late preterm	33–36	1.19*** (1.12–1.27)	<0.001	1.15*** (1.08–1.23)	<0.001	1.13*** (1.06–1.21)	<0.001	1.11** (1.04–1.19)	0.001
Born preterm	<37	1.30*** (1.23–1.38)	<0.001	1.26*** (1.20–1.34)	<0.001	1.24*** (1.17–1.31)	<0.001	1.15*** (1.09–1.22)	<0.001
Born postterm	>41	1.25 (0.93–1.67)	0.140	0.90 (0.67–1.21)	0.476	0.88 (0.65–1.18)	0.381	0.91 (0.68–1.22)	0.517

**$p < 0.01$, ***$p < 0.001$. The odds of children born at term (gestational age between 37 and 41 weeks) developing ADHD were set as reference.

Model 1 adjusted for maternal age at delivery, sex, birth year, birth order, and socioeconomic status (estimated by regional median household income in Hong Kong and payment method). Model 2 adjusted for all factors in model 1 and maternal psychiatric conditions. Model 3 adjusted for all factors in model 1 and significant postnatal risk factors including respiratory disease, intraventricular haemorrhage, and retinopathy of prematurity. Abbreviation: CI, confidence interval.

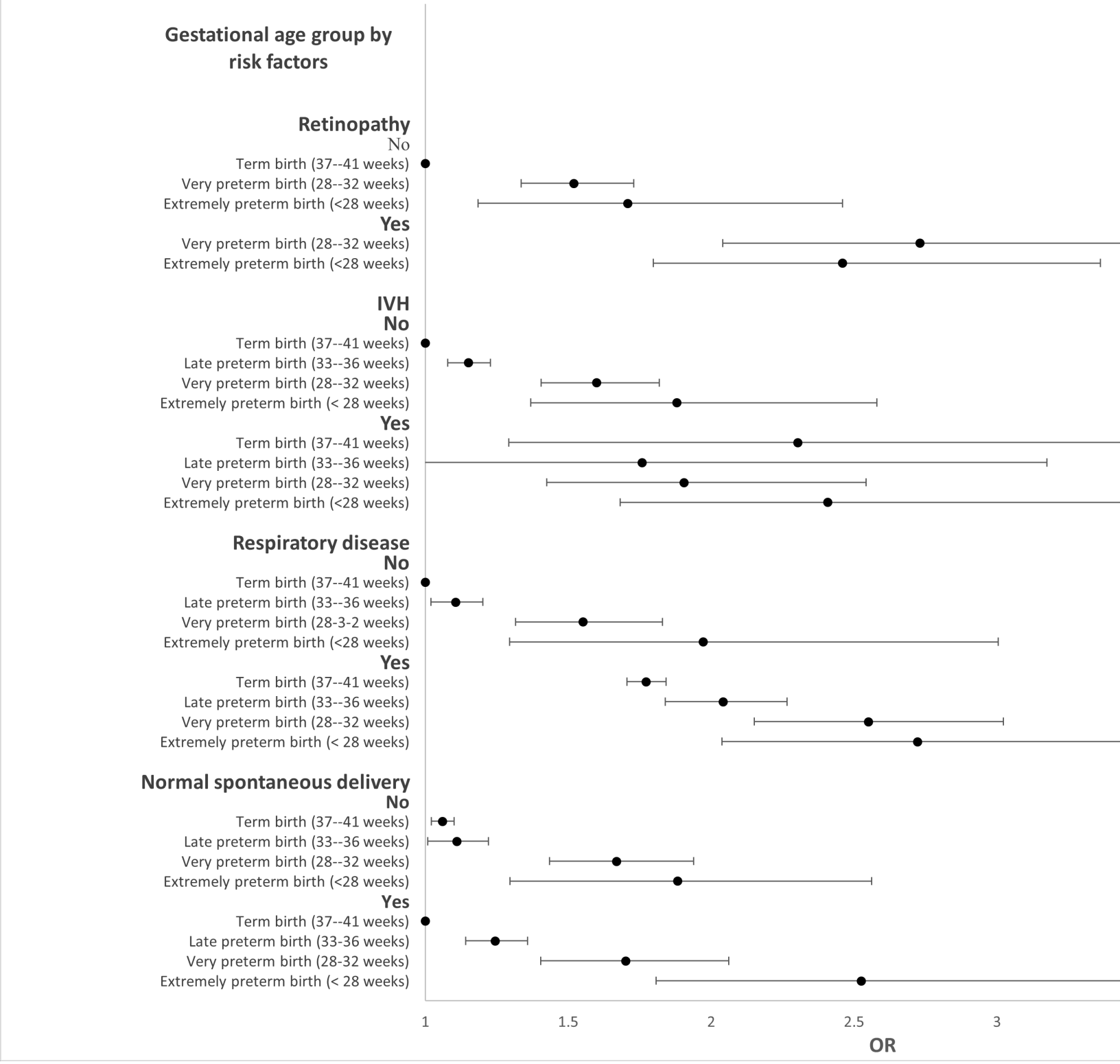
Table 3: Proportion mediated by risk factors in the association between preterm birth and attention-deficit/hyperactivity disorder

	Gestational age, weeks	Respiratory diseases		Retinopathy of prematurity		IVH	
		Proportion mediated	*p*	Proportion mediated	*p*	Proportion mediated	*p*
Born extremely preterm	<28	55.0%	0.076	43.0%	0.282	42.2%	0.146
Born very preterm	28–32	29.4%***	<0.001	18.3%***	<0.001	9.1%	0.170
Born late preterm	33–36	23.2%***	<0.001	NA	NA	4.1%*	0.016
Born preterm	<37	24.7%***	<0.001	10.8%***	<0.001	6.3%*	0.03

*$p < 0.05$, ***$p < 0.001$. Abbreviations: IVH, intraventricular haemorrhage; NA, not applicable.

Figure legend

Figure 1: Risk of attention-deficit/hyperactivity disorder (ADHD) stratified by gestational age and risk factors. The odds ratio (OR) was adjusted for maternal age at delivery, sex, birth year, birth order, and socioeconomic status (estimated by regional median household income in Hong Kong and payment method). Children born at term without a certain risk factor were set as the reference (e.g. the risk of developing ADHD in children with or without intraventricular haemorrhage [IVH] was compared to children born at term without a diagnosis of IVH).


Gestational age group by risk factors
Retinopathy
No
Term birth (37--41 weeks)
Very preterm birth (28--32 weeks)
Extremely preterm birth (<28 weeks)
Yes
Very preterm birth (28--32 weeks)
Extremely preterm birth (<28 weeks)
IVH
No
Term birth (37--41 weeks)
Late preterm birth (33--36 weeks)
Very preterm birth (28--32 weeks)
Extremely preterm birth (< 28 weeks)
Yes
Term birth (37--41 weeks)
Late preterm birth (33--36 weeks)
Very preterm birth (28--32 weeks)
Extremely preterm birth (<28 weeks)
Respiratory disease
No
Term birth (37--41 weeks)
Late preterm birth (33--36 weeks)
Very preterm birth (28-3-2 weeks)
Extremely preterm birth (<28 weeks)
Yes
Term birth (37--41 weeks)
Late preterm birth (33--36 weeks)
Very preterm birth (28--32 weeks)
Extremely preterm birth (< 28 weeks)
Normal spontaneous delivery
No
Term birth (37--41 weeks)
Late preterm birth (33--36 weeks)
Very preterm birth (28--32 weeks)
Extremely preterm birth (<28 weeks)
Yes
Term birth (37--41 weeks)
Late preterm birth (33-36 weeks)
Very preterm birth (28-32 weeks)
Extremely preterm birth (< 28 weeks)
1
1.5
2
2.5
3
OR

Supplementary sensitivity analysis

The follow-up times were different among the birth cohort, as children were born at different times but were all followed up to the same end point. We conducted a sensitivity analysis to ensure this follow-up would not affect our conclusions. A Cox proportional hazard model [1] was used to model the association between preterm and the rate of ADHD. Children with no ADHD diagnosis/prescription were considered censored, and their time-to-event was from birth to the end of follow-up (11/11/2020). For children with ADHD diagnosis, the time-to-event was from birth to the first ADHD diagnosis/prescription. Adjustment models were the same as in the logistic regression models. The analysis was conducted using the 'survival' package in R.

As shown in TableS4, the hazard ratios (HR) of ADHD estimated using the Cox regression model were consistent with the odds ratios (OR) shown in Table 2. The differential follow-up times did not affect the conclusions in this study.

Table S5. The hazard ratios for developing ADHD by gestational age.

	GA	Unadjusted model		Model 1		Model 2		Model 3	
		HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Preterm	< 37	1.30 *** (1.23, 1.37)	< .001	1.26 *** (1.19, 1.33)	< .001	1.23 *** (1.17, 1.30)	< .001	1.15*** (1.09, 1.22)	< .001
Late preterm	33-36	1.19 *** (1.12, 1.27)	< .001	1.15 *** (1.08, 1.23)	< .001	1.13 *** (1.06, 1.20)	< .001	1.11** (1.04, 1.18)	.001
Very preterm	28-32	1.67 *** (1.49, 1.87)	< .001	1.60 *** (1.42, 1.79)	< .001	1.58 *** (1.42, 1.78)	<.001	1.32*** (1.16, 1.50)	< .001
Extremely preterm	< 28	2.06 *** (1.65, 2.58)	< .001	2.05 *** (1.64, 2.56)	< .001	1.95 *** (1.55, 2.44)	< .001	1.22 (0.83, 1.78)	.306

GA: Gestational age; HR: hazard ratio
* p < .05, ** P < .01, *** P < .001.
Term birth children (GA between 37 and 41 weeks) were set as the reference group.
Model 1 adjusted for maternal age at delivery, sex, birth year, birth order, and socioeconomic status (estimated by regional median household income in Hong Kong and payment method)
Model 2 adjusted for all factors in Model 1 plus maternal psychiatric conditions.
Model 3 adjusted for all factors in Model 1 plus significant postnatal risk factors including respiratory disease, IVH, and retinopathy.

Table S6. The number of ADHD cases in extremely preterm children with multiple postnatal complications

Postnatal complications include respiratory disease, patent ductus arteriosus, necrotizing enterocolitis, intraventricular haemorrhage, retinopathy of prematurity, and cerebral palsy.

Number of postnatal complications	Count	Percentage	ADHD cases	Percentage of ADHD cases
0	84	8.7%	4	4.8%
1	184	19.1%	13	7.1%
2	261	27.2%	20	7.7%
3	245	25.5%	25	10.2%
4 or more	187	19.5%	15	8.0%

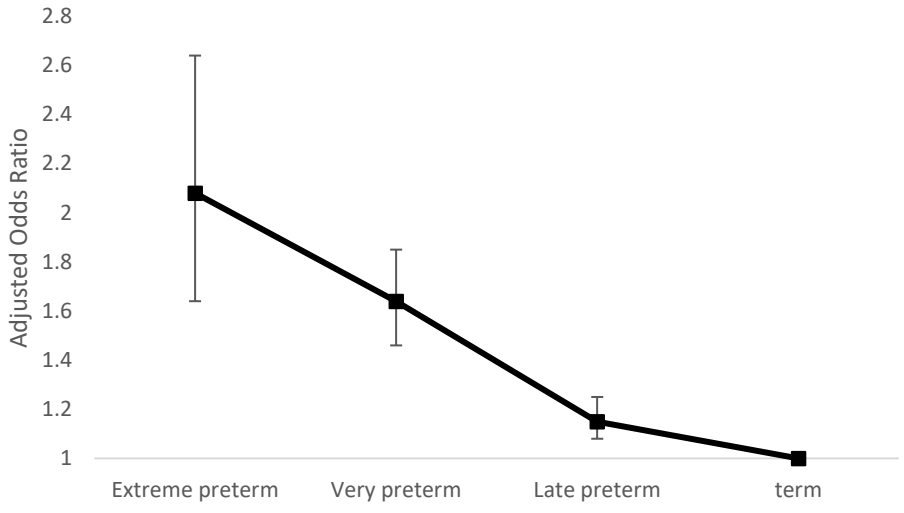


Figure S1a. **Risk of ADHD in different preterm categories.** Adjusted for for maternal age at delivery, sex, birth year, birth order and social-economic status (estimated by regional median household income in Hong Kong and payment method). Error bars represent 95% confidence intervals.

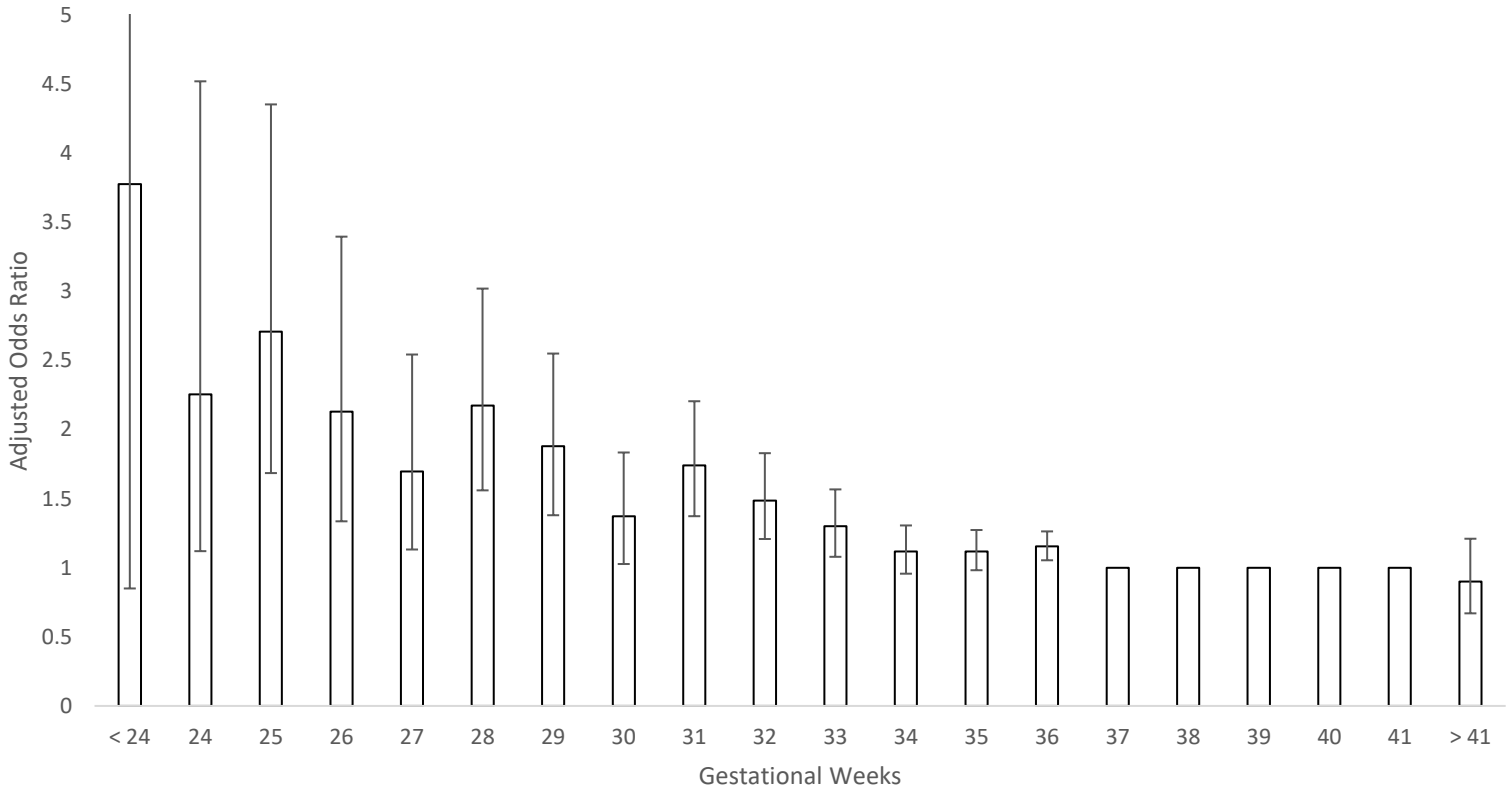


Figure S1b. **Risk of ADHD by gestational weeks.** Adjusted for for maternal age at delivery, sex, birth year, birth order and social-economic status (estimated by regional median household income in Hong Kong and payment method). The risk of term birth children (gestational age between 37-41 weeks) were set as reference. Error bars represent 95% confidence intervals.

Table S1: List of International Classification of Diseases (ICD-9) codes corresponding and age of diagnosis for diseases covered in this research

Diagnosis	**ICD-9 code**	**Mean (SD) age of diagnosis in years**	**Interquartile range**
Attention deficit hyperactivity disorder	314.01	8.40 (0.19)	2.39
Respiratory infection	460 -519	1.04 (0.13)	0.93
Cerebral palsy	343.9	3.05 (2.26)	2.06
Retinopathy of prematurity	362.2	At birth	N/A
Patent ductus arteriosus	747.0	At birth	N/A
Necrotizing enterocolitis	777.5	At birth	N/A
Intraventricular haemorrhage	772.10	At birth	N/A
Maternal psychiatric history	290 - 319	N/A	N/A

Table S2. Multinominal logistic regression for ADHD with the focal predictor of preterm birth and other potential mediators and confounding variables.

							95% C.I. for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Preterm birth [a]	.108	.025	19.004	1	<.001	1.114	1.061	1.170
Respiratory disease	.568	.019	935.516	1	<.001	1.765	1.702	1.831
Retinopathy of prematurity	.403	.126	10.205	1	.001	1.496	1.168	1.915
IVH	.199	.118	2.870	1	.090	1.221	.969	1.538
PDA	.072	.084	.720	1	.396	1.074	.910	1.268
NEC	-.136	.168	.649	1	.421	.873	.628	1.215
Cerebral palsy	-.219	.227	.929	1	.335	.803	.515	1.254
Admission to NICU for > 24 hours	.028	.022	1.614	1	.204	1.028	.985	1.074
SES	-.044	.046	.916	1	.338	.957	.873	1.048
Maternal age	-1.167	.169	47.429	1	<.001	.311	.223	.434
Birth year	-122.519	2.853	1844.513	1	.000	.000	.000	.000
Sex	-1.173	.020	3385.805	1	.000	.309	.297	.322
Birth order	-.105	.021	25.252	1	<.001	.900	.864	.938
Public assistance	.848	.073	136.407	1	<.001	2.334	2.025	2.691
Constant	243.725	5.722	1814.176	1	.000			

a. Preterm birth is coded as a binary variable indicating gestational age < 37 weeks.

IVH: Intraventricular hemorrhage, PDA: Patent ductus arteriosus NEC: Necrotizing enterocolitis

Table S3. Multinominal logistic regression for ADHD with the focal predictor of prematurity and other potential mediators and confounding variables

							95% C.I. for EXP(B)	
	B	S.E.	Wald	df	Sig.	Exp(B)	Lower	Upper
Prematurity [a]	.107	.025	18.482	1	.000	1.113	1.060	1.168
Respiratory Disease	**.569**	**.019**	**935.932**	**1**	**.000**	**1.766**	**1.703**	**1.831**
Retinopathy of prematurity	**.401**	**.126**	**10.130**	**1**	**.001**	**1.493**	**1.167**	**1.912**
IVH	**.199**	**.118**	**2.876**	**1**	**.090**	**1.221**	**.969**	**1.537**
PDA	.069	.084	.675	1	.411	1.072	.908	1.265
NEC	-.137	.168	.665	1	.415	.872	.627	1.212
Cerebral palsy	-.239	.333	.517	1	.472	.787	.410	1.511
Admission to NICU for > 24 hours	.027	.022	1.463	1	.226	1.027	.984	1.072
SES	-.046	.046	.991	1	.319	.955	.872	1.046
Maternal age	-1.163	.169	47.100	1	.000	.313	.224	.436
Birth year	-122.544	2.853	1845.074	1	.000	.000	.000	.000
Sex	-1.173	.020	3386.868	1	.000	.309	.297	.322
Birth order	-.106	.021	25.646	1	.000	.900	.863	.937
Public Assistance	.843	.073	134.633	1	.000	2.323	2.015	2.679
Constant	243.742	5.722	1814.323	1	.000			

a. Prematurity is a 4-point continuous variable (0 term birth, 1 late preterm, 2 very preterm, 3 extremely preterm)

IVH: Intraventricular haemorrhage, PDA: Patent ductus arteriosus NEC: Necrotizing enterocolitis

Table 2.6. Intercorrelation between risk factors related to preterm birth

	Respiratory disease	Retinopathy	Intraventricular haemorrhage	Patent ductus arteriosus	Necrotizing enterocolitis	Cerebral palsy	Admission to NICU for > 24 hours
Respiratory disease	1						
Retinopathy	.042**	1					
Intraventricular haemorrhage	.039**	.341**	1				
Patent ductus arteriosus	.059**	.255**	.249**	1			
Necrotizing enterocolitis	.027**	.133**	.182**	.134**	1		
Cerebral palsy	.032**	.092**	.116**	.083**	.061**	1	
Admission to NICU for > 24 hours	.049**	.065**	.062**	.099**	.065**	.037**	1

Note. Correlations are shown in Phi coefficient. ** $p < 0.01$.