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Independent and joint association of cord plasma pantothenate and cysteine levels with autism spectrum disorders and other neurodevelopmental disabilities in children born term and preterm

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Abstract

Background: Pantothenate (vitamin B5) is a precursor for coenzyme A (CoA) synthesis, which serves as a cofactor for hundreds of metabolic reactions. Cysteine is an amino acid in the CoA synthesis pathway. To date, research on the combined role of early life pantothenate and cysteine levels in childhood neurodevelopmental disabilities is scarce.

Objective: To study the association between cord pantothenate and cysteine levels and risk of autism spectrum disorder (ASD), attention deficit hyperactivity disorder (ADHD) and other developmental disabilities (DD) in children born term and preterm.

Methods: The study sample (n = 996, 177 born preterm) derived from the Boston Birth Cohort included 416 neurotypical children, 87 ASD, 269 ADHD, and 224 other DD children, who were mutually exclusive. Participants were enrolled at birth and were followed up prospectively (from October 1, 1998, to June 30, 2018) at the Boston Medical Center. Cord blood sample was collected at birth. Plasma pantothenate and cysteine levels were measured using liquid chromatography-tandem mass spectrometry.

Results: Higher cord pantothenate (≥50th percentile *vs.* <50th percentile) was associated with a greater risk of ASD (adjusted odds ratio [aOR]: 1.94, 95% confidence interval [CI]: 1.06, 3.55) and ADHD (aOR: 1.66, 95% CI: 1.14, 2.40), after adjusting for potential confounders. However, cord cysteine alone was not associated with risk of ASD, ADHD, or other DD. When considering the joint association, greater ASD risk was noted when both cord pantothenate and cysteine levels were elevated (≥50th percentile) (aOR: 3.11, 95% CI: 1.24, 7.79), when compared to children with low cord pantothenate (<50th percentile) and high cysteine. Even though preterm and higher pantothenate independently increased the ASD risk, the greatest risk was found in preterm children who also had elevated pantothenate (≥50th percentile), which was true for all three outcomes: ASD (aOR: 5.36, 95% CI: 2.09, 13.75), ADHD (aOR: 3.31, 95% CI: 1.78, 6.16), and other DD (aOR: 3.39, 95% CI: 1.85, 6.24).

Conclusions: In this prospective birth cohort, we showed that higher cord pantothenate individually and in combination with higher cysteine or preterm birth were associated with increased risk of ASD and ADHD. More study is needed to explore this biologically plausible pathway.

Keywords: Pantothenate, Pantothenic acid, Vitamin B5, Cysteine, ASD, ADHD

Introduction

Autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD) are neurodevelopmental disorders with onset often in early childhood. ASD is characterized by restrictive repetitive behavior, and impairments in social communication. According to recent estimates, one in 39 children aged 8 years are diagnosed with ASD in the United States.[1] ADHD is characterized by the presence of impairing symptoms of inattention, hyperactivity-impulsivity or both, with approximately 10% in the United States diagnosed with ADHD.[2] The prevalence of both ASD and ADHD is increasing and the symptoms

Data described in the manuscript, code book, and analytic code is available upon request pending IRB review and approval.

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and impairments often persist until adulthood.[3] Recent studies suggest that participants with ASD and ADHD may also manifest with mitochondrial dysfunction and oxidative stress, suggesting that these conditions may be a result of systemic physiological abnormalities.[4]

The etiology of neurodevelopmental disabilities (NDDs) are complex as genetic, environmental factors and their interactions are known to play an important role. Nutrition is one such key modifiable factor that could be influenced by both genes and environment. Although there are about 40 essential macro and micronutrients, only a few (eg, folate, vitamin B12, fatty acids) have been studied in the context of ASD and ADHD.[5–7] There is very limited research on essential nutrients such as pantothenate, also known as pantothenic acid or vitamin B5. Pantothenate is found in almost all foods and thus deficiency is relatively rare. This ubiquitous nutrient's main role is to serve as a key precursor for the synthesis of coenzyme A (CoA) and acyl carrier protein, using a process that is highly conserved across species.[8–10] CoA is an integral cofactor for hundreds of metabolic reactions, including the tricarboxylic acid cycle, fatty acid metabolism and amino acid synthesis, cholesterol and the neurotransmitter acetylcholine, and myriad of other anabolic and catabolic processes.[10–13]

CoA is synthesized from pantothenate in a five-step pathway, starting with the phosphorylation of pantothenate to 4′phosphopantothenate (Figure 1).[14] This first step is a major rate-limiting and control step of the entire process.[15] Following this, cysteine, an essential amino acid is condensed with 4′phosphopantothenate to form 4′phosphopantothenoyl-L-cysteine.[15] After the decarboxylation reaction, a few intermediate conversions lead to CoA production. When there are defects in pantothenate metabolic pathway, CoA biosynthesis is disturbed with diminished CoA pool, which is known to be associated with neurodegenerative and neurodevelopmental disorders.[13,15,16] Dysfunction in the CoA biosynthesis pathway is thought to impact mitochondrial integrity,[11] which is one of the main metabolic abnormalities observed in ASD and ADHD.[17–19]

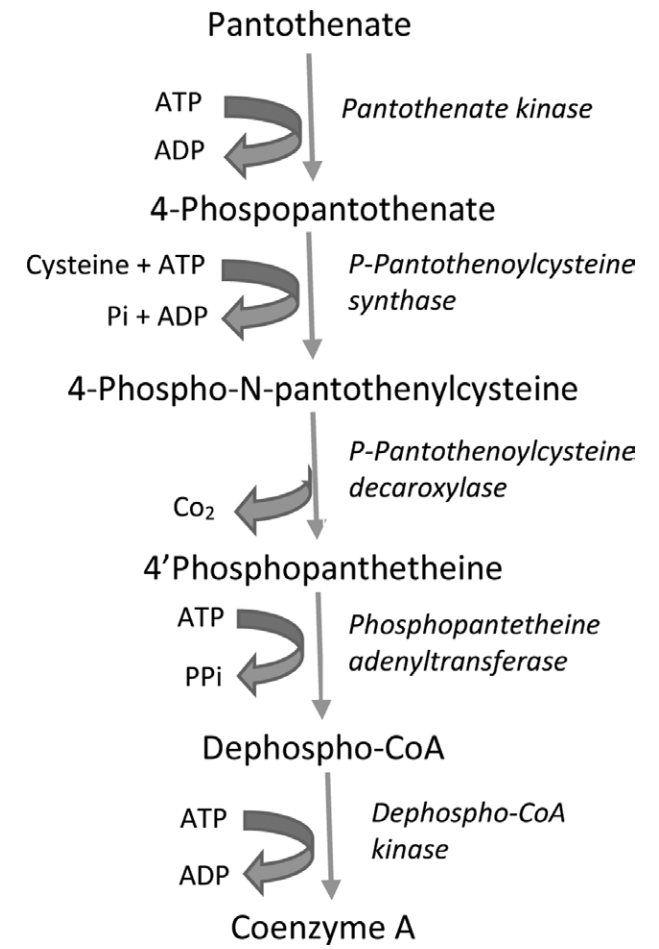

Figure 1: Pantothenate metabolism leading to coenzyme A synthesis.

A few recent studies have shown that pantothenate may be implicated in Alzheimer's disease, Huntington's disease, and Parkinson's disease and a rare condition called pantothenate kinase-associated neurodegeneration (PKAN), which primarily manifests in children.[14,20,21] A recent study also showed that pantothenate-derivative may be altered in preterm birth (PTB),[22] which is a known risk factor for NDD.[23] Despite these emerging studies, there is still a dearth of knowledge on the role of pantothenate in NDDs. To understand and disentangle this relationship, our study assessed the association between maternal, cord pantothenate levels and subsequent risk of ASD, ADHD, and other developmental disabilities (DD). Furthermore, we hypothesized that children born preterm and with elevated cord plasma pantothenate level (likely indicator of dysfunction in CoA metabolic pathway) were more likely to develop ASD, ADHD, and other DD. The Boston Birth Cohort (BBC) offers the opportunity to test this hypothesis given the high proportion of PTB.

Methods

Participation and enrollment in the BBC has been documented previously.[24] Briefly, in this preterm-enriched birth cohort for every preterm (defined as <37 weeks of gestation) and/or low birth weight baby (defined as <2500 g), approximately two term and normal birth weight babies and their mothers were enrolled in the study. Mothers who had multiple pregnancies (ie, twins, triplets) or who gave birth to children with major birth defects were excluded. Shortly after delivery, research staff approached mothers to participate in the study and ~90% of them consented. There was no significant difference between participants and non-participants on characteristics such as infant birth weight, maternal race, and ethnicity or other sociodemographic characteristics.[25] Using a standardized questionnaire, trained research staff interviewed the mothers 24 to 72 hours postpartum. Laboratory reports, pertinent clinical information, pregnancy complications, labor and delivery course, and birth outcomes were obtained by reviewing maternal and infant records.

A subset of the participants from the original cohort continued to receive pediatric care at the Boston Medical Center (BMC) and were followed from birth to 21 years of age and were included in this study. These mother-infant dyads recruited at birth remained in the follow-up study from October 1, 1998, to June 30, 2018. There were no major differences in the baseline demographic and clinical characteristics between those that continued to be part of the postnatal follow-up and those that did not.[25] Of the total of 3165 participants that were followed up in the BBC, 996 participants had available cord metabolomic data (Supplementary eFigure 1, http://links.lww.com/PN9/A23). Maternal pantothenate was available in a subset of these participants (n = 417).

Written informed consent was obtained from the mothers and verbal or written consent was obtained from the participating youth, as appropriate. Personal identifier information was removed from the research database and was accessible only to authorized investigators. The Institutional Review Boards of the Boston University Medical Center and the Johns Hopkins Bloomberg School of Public Health approved the study protocol. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology reporting guideline for cohort studies.

Exposure

Umbilical cord blood samples were collected at the time of delivery, which was processed and fractioned into cells and plasma shortly after collection by the research team at BMC. Quantitative profiling of the metabolites was assessed in a random subset of youth as part of the metabolome panel. The metabolites, including pantothenate and cysteine, were analyzed using liquid chromatography-tandem mass spectrometry techniques at the Broad Institute Metabolite Profiling Laboratory at the Massachusetts Institute of Technology. Specifically, hydrophilic interaction liquid chromatography in the positive ionization mode was used for the analyses. Further details on laboratory methods, quality control, and data processing are presented elsewhere.[24,26,27]

Outcome

We obtained primary and secondary diagnoses using *International Classification of Diseases, Ninth Revision (ICD-9)* or *International Classification of Diseases, Tenth Revision (ICD-10) codes*, for all postnatal clinical visits since 2003. Children in the ASD group included those ever diagnosed with autism (ICD-9 code 299.00, 299.01; ICD-10 code 84.0), Asperger syndrome (ICD-9 code 299.80; ICD-10 code 84.5, 84.8), and/or pervasive developmental disorder not otherwise specified (ICD-9 code 299.90; ICD-10 code 84.9). Children with concurrent diagnoses, such as ASD and ADHD, or ASD and other DDs, were categorized as having ASD. ADHD group included those with ADHD-related codes (ICD-9 codes 314.0-314.9 or ICD-10 codes F90.0-F90.9) but excluded anyone with ASD diagnosis. Other DD groups included children diagnosed with mental, behavioral, and neurodevelopmental disorders (ICD-9 codes 290-319 or ICD-10 codes F01-F99) but excluded those with ASD and ADHD diagnosis. The neurotypical groups were those never diagnosed with ASD, ADHD, and other DD (including intellectual disabilities).

Covariates

Based on the existing literature and our previous work, we selected the following covariates a priori: maternal pre-pregnancy body mass index (BMI), diabetes status during pregnancy, maternal race/ethnicity, maternal age at delivery, parity (not including the index pregnancy), maternal education (high school or less *vs.* some college or more), smoking tobacco before or during pregnancy, child's sex, preterm birth, and year of baby's birth. Maternal pre-pregnancy weight and height was collected using a standardized questionnaire. Maternal diabetes status was categorized into the following: (1) normal (ie, no pregestational or gestational diabetes diagnosis); (2) gestational diabetes (ever diagnosed with diabetes mellitus complicating pregnancy); and (3) pregestational diabetes (ever diagnosed with overt diabetes during pre-pregnancy or in the first trimester). Maternal race/ethnicity was self-reported and was grouped into Black, White, Hispanic and others (which included Asian, Pacific Islander, more than one race, and other). Neonates who were delivered ≥37 completed weeks of gestation were categorized as term and <37 weeks were considered preterm.

Statistical analysis

Cord pantothenate and cysteine were normalized using rank-based inverse normal transformation (similar to Z score) and was used for all subsequent analyses. In the main analysis, cord pantothenate and cysteine were considered a continuous variable, stratified as quartiles and at the median. Pre-determined logistic regression models were applied to estimate the crude and adjusted associations between cord pantothenate, cysteine, and ASD. Our final model adjusted for maternal variables (age, education, race/ethnicity, diabetes status, BMI, smoking, parity) and child's sex, preterm birth and year of baby's birth. We conducted a joint analysis to assess an association between pantothenate, cysteine and ASD, ADHD, and other DD after accounting for the same covariates described earlier. In the joint analysis, low pantothenate and high cysteine were considered as referent group, as adequate cysteine levels are necessary for metabolizing pantothenate. Simple imputation was used for sociodemographic characteristics that was missing. The median was imputed for continuous variables and for categorical, the most frequent values were imputed. All results are present as odds ratios. Two-sided tests were used with a 0.05 significance level. Data were analyzed using STATA version 13.0 (StataCorp, College Station, TX, USA). Data described in the article, code book, and analytic code are available upon request pending IRB review and approval.

Results

A total of 996 children were included in the analysis, of which 87 were ASD only, 269 were ADHD only, 224 were other DD, and 416 were children with neurotypical development (Supplementary eFigure 1, http://links.lww.com/PN9/A23). Table 1 describes the demographic and clinical characteristics of mothers and children and have been documented in earlier studies in this cohort. When compared to mothers of neurotypical children, their counterparts in the ASD group were more likely to be older (>35 years of age, 18.4% *vs.* 16.8%, $P = 0.009$), had some college education or more (49.4% *vs.* 31.5%, $P = 0.001$) and had gestational diabetes or diabetes mellitus (18.8% *vs.* 14.2%, $P = 0.04$). Similarly, mothers of children who were subsequently diagnosed with ADHD had higher pre-pregnancy BMI (≥30 kg/m^2) (25.4% *vs.* 19.0%, $P = 0.05$) and were more likely to have smoked tobacco during pregnancy or 3 months prior (22.3% *vs.* 12.5%, $P = 0.002$). Mothers of children who were later diagnosed with other DD were more likely to have had gestational diabetes (9.8% *vs.* 5.8%) or diabetes mellitus (7.6% *vs.* 3.4%), when compared to their neurotypical counterparts.

Child's sex was an important risk factor for all outcomes considered, in that males were more likely to be diagnosed with ASD (78.2% *vs.* 38.0%, $P < 0.001$), ADHD (77.0% *vs.* 38.0%, $P < 0.001$), or with other DD (52.2% *vs.* 38.0%, $P = 0.001$). Similarly, children born preterm consistently had greater risk for ASD (28.7% *vs.* 10.1%, $P < 0.001$), ADHD (21.2% *vs.* 10.1%,

Table 1

Characteristics of study participants by case status.

Characteristics	Neurotypical (*n* = 416)	ASD (*n* = 87)	*P* value	ADHD (*n* = 269)	*P* value	Other DD (*n* = 224)	*P* value
Maternal age at birth (y)			0.009		0.77		0.42
<20	41 (9.9)	0 (0.0)		26 (9.7)		18 (8.0)	
20–34	305 (73.3)	71 (81.6)		192 (71.4)		160 (71.4)	
≥35	70 (16.8)	16 (18.4)		51 (19.0)		46 (20.5)	
Parity (%)			0.38		0.92		0.95
0	170 (40.9)	40 (46.0)		111 (41.3)		91 (40.6)	
1 or more	246 (59.1)	47 (54.0)		158 (58.7)		133 (59.4)	
Mother's education (%)			0.001		0.43		0.19
High school or less	285 (68.5)	44 (50.6)		192 (71.4)		142 (63.4)	
Some college or more	131 (31.5)	43 (49.4)		77 (28.6)		82 (36.6)	
Maternal BMI (%)			0.15		0.05		0.16
<30	337 (81.0)	63 (74.1)		200 (74.6)		170 (76.2)	
≥30	79 (19.0)	22 (25.9)		68 (25.4)		53 (23.8)	
Diabetes (%)			0.04		0.3		0.007
No	378 (90.9)	71 (81.6)		232 (86.9)		185 (82.6)	
Gestational diabetes mellitus	24 (5.8)	11 (12.6)		22 (8.2)		22 (9.8)	
Diabetes mellitus	14 (3.4)	5 (5.8)		13 (4.9)		17 (7.6)	
Smoking during and 3 months prior to pregnancy (%)			0.13		0.002		0.06
No	357 (85.8)	68 (78.2)		207 (77.0)		182 (81.3)	
Yes	52 (12.5)	18 (20.7)		60 (22.3)		41 (18.3)	
Missing	7 (1.7)	1 (1.2)		2 (0.7)		1 (0.5)	
Child							
Sex (%)			<0.001		<0.001		0.001
Male	158 (38.0)	68 (78.2)		207 (77.0)		117 (52.2)	
Female	258 (62.0)	19 (21.8)		62 (23.1)		107 (52.2)	
Race-ethnicity (%)			0.08		0.10		0.01
Black	247 (59.8)	36 (48.0)		156 (59.1)		132 (59.7)	
White	21 (5.1)	4 (5.3)		23 (8.7)		6 (2.7)	
Hispanic	83 (20.1)	25 (33.3)		58 (22.0)		64 (29.0)	
Other	62 (15.0)	10 (13.3)		27 (10.2)		19 (8.6)	
Gestational age (%)			<0.001		<0.001		<0.001
Term	374 (89.9)	62 (71.3)		212 (78.8)		171 (76.3)	
Preterm (<37 weeks)	42 (10.1)	25 (28.7)		57 (21.2)		53 (23.7)	
Year of birth (%)			0.001		0.004		0.002
1999–2006	187 (45.0)	23 (26.4)		151 (56.1)		73 (32.6)	
2007–2013	229 (55.1)	64 (73.6)		118 (43.9)		151 (67.4)	
Cord pantothenate	-0.14 (1.0)	0.24 (0.9)	0.001	0.14 (1.0)	<0.001	-0.02 (1.0)	0.15
Maternal pantothenate	0.04 (1.0)	0.01 (0.8)	0.81	-0.03 (1.0)	0.42	-0.07 (0.9)	0.20
Cord cysteine	-0.04 (0.9)	0.13 (1.1)	0.12	-0.02 (1.0)	0.79	0.05 (1.0)	0.25

ASD, autism spectrum disorder; NT, neurotypical

$P < 0.001$), and other DD (23.7% *vs.* 10.1%, $P < 0.001$). Children born after 2007 also had a greater risk of ASD (73.6% *vs.* 55.1%, $P = 0.001$) and other DD (67.4% *vs.* 55.1%, $P = 0.001$); and children born before 2007 had lower ADHD risk (55.1% *vs.* 43.9%, $P = 0.001$).

When compared to their neurotypical counterparts, cord pantothenate was significantly higher in those subsequently diagnosed with ASD ($P = 0.001$) and ADHD ($P < 0.001$), but not other DD. There were no significant differences in maternal pantothenate, or cord cysteine between neurotypical children and those with ASD, ADHD and other DD. The distribution of cord pantothenate for children with ASD ($P = 0.001$) and ADHD ($P < 0.001$) shifted slightly to the right, when compared to neurotypical children (Figure 2A and B), but this was not the case for children with other DD (Figure 2C). There was some correlation between maternal and cord pantothenate levels ($r = 0.3433$) and this was somewhat similar irrespective of the case status (neurotypical children, $r = 0.4107$, ASD children, $r = 0.4051$, ADHD children, $r = 0.2765$, other DD, $r = 0.2865$) (Supplementary eFigure 2, http://links.lww.com/PN9/A23). There was no significant difference in the distribution by case status of cord cysteine levels (Supplementary eFigure 3, http://links.lww.com/PN9/A23).

Table 2 presents the association between cord pantothenate and the subsequent risk of ASD, ADHD, and other DD. Higher cord pantothenate was associated with an increased risk of ASD (odds ratio [OR]: 1.48, 95% confidence interval [CI]: 1.16, 1.88). However, this association attenuated after adjusting for potential confounders (OR: 1.27, 95% CI: 0.93, 1.72). When stratified at the median, those with cord pantothenate above the median had a greater subsequent risk of ASD (adjusted OR [aOR]: 1.94, 95% CI: 1.06, 3.55). But these findings were not consistent when cord pantothenate was stratified by quartiles. Cord pantothenate was associated with a greater risk of ADHD and these findings were consistent when considered continuously (aOR: 1.29, 95% CI: 1.07, 1.56) or when stratified at the median (aOR: 1.66, 95% CI: 1.14, 2.40). When cord pantothenate was stratified by quartiles, greater ADHD risk was noted among those with higher levels of cord pantothenate ($aOR_{quartile\ 3}$: 1.68, 95% CI: 1.01, 2.79) and ($aOR_{quartile\ 4}$: 1.84, 95% CI: 1.08, 3.15) when compared to those with lowest cord pantothenate levels. Cord pantothenate levels were not associated with the risk of other DD.

Next, we considered the individual and joint associations between cysteine and risk of ASD, ADHD, and other DD, since cysteine is essential for the conversion of intermediate

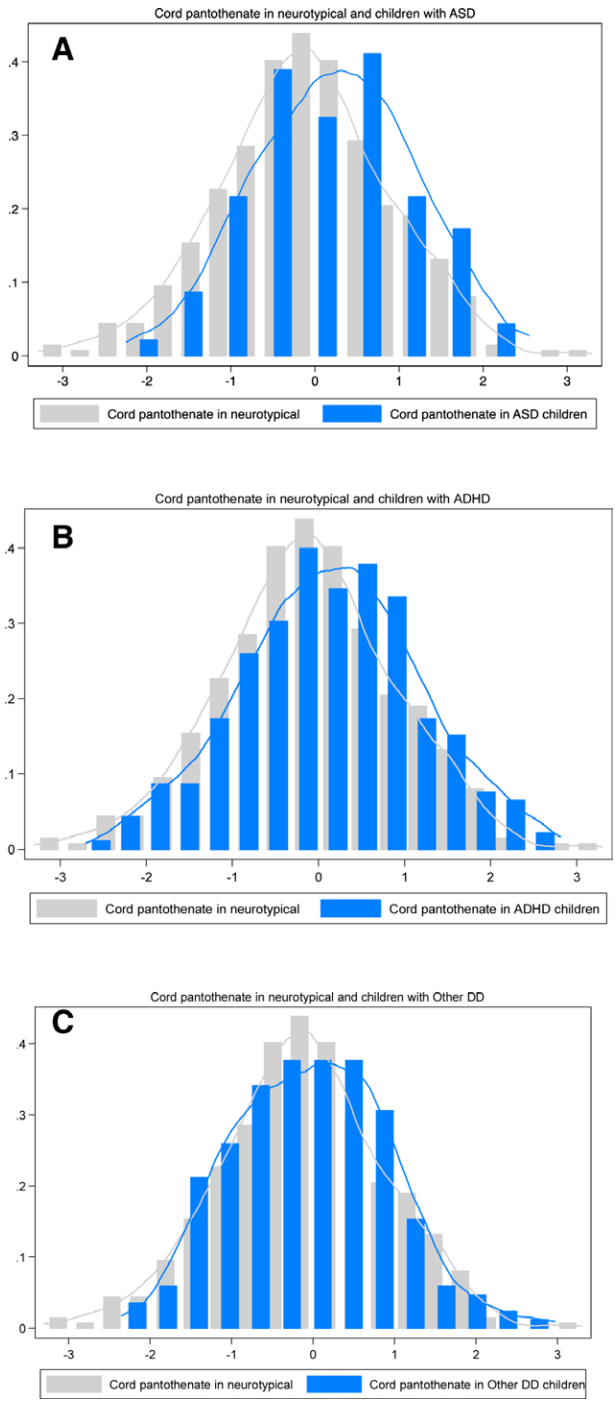

Figure 2: Density distribution of cord pantothenate by case status.

pantothenate metabolites in the CoA synthesis pathway. Cord cysteine was not associated with the subsequent risk of ASD, ADHD, and other DD and these findings were consistent after stratifying cysteine at the median or by quartiles (Table 2). When considering the joint association between cysteine and pantothenate (referent group, cord pantothenate, <50th percentile and cord cysteine ≥50th percentile), greater ASD risk was noted with high cord pantothenate (≥50th percentile) and cord cysteine levels (≥50th percentile) (aOR: 3.11, 95% CI: 1.24, 7.79) (Table 3). However, ASD risk was not statistically significant in other instances. The risk of ADHD was not significantly different when considering the joint association, except with high pantothenate (≥50th percentile) and low cysteine (<50th percentile), compared to the referent group. The risk of other DD did not alter with the joint associations of cord pantothenate and cord cysteine. There was no statistically significant interaction between cord pantothenate and cord cysteine ($P > 0.05$) for any of these outcomes.

Since PTB is a known risk for NDD, we considered the joint association between gestational age and pantothenate and risk of ASD, ADHD, and other DD. The density plot distribution showed a clear shift of cord pantothenate levels in children born preterm and/or subsequently diagnosed with ASD (Figure 3). Compared to term children with low cord pantothenate levels (<50th percentile), their counterparts with high cord pantothenate (≥50th percentile) had a greater risk of ASD (aOR: 2.02, 95% CI: 1.04, 3.94) and ADHD (aOR: 1.55, 95% CI: 1.04, 2.30) (Table 3). Children who had low pantothenate (<50th percentile) but were born preterm had elevated ASD risk (aOR: 3.28, 95% CI: 1.04, 10.31), but not ADHD (aOR: 1.26, 95% CI: 0.52, 3.09). Finally, preterm children with high pantothenate had the greatest risk for all NDD (ASD [aOR: 5.36, 95% CI: 2.09, 13.75], ADHD [aOR: 3.31, 95% CI: 1.78, 6.16], and other DD [aOR: 3.39, 1.85, 6.24]).

Maternal pantothenate was not associated with the subsequent risk of ASD (OR: 1.06, 95% CI: 0.74, 1.53), ADHD, or other DD (Supplementary eTable 1, http://links.lww.com/PN9/A23). These findings were consistent after stratifying maternal pantothenate as quartiles or at the median. Next, we investigated whether certain covariates influenced cord pantothenate levels and after accounting for other covariates in the model, we found that maternal age, race/ethnicity, parity, education, preterm delivery, and year of birth were significantly associated (Supplementary eTable 2, http://links.lww.com/PN9/A23). After accounting for all other covariates, we found that maternal pantothenate levels were significantly associated with the followed covariates: maternal BMI, diabetes mellitus status, maternal education, tobacco smoking status during pregnancy, parity, maternal race/ethnicity, and year of birth of the child (Supplementary eTable 3, http://links.lww.com/PN9/A23). We repeated the main analysis by stratifying cord pantothenate at the median, and considering the findings by different high-risk categories (Supplementary eTable 4, http://links.lww.com/PN9/A23). The association between cord pantothenate and ASD did not differ by most of the subgroups for ASD, ADHD and other DD. There was no statistically significant interaction between cord pantothenate and any of these risk factors across outcomes.

Discussion

To our knowledge, this is the first prospective cohort study to demonstrate an association between higher cord pantothenate and subsequent ASD and ADHD risks. Elevated cord pantothenate (≥50th percentile) was associated with a greater ASD risk; however, these findings were not consistent in all models. Our study also showed that a joint association between higher cord pantothenate and higher cord cysteine was associated with a greater risk of ASD. Similarly, preterm babies and those with higher cord pantothenate levels had elevated ASD risk, the greatest risk was observed in those born preterm and had higher cord pantothenate levels.

Table 2

Association between cord pantothenate, cysteine and neurodevelopmental disabilities.

Cord pantothenate*†	NT, *n*	ASD, *n*	Unadjusted	Adjusted	ADHD, *n*	Unadjusted	Adjusted	Other DD, *n*	Unadjusted	Adjusted
Continuous	416	87	1.48 (1.16, 1.88)	1.27 (0.93, 1.72)	269	1.31 (1.13, 1.53)	1.29 (1.07, 1.56)	224	1.13 (0.96, 1.33)	1.07 (0.88, 1.29)
Quartiles										
Q1	116	14	Ref	Ref	58	Ref	Ref	61	Ref	Ref
Q2	117	20	1.42 (0.68, 2.94)	0.98 (0.41, 2.33)	60	1.03 (0.66, 1.60)	1.12 (0.67, 1.85)	52	0.85 (0.54, 1.33)	0.77 (0.47, 1.25)
Q3	96	26	2.24 (1.11, 4.54)	2.07 (0.91, 4.72)	69	1.44 (0.92, 2.24)	1.68 (1.01, 2.79)	58	1.15 (0.73, 1.80)	1.12 (0.69, 1.82)
Q4	87	27	2.57 (1.27, 5.19)	1.75 (0.73, 4.19)	82	1.89 (1.22, 2.92)	1.84 (1.08, 3.15)	53	1.16 (0.73, 1.84)	1.00 (0.58, 1.72)
Median										
<50th percentile	233	34	Ref	Ref	118	Ref	Ref	113	Ref	Ref
≥50th percentile	183	53	1.98 (1.24, 3.18)	1.94 (1.06, 3.55)	151	1.63 (1.20, 2.22)	1.66 (1.14, 2.40)	111	1.25 (0.90, 1.73)	1.22 (0.84, 1.76)
Cord cysteine										
Continuous	416	87	1.21 (0.95, 1.54)	0.94 (0.71, 1.26)	269	1.02 (0.87, 1.19)	1.01 (0.84, 1.21)	224	1.10 (0.93, 1.31)	1.00 (0.83, 1.20)
Quartiles										
Q1	105	21	Ref	Ref	66	Ref	Ref	57	Ref	Ref
Q2	110	19	0.86 (0.44, 1.70)	0.72 (0.33, 1.59)	74	1.07 (0.70, 1.64)	1.11 (0.68, 1.81)	46	0.77 (0.48, 1.23)	0.77 (0.47, 1.28)
Q3	105	14	0.67 (0.32, 1.38)	0.54 (0.23, 1.29)	66	1.00 (0.65, 1.55)	1.05 (0.64, 1.72)	64	1.12 (0.71, 1.76)	1.15 (0.71, 1.86)
Q4	96	33	1.72 (0.93, 3.17)	1.03 (0.48, 2.21)	63	1.04 (0.67, 1.63)	1.02 (0.62, 1.72)	57	1.09 (0.69, 1.73)	0.84 (0.50, 1.39)
Median										
<50th percentile	215	40	Ref	Ref	140	Ref	Ref	103	Ref	Ref
≥50th percentile	201	47	1.26 (0.79, 2.00)	0.93 (0.53, 1.64)	129	0.99 (0.73, 1.34)	0.98 (0.69, 1.40)	121	1.26 (0.91, 1.74)	1.12 (0.79, 1.60)

*Adjusted model: Maternal age, maternal educational status, parity, smoking status, race/ethnicity, maternal BMI, maternal diabetes, preterm, sex, year of birth.
†Interaction between cord pantothenate and cysteine was not statistically significant. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; DD, developmental disability; NT, neurotypical.

Despite its importance as an essential micronutrient, research on pantothenate is scant especially in the first 1000 days. In a study conducted in African American women, levels of pantothenol (an alcohol derivative of pantothenol), CoA synthesis inhibitor, were elevated 8-folds in PTB.[22] Emerging studies suggest that pantothenate may be implicated in neurodegenerative diseases, with lower pantothenate levels reported in patients with Alzheimer's disease, Huntington's disease, and Parkinson's disease.[14,20] On the other hand, circulating pantothenate was elevated among those that had greater odds of cognitive decline over a 12-year follow-up.[28] Another study showed that an increase in pantothenate in the diet was associated with greater cerebral amyloid-β peptide (Aβ) burden, a hallmark pathology associated with Alzheimer's disease.[21] Beyond the neurodegenerative disabilities, pantothenate has been studied in other conditions such as type 2 diabetes, inflammation, all-cause mortality, with some showing protective[29] and others showing detrimental associations.[30,31] These findings suggest that optimal pantothenate levels are important for health and that both deficient and elevated levels may potentially have adverse effects.

Aberration in the pantothenate pathway is well-documented in a rare condition called PKAN with characteristic symptoms including developmental delay, progressive impairment of speech, locomotor and cognitive functioning.[11,15,32,33] This condition primarily manifests in early childhood. Studies have reported psychological and behavioral disturbance (ie, compulsive behavior, emotional liability, anxiety, depression, attention deficiency) in those with early onset PKAN[33] and at least one case report has noted a comorbidity between PKAN and ASD.[34] PKAN also shares several hallmarks of neurodegenerative disease such as Alzheimer's and Parkinson's diseases.[32] Accumulation of cysteine, pantothenate, and other metabolites of the CoA synthesis pathway has been reported in PKAN,[16] and this is consistent with our findings of the joint association of cysteine, pantothenate, and risk of ASD. Previous studies have shown that this accumulation (especially cysteine) is thought to increase oxidative stress and neurotoxic effects.[32,35]

There is growing evidence that these complex NDDs may be a manifestation of molecular defects that perturb myriad of cellular processes leading to direct effects and adaptations that compromise the neuronal development. Alterations in CoA, mitochondrial dysfunction and other downstream effects in ASD has been reported in many studies[4,36,37]; but the underlying mechanism at the cellular or molecular level is less clear. It has been hypothesized that the site of defect may reside upstream, such as in the pantothenate metabolic pathway that may lead to impaired cellular CoA.

Our study lends support to this hypothesis and sheds light on the need to potentially consider upstream metabolites and their pathways to better understand the underlying etiology. Furthermore, the temporal relationship between pathophysiological abnormalities and ASD etiology is often unclear, as studies are conducted in participants after the diagnosis.[38,39] In our study, we demonstrate that pantothenate, a precursor of CoA involved in energy metabolism, is altered prior to ASD diagnosis. This supports the hypothesis that metabolic changes in the pantothenate pathway leading to CoA production precede the diagnosis and is not merely an epiphenomenon of ASD. Furthermore, the greatest risk noted in preterm babies with elevated cord pantothenate suggests that this could be another potential pathway through which preterm birth may influence NDDs.

Pantothenate absorption in the human fetus is not well-characterized.[14,40] Emerging evidence suggests that pantothenate

Table 3
Joint association between cord pantothenate, cysteine, preterm birth, and neurodevelopmental disabilities.

	NT, *n*	ASD, *n*	Unadjusted	Adjusted	ADHD, *n*	Unadjusted	Adjusted	Other DD, *n*	Unadjusted	Adjusted
Joint association between cord pantothenate and cysteine*†‡										
Low pantothenate + high cysteine	108	13	Ref	Ref	56	Ref	Ref	56	Ref	Ref
Low pantothenate + low cysteine	125	21	1.40 (0.67, 2.92)	1.89 (0.75, 4.76)	62	0.96 (0.61, 1.49)	0.97 (0.59, 1.60)	57	0.88 (0.56, 1.38)	0.88 (0.54, 1.43)
High pantothenate + low cysteine	90	19	1.75 (0.82, 3.75)	2.60 (0.98, 6.86)	78	1.67 (1.07, 2.60)	1.69 (1.01, 2.85)	46	0.99 (0.61, 1.59)	1.09 (0.65, 1.85)
High pantothenate + high cysteine	93	34	3.04 (1.51, 6.10)	3.11 (1.24, 7.79)	73	1.51 (0.97, 2.36)	1.57 (0.93, 2.65)	65	1.35 (0.86, 2.12)	1.19 (0.72, 1.96)
Joint association between cord pantothenate and preterm birth§ //										
Low pantothenate + term birth	217	26	Ref	Ref	106	Ref	Ref	98	Ref	Ref
High pantothenate + term birth	157	36	1.91 (1.11, 3.30)	2.02 (1.04, 3.94)	106	1.38 (0.99, 1.94)	1.55 (1.04, 2.30)	73	1.03 (0.71, 1.48)	1.10 (0.74, 1.63)
Low pantothenate + preterm birth	16	8	4.17 (1.63, 10.70)	3.28 (1.04, 10.31)	12	1.54 (0.70, 3.36)	1.26 (0.52, 3.09)	15	2.08 (0.99, 4.37)	1.51 (0.68, 3.36)
High pantothenate + preterm birth	26	17	5.46 (2.62, 11.37)	5.36 (2.09, 13.75)	45	3.54 (2.07, 6.05)	3.31 (1.78, 6.16)	38	3.24 (1.86, 5.63)	3.39 (1.85, 6.24)

*Adjusted model: Maternal age, maternal educational status, parity, smoking status, race/ethnicity, maternal BMI, maternal diabetes, preterm, sex, year of birth.
†Interaction between cord pantothenate and cysteine was not statistically significant.
‡Low pantothenate: <50th percentile; Low cysteine: <50th percentile; High pantothenate: ≥ 50th percentile; High cysteine: ≥ 50th percentile.
§Adjusted model: Maternal age, maternal educational status, parity, smoking status, race/ethnicity, maternal BMI, maternal diabetes, sex, year of birth.
// Low pantothenate: <50th percentile; High pantothenate: ≥ 50th percentile. ADHD, attention deficit hyperactivity disorder; ASD, autism spectrum disorder; DD, developmental disability; NT, neurotypical.

Figure 3: Density distribution of cord pantothenate by preterm and ASD status.

is not synthesized in the brain and is supplied from the blood across the blood–brain barrier. Pantothenate is thought to be transported through SLC5A6, which is expressed in human-brain microvessels and is localized primarily in myelin in the white matter.[41] Animal models has shown that pantothenate concentrations in the brain are 50-fold higher than the plasma, suggesting that this micronutrient is actively transported.[41] However, it is unclear if this is the case in humans. More studies are needed to understand pantothenate metabolism and transport of this nutrient to the fetus during pregnancy.

The source of elevated pantothenate in the cord blood in our study is unclear. Based on our data, it is reasonable to assume that cord pantothenate is moderately reflective of maternal levels, and this is consistent with other studies.[42,43] However, given that only cord (and not maternal pantothenate) was implicated in the child's ASD risk suggests that the metabolism in the fetus may play a proximal role in this association.

Limitations

Our findings should be considered in the context of some limitations. First, we included one-time measurement of cord pantothenate at birth and did not measure it subsequently to understand how it varied with age. Despite this, an association with ASD and ADHD suggests the need to investigate this relationship

further. Second, phosphorylation of pantothenate is considered to be the rate-limiting step of this pathway and hence was measured in this study.[15] However, future studies can consider assessing additional intermediate metabolites in the pathway (such as 4-phosphopantothenate, 4′-phosphopantothenoylcysteine, 4′-phosphopantethenine and CoA), although it is difficult to measure the latter and is even more challenged by the lack of gold-standard methods.[8,10] Furthermore, the metabolites in this study generated relative intensities rather than actual metabolic concentrations. Third, this study characterized ASD, ADHD, other DD *vs*. neurotypical based on clinician diagnosis, as documented in the EMR, which could have led to potential misclassification. However, this misclassification may have been non-differential given the prospective design and objective laboratory measurements assessed by personnel who were unaware of the case status. As such, any misclassification could have biased the results towards the null. Fourth, this study included only those participants who continued to seek pediatric care at the BMC. Selection bias may thus be a concern, but the baseline characteristics of the participants initially enrolled in the study and those that remained in the study were comparable. Fifth, because of our observational design, the possibility of residual confounding cannot be fully excluded. Finally, our study was conducted in a high-risk population, which is predominantly urban, low-income, racially diverse with a high proportion of preterm births. Our study has contributed new information on this traditionally understudied US population, but caution should be exercised when extrapolating the findings to other populations, which may not have similar characteristics.

Conclusions

In summary, this is the first prospective birth cohort study to assess the individual and combined associations between cord plasma pantothenate and cysteine levels and subsequent risk of NDDs including ASD, ADHD, and other DD. We found that higher cord pantothenate was associated with greater ADHD and ASD risk. The joint association between higher cord pantothenate and cysteine with ASD risk provide clues for possible abnormalities in the CoA biosynthesis pathway. Furthermore, greater risk noted in preterm babies with higher cord pantothenate levels sheds light into another potential mechanism through which preterm birth may influence NDDs. Until now, very few studies have studied pantothenate in the context of NDDs and there remains large gaps in our understanding of the molecular and cellular mechanisms underlying the metabolism of this micronutrient, especially during the prenatal period and long-term health implications. Our results should be considered hypothesis-generating as not much has been explored until now. If our findings are replicated, metabolites in the pantothenate pathway, especially cysteine and pantothenate, along with preterm birth status, could jointly be considered in assessing a child's future risk of ASD and ADHD.

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Author Contributions

RR and XW designed research; CP, WA, MA, XW supervised field data collection; RR, XH, XW analyzed data and conducted statistical analysis; GW and XH performed laboratory analyses. RR, XW wrote the draft and revised the paper; RR and XW take primary responsibility for final content. All authors reviewed and provided important intellectual contributions to the initial manuscript and this revision and approved the final version of this manuscript.

Conflicts of Interest

None declared.

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