



Preterm birth subtypes, placental pathology findings, and risk of neurodevelopmental disabilities during childhood



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ABSTRACT

Introduction: Preterm birth (PTB) and in-utero inflammation are recognized risk factors of neurodevelopmental disabilities (NDDs); however, their combined role in NDDs is unknown. We examined the independent and joint association of PTB and placental histological findings with the childhood risk of NDDs (overall and by subgroups including autism spectrum disorder (ASD) and ADHD).

Methods: We analyzed data from the Boston Birth Cohort, where mother-infant pairs were enrolled at birth and followed from birth onwards. Birth outcomes, placental pathology and NDDs were obtained from electronic medical records. Placental pathology was categorized using a standardized classification system proposed by the Amsterdam Placental Workshop Group.

Results: PTB (all, including spontaneous, medically indicated) was an independent risk factor for NDDs. Placental histological chorioamnionitis (CA) and PTB additively increased the odds of NDDs (aOR: 2.16, 95% CI: 1.37, 3.39), as well as ADHD (aOR: 2.75, 95% CI: 1.55, 4.90), other developmental disabilities (aOR: 1.96, 95% CI: 1.18, 3.25) and possibly ASD (aOR: 2.31, 95% CI: 0.99, 5.39). The above associations were more pronounced in spontaneous than medically indicated PTB. PTB alone in the absence of CA only had a moderate association with ASD and ADHD. Placental maternal vascular malperfusion alone or in combination with PTB was not associated with the risk of NDDs.

Discussion: Our study provided new insights on PTB and NDDs by further considering preterm subtypes and placental histology. We revealed that children of spontaneous PTB along with histological CA were at the highest risk for a spectrum of NDDs.

1. Introduction

Neurodevelopmental disabilities (NDDs) are a group of conditions, characterized by limitations in several developmental domains, which have an onset in the early developmental period [1,2]. Autism

Spectrum Disorder (ASD) and Attention Deficit Hyperactivity Disorder (ADHD) are the most common neurodevelopmental conditions with a prevalence of ~1.5% and 5–10%, respectively [2–4]. There are important commonalities between these conditions, with studies showing higher rates of co-occurrence among children with ASD and ADHD [5].

Abbreviations: ASD, Autism Spectrum Disorder; ADHD, Attention Deficit Hyperactivity Disorder; CA, Chorioamnionitis; DD, Developmental Disabilities; EMR, Electronic medical records; MVM, Maternal vascular malperfusion; NDD, Neurodevelopmental disabilities; PTB, Preterm birth

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Similarly, young children with ASD often share features with children with NDDs such as global developmental delay and language delay [6]. To date, few studies have examined whether there are common early life antecedents underlying the co-morbidities. This report will focus on two early life factors: preterm birth (PTB) and placental histological findings.

PTB (defined as < 37 weeks of gestation) is a known risk factor for a range of NDDs [7–9]. PTB represents a heterogeneous entity with different underlying pathophysiologies [10]; however, preterm sub-types (such as spontaneous vs. medically indicated PTB) have not been frequently considered in epidemiological studies that assess NDD outcomes. PTB is also associated with placental pathology [11–13]. Specifically, histological chorioamnionitis (CA), a condition of intrauterine infection/inflammation and maternal vascular malperfusion (MVM) are the 2 most common pathological placental conditions associated with PTB [14–19]. While the relationship between CA, MVM and some of the early morbidities has been extensively studied, there is a dearth of cohort studies that have assessed the long-term associations of these placental pathologies with NDDs [12,20,21]. This is not surprising given the challenges of studying incident NDDs, which does not manifest immediately after birth, but only long after the placenta is discarded [22,23]. There are important gaps in this field and it is unclear whether placental pathological findings in combination with PTB influence neurodevelopment later in life [20].

By analyzing data from a large prospective birth cohort, we sought to address aforementioned gaps by examining the individual and joint effects of PTB and placental histological findings (specifically CA, MVM) on the risk of NDDs, defined as the presence of ASD, ADHD or other developmental disabilities (DD) in childhood. We further examined whether the associations differ by preterm subtypes (spontaneous vs. medically indicated) and by specific neurodevelopmental conditions, such as ASD, ADHD and other DD. Dysfunction of the placenta exposes the fetus to an unfavorable intrauterine environment, which may potentially facilitate preterm delivery and damage the developing brain [14]. Given the critical role the placenta plays in fetal growth and development, exploration of its underlying pathology along with PTB may possibly hold important clues about the pathogenesis of NDDs.

2. Methods

2.1. Participation and data collection procedure

The Boston Birth Cohort (BBC) is a prospective cohort study that was initiated to investigate the environmental and genetic determinants of preterm delivery. Exclusion criteria for initial enrollment were multiple-gestation pregnancies, chromosomal abnormalities, major birth defects and preterm deliveries as a result of maternal trauma. Between 1998 and 2015, mothers who delivered at the Boston Medical Center were invited to participate in the study. After obtaining informed consent, mothers were interviewed 24–72 h after delivery and a standardized questionnaire was used to collect demographic data, medical, reproductive history and substance abuse [24,25]. A standardized abstraction form was used to extract data from medical records review, including prenatal and intrapartum clinical care, pregnancy complications, birth outcomes, ultrasonographic findings, laboratory test results and placental pathology reports [24]. A sub-set of the originally enrolled children who continued to receive pediatric care at the BMC were included in this study, and they were followed-up until 2018. The Institutional Review Boards (IRB) of Boston University Medical Center and Johns Hopkins Bloomberg School of Public Health approved both the baseline and follow-up studies.

2.2. Exposure

Placentas were obtained by the labor and delivery nurse at the time

of delivery and were sent to the BMC's perinatal pathologist to be processed and reviewed. During the course of the BBC study, a new pathologist took over the examination of the placenta. Prior to this transition, for training purposes, a sub-set of placental pathology slides ($n = 298$) was randomly selected and independently reviewed by two placenta pathologists, who then compared the readings and reached consensus on the review of pathology findings [24].

In accordance with the College of American Pathologists guidelines [26], the perinatal pathologists examined all placentas when clinically indicated. Perinatal pathologists had no knowledge of subsequent neurodevelopmental outcomes. Fresh placentas were fixed with 10% neutral buffered formalin for at least 24–48 h. Placental disc was serially sectioned every 2–3 cm and dissection of placental plate was performed for diagnostic interpretation. A rolled section of membranes and umbilical cord in cassette 1, and three transmural/full thickness sections of placental plate, including fetal and maternal surfaces, in cassettes 2–4, were routinely sampled. Grossly identified lesions were further sampled. Pathological placental lesions were diagnosed based on commonly used, recommended criteria [24]. For the purposes of this project, a placental pathologist recoded the placental diagnosis into predominantly eight categories, in line with the classification proposed by Redline [27,28]. A second perinatal pathologist further confirmed the coding. Broadly, the categories were: CA; MVM; marginal (venous) abruption; umbilical cord obstruction; fetal vascular malperfusion; villous stromal-vascular abnormalities; and a miscellaneous group (Supplemental Table 1).

As described earlier [29–31], gestational age at birth was characterized based on first day of last menstrual period data and early ultrasound data. Children with gestational age ≥ 37 completed weeks of gestation were categorized as full-term and those < 37 weeks were categorized as preterm. Preterm children were further categorized into spontaneous and medically indicated preterm based on maternal prenatal and perinatal medical records [32].

2.3. Definitions for ASD, ADHD, other DD and neurotypical children

Information regarding child's neurodevelopmental outcomes was documented in the electronic medical records (EMR). Based on EMR ICD codes, children that were ever diagnosed with autism (299.00), Asperger syndrome (299.80), and/or pervasive developmental disorder not otherwise specified (299.90) constituted the ASD cases. Children ever diagnosed with ADHD (314.0–314.9) constituted the ADHD cases. Children ever diagnosed with language delay, coordination disorders, or learning disorders (315.0–315.5) constituted the other DD cases. Neurotypical children were those that were never diagnosed with ASD, ADHD, other DD, intellectual disabilities, oppositional defiant disorder, conduct disorder or congenital anomalies.

2.4. Covariates

Covariates were selected *a priori* based on the existing literature, including our own work in the BBC [30,33–35]. Covariates that were used for adjustments included maternal age at delivery, smoking during pregnancy (ever smoked 3 months before pregnancy/during pregnancy vs. not smoked before pregnancy/during pregnancy), parity (not including the index pregnancy), maternal education (high school or less vs. some college or more), race/ethnicity (black, white, Hispanic and Other) and child's sex (female vs. male). Missingness in covariates was minimal and handled by assigning them to the largest categories. Since gestational age is in the causal pathway between the placental pathology and NDDs, it was not adjusted for, but rather assessed in the additive model.

2.5. Statistical analysis

The outcomes in this study were ASD, ADHD and other DD, that

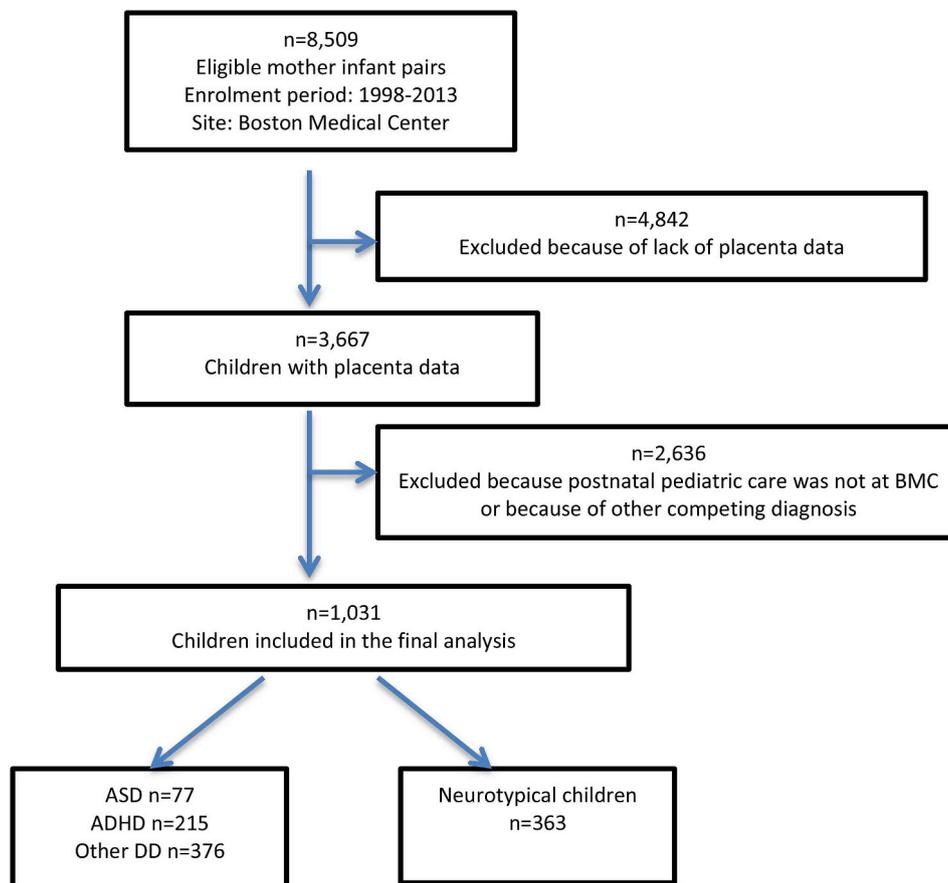


Fig. 1. Flowchart of initial enrolment and postnatal follow-up of the Boston Birth Cohort and the Sample Included in the analysis.

were assessed separately and together as NDDs. The exposure was PTB and placental pathology, specifically CA and MVM. Exposures were considered as dichotomous variables. The characteristics of the study sample for neurotypical and NDDs (i.e. children with ASD, ADHD and other DD) were calculated using chi-square tests for categorical variables and ANOVA for continuous variables. Logistic regression models were applied to assess the crude and adjusted associations between exposures and outcomes. For PTB and placental pathology, we performed an independent analysis, followed by an analysis to assess the joint effects. All results are presented as odds ratio. Throughout, we used 2-sided statistical tests with a significance level of 0.05. Data were analyzed using STATA version 13.0 (StataCorp, College Station, TX).

3. Results

This study included 363 neurotypical children and 77 ASD, 215 ADHD and 376 other DD children (Fig. 1). The demographic and clinical characteristics of mothers and children are presented in Table 1 and have been documented earlier in this cohort [25,31,36,37]. We found that higher maternal BMI, diabetes mellitus, maternal smoking during pregnancy, male sex, PTB and low birth weight were more frequent in children with NDDs (Table 1). There were no significant differences in the incidence of placental pathology between neurotypical children and those with NDDs (Table 1).

Maternal and child characteristics of term and preterm children are presented in Supplemental Table 1 and placental diagnostic categories and frequency of placenta pathology findings stratified by term and PTBs are presented in Supplemental Tables 2 and 3. Compared to children born at term, preterm children had increased odds of NDDs in both unadjusted and adjusted models (aOR: 1.62, 95% CI: 1.24, 2.11) (Table 2). When stratified further, the increased odds were noted for

both spontaneous PTB (aOR: 1.69, 95% CI: 1.24, 2.31) and medically indicated PTB (aOR: 1.51, 95% CI: 1.06, 2.15). However, exposure to CA alone was not associated with increased odds of NDDs (aOR: 1.27, 95% CI: 0.93, 1.72).

We assessed the combined association of PTB and CA on the odds of NDDs. PTB increased the odds of NDDs, both in the absence (aOR: 1.55, 95% CI: 1.14, 2.10) and presence of CA (aOR: 2.16, 95% CI: 1.37, 3.39), when compared to term babies without CA exposure. Similarly, for spontaneous PTB babies, the odds of NDDs increased among those without (aOR: 1.47, 95% CI: 1.01, 2.14) or with CA (aOR: 2.38, 95% CI: 1.46, 3.88). Among medically indicated preterm babies, increased odds of NDDs were noted only in those not exposed to CA (aOR: 1.59, 95% CI: 1.08, 2.33) (Table 2). There was no statistically significant interaction between PTB (including spontaneous, medically indicated), CA and odds of NDDs (data not shown).

Next, we looked at the individual and joint associations of PTB and placental pathology with specific outcomes – ASD, ADHD and other DD (Table 3). Compared to term children, those born preterm were at increased odds of ASD (aOR: 2.06, 95% CI: 1.22, 3.49) and other DD (aOR: 1.68, 95% CI: 1.25, 2.27). While spontaneous PTB was also associated with greater odds of ASD (aOR: 2.10, 95% CI: 1.15, 3.85), increased odds of other DD was observed in both spontaneous (aOR: 1.75, 95% CI: 1.24, 2.48) and medically indicated preterm babies (aOR: 1.57, 95% CI: 1.05, 2.33). CA was associated with increased odds of ADHD in both unadjusted and adjusted models (aOR: 1.74, 95% CI: 1.15, 2.62).

Compared to term children that were not exposed to CA, increased odds of ADHD (aOR: 2.75, 95% CI: 1.55, 4.90) and other DD (aOR: 1.96, 95% CI: 1.18, 3.25) was observed among preterm babies with CA exposure. This association also approached significance for ASD (aOR: 2.31, 95% CI: 0.99, 5.39). When restricting the analysis to those that

Table 1
Maternal and child characteristics of neurotypical children and those with neurodevelopmental disabilities (NDDs), including ASD, ADHD, and other DD*.

	Overall (n = 1031)	Neurotypical (n = 363)	Neurodevelopmental disabilities (n = 668)	P value
Maternal characteristics				
Age at birth (yrs), mean (SD)	29.0 (6.6)	28.6 (6.6)	29.2 (6.5)	0.14
Parity (%)				0.77
0	465 (45.1)	166 (45.7)	299 (44.8)	
1 or more	566 (54.9)	197 (54.3)	369 (55.2)	
Mother's education (%)				0.64
High School or less	647 (62.8)	221 (60.9)	426 (63.8)	
Some college or more	375 (36.4)	139 (38.3)	236 (35.3)	
Missing	9 (0.9)	3 (0.8)	6 (0.9)	
Maternal BMI (%)				0.01
Underweight (< 18.5) + Normal Weight (≥ 18.5- < 25)	432 (41.9)	173 (47.7)	259 (38.8)	
Overweight (≥ 25- < 30)	281 (27.3)	95 (26.2)	186 (27.8)	
Obesity (≥ 30)	318 (30.8)	95 (26.2)	223 (33.4)	
Diabetes mellitus (%)				0.008
No	878 (85.2)	324 (89.3)	554 (82.9)	
Gestational diabetes	89 (8.6)	27 (7.4)	62 (9.3)	
Pre-gestational diabetes	64 (6.2)	12 (3.3)	52 (7.8)	
Smoking during & 3 months prior to pregnancy (%)				0.003
No	803 (77.9)	300 (82.6)	503 (75.3)	
Yes	224 (21.7)	60 (16.5)	164 (24.6)	
Missing	4 (0.4)	3 (0.8)	1 (0.2)	
Child's characteristics				
Sex (%)				< 0.001
Male	535 (51.9)	144 (39.7)	391 (58.5)	
Female	496 (48.1)	219 (60.3)	277 (41.5)	
Race-ethnicity (%)				0.53
Black	688 (66.7)	232 (63.9)	456 (68.3)	
White	75 (7.3)	29 (8.0)	46 (6.9)	
Hispanic	206 (20.0)	77 (21.2)	129 (19.3)	
Other	62 (6.0)	25 (6.9)	37 (5.5)	
Gestational age (%)				< 0.001
Term	511 (49.6)	211 (58.1)	300 (44.9)	
Preterm (< 37 weeks)	520 (50.4)	152 (41.9)	368 (55.1)	
Birth weight (g)	2460.4 (923.7)	2673.7 (822.8)	2344.5 (955.0)	< 0.001
Major placental pathology categories based on the Amsterdam recommendation				
Intrauterine infection/inflammation				0.14
No	767 (74.4)	280 (77.1)	487 (72.9)	
Yes	264 (25.6)	83 (22.9)	181 (27.1)	
Chronic villitis				0.88
No	1016 (98.6)	358 (98.6)	658 (98.5)	
Yes	15 (1.5)	5 (1.4)	10 (1.5)	
Maternal vascular malperfusion				0.97
No	627 (60.8)	221 (60.9)	406 (60.8)	
Yes	404 (39.2)	142 (39.1)	262 (39.2)	
Marginal (venous) abruption				0.41
No	993 (96.3)	352 (97.0)	641 (96.0)	
Yes	38 (3.7)	11 (3.0)	27 (4.0)	
Umbilical cord (UC) obstruction				0.41
No	1022 (99.1)	361 (99.5)	661 (99.0)	
Yes	9 (0.9)	2 (0.6)	7 (1.1)	
Fetal vascular malperfusion				0.25
No	1013 (98.3)	359 (98.9)	654 (97.9)	
Yes	18 (1.8)	4 (1.1)	14 (2.1)	
Villous stromal-vascular abnormalities				0.11
No	1012 (98.2)	353 (97.3)	659 (98.7)	
Yes	19 (1.8)	10 (2.8)	9 (1.4)	
Miscellaneous findings				0.22
No	294 (28.5)	95 (26.2)	199 (29.8)	
Yes	737 (71.5)	268 (73.8)	469 (70.2)	

* ASD – Autism Spectrum Disorder; ADHD – Attention-Deficit/Hyperactivity Disorder; DD – Developmental disabilities.

Percentages may not add up due to rounding.

had spontaneous PTB with CA exposure, the associations became slightly stronger for ASD (aOR: 2.59, 95% CI: 1.04, 6.46), ADHD (aOR: 2.80, 95% CI: 1.49, 5.24) and other DD (aOR: 2.29, 95% CI: 1.33, 3.92). The association between medically indicated PTB with CA approached significance with ADHD (aOR: 2.93, 95% CI: 0.88, 9.74), but not with ASD or other DD (Table 3).

Exposure to MVM was not associated with increased odds of NDDs (aOR: 1.00, 95% CI: 0.76, 1.31) (Table 4). When joint effects of PTB and MVM was considered, PTB without (aOR: 1.95, 95% CI: 1.38, 2.74) or with MVM (aOR: 1.51, 95% CI: 1.04, 2.20) exposure was associated

with increased odds of NDDs. Even in the absence of MVM and CA, PTB was still associated with increased odds of NDDs (aOR: 1.58, 95% CI: 1.08, 2.32). When PTB was further stratified, increased odds of NDDs were observed for both spontaneous PTB without MVM exposure (aOR: 2.01, 95% CI: 1.37, 2.94) and medically indicated PTB without MVM exposure (aOR: 1.79, 95% CI: 1.05, 3.05). There was no statistically significant interaction between PTB (including spontaneous, medically indicated), MVM and odds of NDDs (data not shown).

Table 2

Individual and joint association of preterm birth and histological chorioamnionitis (CA) with child's risk of neurodevelopmental disabilities (NDDs), including ASD, ADHD, and other DD*.

	Total n	NDD n	Unadjusted	Adjusted**
Individual associations				
Term	511	300	1.0 (Ref)	
Preterm	520	368	1.70 (1.32, 2.20)	1.62 (1.24, 2.11)
Spontaneous	316	227	1.79 (1.33, 2.43)	1.69 (1.24, 2.31)
Medically indicated	204	141	1.57 (1.11, 2.22)	1.51 (1.06, 2.15)
No CA	767	487	1.0 (Ref)	
CA	264	181	1.25 (0.93, 1.69)	1.27 (0.93, 1.72)
Combined association of preterm with CA				
Term, no CA	383	222	1.0 (Ref)	
Term, CA	128	78	1.13 (0.75, 1.70)	1.16 (0.76, 1.77)
Preterm, no CA	384	265	1.61 (1.20, 2.17)	1.55 (1.14, 2.10)
Preterm, CA	136	103	2.26 (1.46, 3.52)	2.16 (1.37, 3.39)
Combined association of spontaneous preterm with CA				
Term, no CA	383	222	1.0 (Ref)	
Term, CA	128	78	1.13 (0.75, 1.70)	1.12 (0.73, 1.72)
Spontaneous preterm, no CA	199	137	1.60 (1.12, 2.30)	1.47 (1.01, 2.14)
Spontaneous preterm, CA	117	90	2.42 (1.50, 3.89)	2.38 (1.46, 3.88)
Combined association of medically indicated preterm with CA				
Term, no CA	383	222	1.0 (Ref)	
Term, CA	128	78	1.13 (0.75, 1.70)	1.17 (0.77, 1.80)
Medically indicated preterm, no CA	185	128	1.63 (1.12, 2.36)	1.59 (1.08, 2.33)
Medically indicated preterm, CA	19	13	1.57 (0.58, 4.22)	1.38 (0.49, 3.87)

*ASD – Autism Spectrum Disorder; ADHD – Attention-Deficit/Hyperactivity Disorder; DD – Developmental disabilities.

** Adjusted for maternal smoking, age, education, parity, race and child's sex.

Test of interactions were performed for all the above analyses, but none reached statistical significance ($p < 0.05$).

4. Discussion

To our knowledge, this is the first prospective birth cohort study to simultaneously assess placental pathology and PTB and its subtypes, in relation to incident NDDs and specific conditions: ASD, ADHD and other DD. Consistent with the literature, our results showed that PTB, especially spontaneous PTB, have an increased odds of NDDs, and specifically ASD and other DD [8,38,39]. Although CA, by itself, was not associated with greater odds of NDDs, we showed that children born preterm with CA exposure had increased odds of NDDs, as well as ADHD, other DD and possibly ASD. We further teased out the differences in NDD risk between overall, spontaneous and medically indicated preterm and provided empirical evidence to support the hypothesis that PTB, especially spontaneous PTB, possibly triggered by infection/inflammation in the presence of CA increases the risk of adverse neurodevelopmental outcomes [40].

It is well known that ASD, ADHD and other DD share a number of commonalities such as early onset, male preponderance, cognitive impairments and delays or deviance in the development of brain structure/function [41]. Because of these shared disturbances, it is theorized that the spectrum of NDDs may share certain underlying pathology, rather than being etiologically discrete entities [1,42]. Recent studies on biological risk factors support the co-occurrence, with factors like PTB, maternal autoimmune disease and maternal infections being associated with many of the neurodevelopmental disorders [5,25]. Our study lends support to the theory that certain prenatal risk factors, along with placental pathology, serve as a common thread across the spectrum of NDDs thereby help explain some of the co-morbidities we observe in children with NDDs.

When considered in the context of existing studies, our findings on ASD are consistent with Straughen et al., the only other study that assessed histological placental inflammation in the context of ASD [43]. However, Straughen et al. did not specially study the effects of placental pathology in children born preterm, which is an important risk factor, as noted in our study. Regarding other DD, the results were also consistent with previous studies, including a meta-analysis that showed an association between CA exposure and other DD such as speech delay and hearing loss [19,21,44]. The increased odds of NDDs observed with

PTB, both in the absence and presence of CA, suggests PTB could increase the risk independent of CA and impact neurodevelopment through multiple pathways resulting in significant brain injury or more subtle impairments in brain development [45].

The underlying mechanism for increased odds of NDDs among preterm babies with CA is complex and not fully understood. It is possible that CA triggers a fetal inflammatory response with release of proinflammatory cytokines that could directly impact the immature brain and increase susceptibility to neurodevelopmental disorders, including ASD and ADHD [46–49]. Evidence suggests that CA, as well as inflammatory cytokines can result in white matter brain lesions [50–52]. Independent studies have shown that white matter alterations are associated with attention deficit [53–55] and ASD [56,57]. Furthermore, a recent study showed that abnormalities in white matter are seen in both ASD and ADHD, suggesting a common underlying neural mechanism for these two frequently co-occurring conditions [58]. Another possible hypothesis is that CA, PTB and NDD are common consequences of the aberrant developmental biology, in which case, CA and PTB may be early indicators of the adverse NDD outcome [59].

An additional finding from this study is the lack of association between term babies exposed to CA and odds of NDDs, as well as individual conditions such as ASD, ADHD and other DD. Literature suggests that, for term babies, CA may be a heterogeneous condition with greater likelihood of localized inflammation and a maternal, rather than fetal origin [60,61]. Thus, the etiology and pathogenesis may differ [60,61], with placental inflammation of fetal origin more predictive of brain injury than placental inflammation of maternal origin [19]. This is further supported by studies on other neurodevelopmental conditions, which have shown the incidence of cerebral palsy is low among those that are born at term or closer to term [60].

Overall, MVM was not associated with NDDs. While our findings did not support the role of MVM in ASD (data not shown), a recent study showed that there might be variations in chorionic surface vascular network between placentas associated with high-risk ASD pregnancies and those from general population [62].

Our study has several strengths. First, this is one of the few prospective birth cohort studies that have concurrently assessed PTB (its subtypes), placental pathology and long-term neurodevelopmental

Table 3
Individual and joint association of preterm birth and histological chorioamnionitis (CA) with child's risk of ASD, ADHD, and other DD*, using a common reference group of neurotypical children.

	Total n	ASD n	Unadjusted	Adjusted	Total n	ADHD n	Unadjusted	Adjusted	Total n	DD n	Unadjusted	Adjusted**
Individual associations												
Term	241	30	1.0 (Ref)		316	105	1.0 (Ref)		376	165	1.0 (Ref)	
Preterm	199	47	2.17 (1.31, 3.60)	2.06 (1.22, 3.49)	262	110	1.45 (1.04, 2.04)	1.34 (0.93, 1.92)	363	211	1.78 (1.33, 2.38)	1.68 (1.25, 2.27)
Spontaneous	118	29	2.29 (1.30, 4.04)	2.10 (1.15, 3.85)	158	69	1.56 (1.05, 2.31)	1.48 (0.97, 2.26)	218	129	1.85 (1.32, 2.60)	1.75 (1.24, 2.48)
Medically Indicated	81	18	2.01 (1.05, 3.84)	1.89 (0.96, 3.70)	104	41	1.31 (0.83, 2.07)	1.15 (0.70, 1.91)	145	82	1.66 (1.13, 2.45)	1.57 (1.05, 2.33)
No CA	340	60	1.0 (Ref)		428	148	1.0 (Ref)		559	279	1.0 (Ref)	
CA	100	17	0.96 (0.53, 1.73)	1.03 (0.56, 1.92)	150	67	1.53 (1.05, 2.23)	1.74 (1.15, 2.62)	180	97	1.17 (0.84, 1.64)	1.17 (0.83, 1.65)
Combined association of preterm with CA												
Term, no CA	185	24	1.0 (Ref)		239	78	1.0 (Ref)		281	120	1.0 (Ref)	
Term, CA	56	6	0.81 (0.31, 2.08)	0.86 (0.32, 2.29)	77	27	1.11 (0.65, 1.91)	1.14 (0.64, 2.03)	95	45	1.21 (0.76, 1.93)	1.25 (0.77, 2.01)
Preterm, no CA	155	36	2.03 (1.15, 3.58)	1.92 (1.06, 3.46)	189	70	1.21 (0.81, 1.81)	1.04 (0.68, 1.60)	278	159	1.79 (1.28, 2.51)	1.73 (1.23, 2.43)
Preterm, CA	44	11	2.24 (1.00, 5.01)	2.31 (0.99, 5.39)	73	40	2.50 (1.47, 4.27)	2.75 (1.55, 4.90)	85	52	2.11 (1.29, 3.47)	1.96 (1.18, 3.25)
Combined association of spontaneous preterm with CA												
Term, no CA	185	24	1.0 (Ref)		239	78	1.0 (Ref)		281	120	1.0 (Ref)	
Term, CA	56	6	0.81 (0.31, 2.08)	0.85 (0.32, 2.26)	77	27	1.11 (0.65, 1.91)	1.11 (0.62, 1.98)	95	45	1.21 (0.76, 1.93)	1.20 (0.74, 1.94)
Spon. preterm, no CA	81	19	2.06 (1.05, 4.01)	1.82 (0.89, 3.70)	99	37	1.23 (0.76, 2.01)	1.04 (0.62, 1.77)	143	81	1.75 (1.17, 2.63)	1.64 (1.08, 2.49)
Spon. preterm, CA	37	10	2.48 (1.07, 5.78)	2.59 (1.04, 6.46)	59	32	2.45 (1.37, 4.37)	2.80 (1.49, 5.24)	75	48	2.39 (1.41, 4.04)	2.29 (1.33, 3.92)
Combined association of medically indicated preterm with CA												
Term, no CA	185	24	1.0 (Ref)		239	78	1.0 (Ref)		281	120	1.0 (Ref)	
Term, CA	56	6	0.81 (0.31, 2.08)	0.86 (0.33, 2.29)	77	27	1.11 (0.65, 1.91)	1.13 (0.63, 2.04)	95	45	1.21 (0.76, 1.93)	1.27 (0.78, 2.05)
Med. Preterm, no CA	74	17	2.00 (1.00, 3.99)	1.90 (0.93, 3.89)	90	33	1.20 (0.72, 1.98)	1.03 (0.59, 1.79)	135	78	1.84 (1.21, 2.78)	1.76 (1.15, 2.70)
Med. Preterm, CA	7	1	1.12 (0.13, 9.69)	1.08 (0.11, 10.21)	14	8	2.75 (0.92, 8.21)	2.93 (0.88, 9.74)	10	4	0.89 (0.25, 3.24)	0.75 (0.19, 2.88)

*ASD – Autism Spectrum Disorder; ADHD – Attention-Deficit/Hyperactivity Disorder; DD – Developmental disabilities; Med. Preterm – Medically indicated preterm; Spon. Preterm – Spontaneous preterm.

** Adjusted for maternal smoking, age, education, parity, race and child's sex.

Test of interactions were performed for all the above analyses, but none reached statistical significance (p < 0.05).

Table 4

Individual and joint association of preterm birth and histological maternal vascular malperfusion (MVM) with child's risk of neurodevelopmental disabilities (NDDs), including ASD, ADHD, and other DD*.

	Total n	NDD n	Unadjusted	Adjusted**
No MVM	627	406	1.0 (Ref)	
MVM	404	262	1.00 (0.77, 1.30)	1.00 (0.76, 1.31)
Combined association of preterm with MVM				
Term, no MVM	317	180	1.0 (Ref)	
Term, MVM	194	120	1.23 (0.86, 1.78)	1.23 (0.85, 1.80)
Preterm, no MVM	310	226	2.05 (1.47, 2.86)	1.95 (1.38, 2.74)
Preterm, MVM	210	142	1.59 (1.10, 2.29)	1.51 (1.04, 2.20)
Preterm, no MVM, no CA	203	140	1.69 (1.17, 2.45)	1.58 (1.08, 2.32)
Preterm, MVM, and CA	29	17	1.08 (0.50, 2.33)	0.90 (0.40, 2.01)
Combined association of spontaneous preterm with MVM				
Term, no MVM	317	180	1.0 (Ref)	
Term, MVM	194	120	1.23 (0.86, 1.78)	1.24 (0.85, 1.82)
Spontaneous preterm, no MVM	225	166	2.14 (1.48, 3.10)	2.01 (1.37, 2.94)
Spontaneous preterm, MVM	91	61	1.55 (0.95, 2.53)	1.50 (0.91, 2.50)
Combined association of medically indicated preterm with MVM				
Term, no MVM	317	180	1.0 (Ref)	
Term, MVM	194	120	1.23 (0.86, 1.78)	1.24 (0.85, 1.81)
Medically indicated preterm, no MVM	85	60	1.83 (1.09, 3.06)	1.79 (1.05, 3.05)
Medically indicated preterm, MVM	119	81	1.62 (1.04, 2.53)	1.53 (0.97, 2.42)

*ASD – Autism Spectrum Disorder; ADHD – Attention-Deficit/Hyperactivity Disorder; DD – Developmental disabilities. CA - Chorioamnionitis.

** Adjusted for maternal smoking, age, education, parity, race and child's sex.

Test of interactions were performed for all the above analyses, but none reached statistical significance ($p < 0.05$).

outcomes. Most studies of placenta and neurodevelopmental outcomes are case reports or case studies, because prospective studies are difficult to conduct, as neurodevelopmental conditions don't manifest immediately after birth [22,23]. Second, our investigation was conducted in a larger birth cohort, whereas most previous studies had much smaller sample sizes. Third, our study's internal validity was strengthened by verification of placental examinations and diagnostic coding done by a perinatal pathologist [24], using a standardized classification system that will enable comparison of this study's findings with future studies [24].

Our study has notable limitations. First, the outcome definitions were based on EMR data and thus, could have been subjected to outcome misclassification. However, this may not be differential, considering the prospective study design. Second, although well-known risk factors of NDDs were adjusted for, there is a possibility of residual confounding. Third, in this birth cohort, placental examination was performed per prenatal and perinatal clinical indications such as preterm, small for gestational age and asphyxia. On one hand, we had an enriched sample with high-risk children; on the other hand, we cannot completely rule out the possibility of selection bias. However, this bias would not have influenced future NDD outcomes given our prospective study design. Also, this study analyzed a sub-set of children who continued to receive pediatric care at the BMC, which could also be a concern for selection bias. However, the associations between well-established factors such as gender of the child and maternal age with NDD were replicated in our study sample, assuaging some of the concerns. Fourth, an absence of definitive immunohistochemical or molecular diagnostic testing for specific placental lesions precludes validation. Fifth, like other studies that employ placental histopathology, sampling limitations in our study could not be completely avoided. In particular, certain lesions (e.g. decidual vasculopathy and infarction) might have been localized and difficult to appreciate in gross examination. However, this limitation was assuaged by having all placental examinations and tissue sampling performed by a perinatal pathologist, grossly examining placental disc every 2–3 cm, and obtaining transmural sections of the placenta along with sections of grossly identified lesions [24]. Sixth, despite showing a joint effect of PTB and CA on NDDs, it was not possible to conduct a mediation analysis since *in utero* temporal ordering of PTB and CA was unclear, as both of these were measured at birth. Seventh, it was challenging to tease out PTB and

antenatal steroid effects on NDD because by clinical indication, very preterm babies were most likely to receive antenatal steroids and also at greatest risk of NDD. Eighth, other DD may comprise of heterogeneous group of conditions and their diagnosis might have been varied based on age of assessment. However, additional stratified analysis in this study based on the length of follow-up did not alter the association between PTB and other DD (data not shown). Finally, our population included urban low-income minority population, who were at high risk for PTBs, and thus, caution should be exercised when generalizing the study findings to populations with different characteristics.

In summary, using a standardized placental pathology classification system, this hypothesis generating study showed that PTB, especially spontaneous PTB, along with histological CA increased the odds of NDDs, including ADHD, other DD and possibly ASD. Further, our findings support the emerging theory that PTB along with histological CA may represent a common prenatal risk factor for NDDs and thus could potentially help explain the co-morbidities we observe in children with NDDs. Our data suggest that placental pathology findings may be valuable, along with types of PTB for identifying newborns at high risk of developing NDDs and could potentially shed light on pathogenic processes underlying NDDs [63]. We hope that our findings will stimulate future clinical and mechanistic studies, which may provide further insight and inform clinical risk assessment and prevention strategies for reducing long-term neurodevelopmental sequelae among high-risk children [12,23].

Declarations of interest

None.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.placenta.2019.06.374>.

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