Chapter 11

Glutamine effects on brain growth in very preterm children in the first year of life

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Abstract

Background Glutamine supplementation in the neonatal period has been associated with increased brain structure volumes at school age in very preterm children. The aim of this study was to clarify the emergence and specificity of differences in brain structure volumes, using growth trajectories of head circumference, weight, and length.

Methods Sixty-five very preterm (<32 weeks gestation) children, who originally took part in a randomized controlled trial on glutamine supplementation, participated. Head circumference, weight, and length, were measured at the neonatal intensive care unit, and at routine follow-up assessments at the outpatient clinic and well baby clinics. Magnetic Resonance Imaging was used to determine brain structure volumes at school age. Growth trajectories were investigated using multilevel modeling analyses.

Results Head circumference in the first year of life was positively associated with white matter volume and grey matter volume (range *r*=.55-.81, all p's<.002) at school age. Furthermore, neonatal glutamine supplementation was associated with increased head circumference growth (p=.008) in the first year of life, but not with increased growth in weight (p=.44) and length (p=.73).

Conclusions This study indicates a specific increase in head circumference growth in very preterm children that received neonatal glutamine supplementation, and suggests that group differences in brain structure volumes at school age may have emerged during the first year of life.

Introduction

With advances in neonatal intensive care, the survival of very preterm (born <32 weeks of gestation) children has improved considerably. However, a variety of risk factors associated with very preterm birth interfere with normal brain maturation processes,[1,2] eventually affecting overall brain development throughout childhood and adolescence.[3,4] Recently, we found that neonatal glutamine supplementation between day three and 30 of life is associated with increased brain structure volumes at school age in very preterm children.[5] However, these promising findings do not give information whether differences in brain structure volumes indeed originated from the intervention period onwards, nor do they elaborate on the specificity of the differences for brain growth. Alternatively, differences in brain structure volumes at school age may have originated from baseline volume differences between the glutamine and placebo group, or may have resulted from differences in body growth due to variation in nutritional factors, such as a potential higher caloric and/or protein intake in the glutamine group.

In this study, we aimed to clarify the emergence and specificity of differences in brain volumes observed at school age between very preterm children that received glutamine supplementation or placebo between day three and 30 of life. In order to clarify the growth trajectory of brain structure volumes in both groups, we used measures of head circumference. Head circumference growth is rapid in the first year of life, and measures of head circumferences have been shown to be strong predictors of brain volumes and associated neurocognitive functioning in childhood.[6-9] We first elucidated the relation between head circumference in the first year of life and brain structure volumes in very preterm children at school age. Second, we investigated differences in the growth trajectories of head circumference between the glutamine group and the placebo group. Finally, growth trajectories of weight, and length were investigated to clarify whether differences in brain structure volumes at school age may have originated from differences in nutritional factors associated with growth, such as caloric and protein intake.

Methods

Sample

A sample of 65 very preterm (<32 weeks gestation) children participated in this study. All very preterm children admitted to the level III neonatal intensive care unit (NICU) of the VU University Medical Center Amsterdam between September 2001 and July 2003 were eligible for inclusion to the randomized controlled trial on the effects of glutamine supplementation.[10] A total of 102 very preterm infants entered the study and received either enteral glutamine supplementation (0.3 g/kg/day) or an isonitrogenous placebo supplementation (alanine) between day three and 30 of life. Of the 102 infants included in the original study, 89 infants (87%) were alive at one year of follow-up. At seven years of age, parents were contacted and invited to participate in the current follow-up study collecting data on growth, neurocognition, and brain development, including Magnetic Resonance Imaging (MRI). Data on growth measures were successfully collected for 65 (73%) very preterm children. In addition, MRI follow-up was successful for 52 very preterm children.[5] Nutritional intake during intervention period and number of serious neonatal infections were monitored.[10] Serious infections included sepsis, meningitis, pyelonephritis, pneumonia, and arthritis, were determined using blood, cerebrospinal fluid, and urine cultures as previously described in more detail.[10] Social economic status (SES) was determined by classifying the highest level of education in a household with a number ranging from one to four. A higher number indicated a higher level of education and a corresponding higher SES. Characteristics of the follow-up sample are shown in Table 1. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the medical ethical committee of the VU University Medical Center. Written informed consent was obtained from all subjects.

Growth measures

Measures of growth, including head circumference (in cm), weight (in kgs), and length (in cm), were collected via three supplementary methods (see Table 2 for an overview). First, growth measures were collected for all very premature children during their stay at the NICU. Second, growth was assessed at multiple standardized follow-up assessments at the hospital and hospital outpatient clinic in the first years of development

for 60 very preterm children. For five children, parents did not show up at follow-up appointments. Third, additional data on growth were collected at well baby clinics for 56 very preterm children. In The Netherlands, all children visit a well baby clinic at similar scheduled time points to evaluate their development using standardized procedures, and to receive immunizations. During these visits, data are collected on head circumference in the first year of life, and weight and length up till four years of age. As a consequence, we were able to investigate the growth trajectory of head circumference up till one year of age, whereas the growth trajectories of weight and length could be investigated up till four years of age. Importantly however, the first year of life is the most crucial period of head circumference growth for boys as well as girls.[11] For the remaining nine children, well baby clinics did not succeed in retrieving the data from their records. Age at measurement was corrected for gestational age.

Structural MRI acquisition and processing

To determine brain volumes at the mean (SD) age of 8.6 (0.3) years, structural MRI images were acquired using a 1.5 Tesla MRI scanner, equipped with an 8-channel phased-array head coil (Siemens Sonata, Erlangen, Germany), at the VU University Medical Center. Anatomical 3D T1-weighted images were obtained in the sagittal plane with an MPRAGE (Magnetization-Prepared Rapid Acquisition Gradient Echo) sequence (TR=2730 ms, TE=3.7 ms, TI=1000 ms, flip angle=7˚, with a 1x1 mm in-plane resolution and a slice thickness of 1 mm). Volumes of white matter and grey matter were determined using techniques as previously described,[5] and included as dependent variables in the analyses.

Statistical analyses

Independent t-test (for normally distributed continuous data), Mann–Whitney U-test (for not normally distributed continuous data), and chi-square test (for dichotomous data) were used to determine whether there were differences between the glutamine and placebo group in gender, SES, gestational age, birth weight for gestational age (BW for GA), nutritional intake during the intervention period, and the incidence of serious neonatal infections. Partial Pearson correlation coefficients between head circumference in the first year of life and volumes of both white matter and grey matter at school age adjusting for age at MRI and age of head circumference measurement were performed, to investigate

whether head circumference in the first year of life is related to brain structure volumes in very preterm children at school age. In addition, partial Pearson correlations between head circumference and incidence of serious neonatal infections, adjusted for age of head circumference measurement, were calculated.

Table 1. Sample characteristics

	Placebo (N=35)		Glutamine (N=30)			
	M	SD	M	SD	p	Effect-size
General characteristics						
Birth weight, in kgs	1.20	0.33	1.27	0.37	.43	0.19
Birth weight for GA, z-value	-0.36	1.38	-0.38	1.91	.96	0.01
Gestational age, in weeks	29.0	1.6	29.7	1.6	.08	0.44
Head circumference at birth, in cm	26.7	2.5	27.5	2.0	.17	0.35
Head circumference for GA, z-value	0.03	1.18	0.08	1.41	.88	0.04
Socio economic status	3.1	0.7	3.3	0.8	.17	0.27
Male gender, n (%)		18 (51)		15 (50)	.91	
Clinical characteristics						
Prenatal corticosteroids, n (%)		31 (89)		21 (70)	.06	
Caesarean delivery, n (%)		20 (57)		17 (57)	.97	
Birth weight < 10th percentile, n (%)		8 (23)		8 (27)	.72	
Apgar score after 5 minutes < 6, n (%)		2 (6)		3 (10)	.52	
1 or more serious infections, n (%)		28 (80)		14 (47)	**.006**	
Number of infections, median (range)		1 (0-3)		0 (0-2)	**.003**	
Maternal HELLP syndrome, n (%)		6 (17)		4 (13)	.67	
Chorioamnionitis, n (%)		11 (31)		7 (23)	.47	
BPD, n (%)		12 (34)		8 (26)	.51	
IVH grade I/II, n (%)		7 (20)		6 (19)	.99	
IVH grade III/IV, n (%)		0 (0)		1 (3)	.28	
PVL, n (%)		3 (9)		1 (3)	.38	
Nutritional intake characteristics						
Energy day 7 (kcal/kg/day)	94.7	21.2	89.1	17.6	.25	0.29
Energy day 14 (kcal/kg/day)	111.3	24.6	111.7	15.9	.94	0.02
Carbohydrates day 7 (mg/kg/day)	8.2	1.6	7.8	1.6	.32	0.25
Carbohydrates day 14 (mg/kg/day)	8.4	1.5	8.1	0.7	.37	0.26
Proteins day 7 (g/kg/day)	2.9	0.7	2.6	0.6	.14	0.46
Proteins day 14 (g/kg/day)	3.3	0.7	3.4	0.5	.82	0.16
Lipids day 7 (g/kg/day)	3.9	1.4	3.6	1.1	.39	0.24
Lipids day 14 (g/kg/day)	5.5	1.7	5.7	1.4	.58	0.13
Breast feeding, n (%)		19 (54)		19 (63)	.46	
Follow-up MRI						
Age at MRI assessment, years	8.6	0.3	8.6	0.4	.55	0.17
White matter volume, cm^3	466.5	49.2	496.5	60.4	**.03**	0.54
Grey matter volume, cm^3	705.4	63.3	727.4	85.6	.39	0.29

Note. BPD = Bronchopulmonary Dysplasia; Maternal HELLP = Hemolysis Elevated Liver enzymes and Low Platelets; IVH = Intraventricular Haemorrhage; MRI = Magnetic Resonance Imaging; PVL = Periventricular Leukomalacia; ROP = Retinopathy of Prematurity. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05). Effect sizes are depicted as Cohen's *d*.

ANOVA was used to explore differences in the number of growth measurements, age at measurements, and average growth outcome, using group (glutamine and placebo) and data collection method (NICU, follow-up, well baby clinic) as fixed factors. In addition, multilevel modeling was performed to investigate growth trajectories of head circumference, weight, and length, using the multilevel modeling program MLwiN.[12] Multilevel modeling is an extension of regular regression analysis, which is appropriate when data are hierarchically structured (in the current study multiple measurements for each child). Using multilevel analysis, individual growth curves as well as growth curves for predefined groups can be estimated.[13] Given the nature of our data, this statistical technique has two major advantages. First, multilevel modeling allows for differences in the number of measurements per child. Second, multilevel modeling allows variation in the time point that measurements are performed. Three different growth models for head circumference, weight, and height were examined with age (including 2nd, 3rd, 4th, and 5th order effects of age), group (glutamine and placebo), and interaction effects between age and group as explanatory variables, using a stepwise approach. Group differences were quantified in terms of Cohen's *d* effect-sizes[14] with values of 0.20, 0.50 and 0.80 as small, medium and large effects, respectively. Testing was performed two-sided, and α was set at .05.

Results

Sample

Patient characteristics of the glutamine and placebo group are shown in Table 1. Baseline characteristics were not different in the study group of 65 very preterm children, the 24 very preterm children lost to follow-up, and the 52 very preterm children included at MRI follow-up (all p's>.05). In line with the results of the initial study cohort,[10] the incidence of serious neonatal infections was lower (p=.006), and white matter volume was increased (*d*=0.54, p=.03) in the glutamine group as compared to the placebo group. Furthermore, gender, SES, nutritional intake during intervention period, and clinical characteristics other than the incidence of serious neonatal infections, were not different between both groups, indicating no differences in background characteristics and illness severity (Table 1). However, there was a threshold significant difference for prenatal steroid treatment in the placebo group as compared to the glutamine group (p=.06). To exclude a possible effect of

differences in the use of prenatal corticosteroids on our findings, we additionally included the use of prenatal corticosteroids as covariate in those analyses that indicated differences between the glutamine and placebo group. Finally, growth parameters at birth (head circumference, weight, and length, Table 1), nutritional intake at the NICU (Table 1), the number of measurements (Table 2), and age at measurement (Table 2), were not different between both groups.

Head circumference and brain structure volumes

Partial correlations, adjusted for age at MRI scan and age at head circumference measurement, showed that average head circumference in the first year of life was significantly associated with larger white matter volume and grey matter volume at school age for the whole group (r=.70, p<.001 and r=.70, p<.001, respectively), as well as for the glutamine (r=.81, p<.001 and r=.75, p<.001, respectively) and placebo group (r=.55, p=.002 and r=.62, p<.001, respectively), separately. In addition, a partial correlation, adjusted for age at head circumference measurement, showed that a lower incidence of serious neonatal infections was significantly associated with larger average head circumference in the first year of life in the whole group (r=-.25, p=.05).

Table 2. Overview of collected data on growth measures for the glutamine and placebo group

	Placebo (N=35)			Glutamine (N=30)				
	M	SD	Range	M	SD	Range	p[1]	Effect-size
Average data available, in number								
Weight measurements	13.8	5.1	6 – 28	15.8	6.5	5 – 33	.23	0.34
Length measurements	13.2	4.4	5 – 21	14.7	4.8	4 – 25	.47	0.32
Head Circumference measurements	10.0	3.6	2 – 16	11.5	3.7	5 – 20	.29	0.41
Average age at data collection, in months[2]								
Weight, in kgs	8.5	2.5	-3 – 48	9.2	3.3	-3 – 48	.36	0.24
Length, in cm	8.5	2.7	-3 – 48	9.5	2.6	-3 – 48	.22	0.38
Head Circumference, in cm	1.9	1.4	-3 – 12	2.2	1.1	-3 – 12	.41	0.24

Note. [1]tested using ANOVA; [2]Term age = 0 months. M and SD pertain to mean and standard deviation, respectively. Bold numbers pertain to a significant p-value (p<.05). Effect sizes are depicted as Cohen's *d*.

Growth trajectories

The growth trajectories for head circumference in the first year of life for glutamine and placebo groups are shown in Figure 1. The parameter estimates of the final multilevel growth models are presented in Table 3. There was no main effect of group on head

circumference (p=.58), but there was a significant interaction between group and age for head circumference growth (p=.008), indicating that infants in the glutamine group had a significant larger increase in head circumference compared to the placebo group in the first year of life. Because there was a threshold significant difference in the use of prenatal corticosteroids between both groups, we additionally included prenatal corticosteroids use as covariate in the growth trajectory analysis, which did not alter the significance of the interaction between group and age (p=.008). Post-hoc analyses indicated that head circumference was significantly higher in the glutamine group compared to the placebo group (Mean difference=1.03, pooled SD=1.39, *d*=0.74, p<.001) at the end of the first year of life.

There were no main effects of group on weight (p=.60, Table 3) and length (p=.42) in the first four years of life between the glutamine and placebo group. In addition, there were no significant interaction effects between group and age for both weight (p=.44, Figure 2) and length (p=.73), indicating no evidence for any differences in the growth trajectories of weight and length between the glutamine and placebo groups in the first four years of life.

Figure 1. Growth trajectory of head circumference in the first year of life
Dotted lines indicate 95% confidence intervals

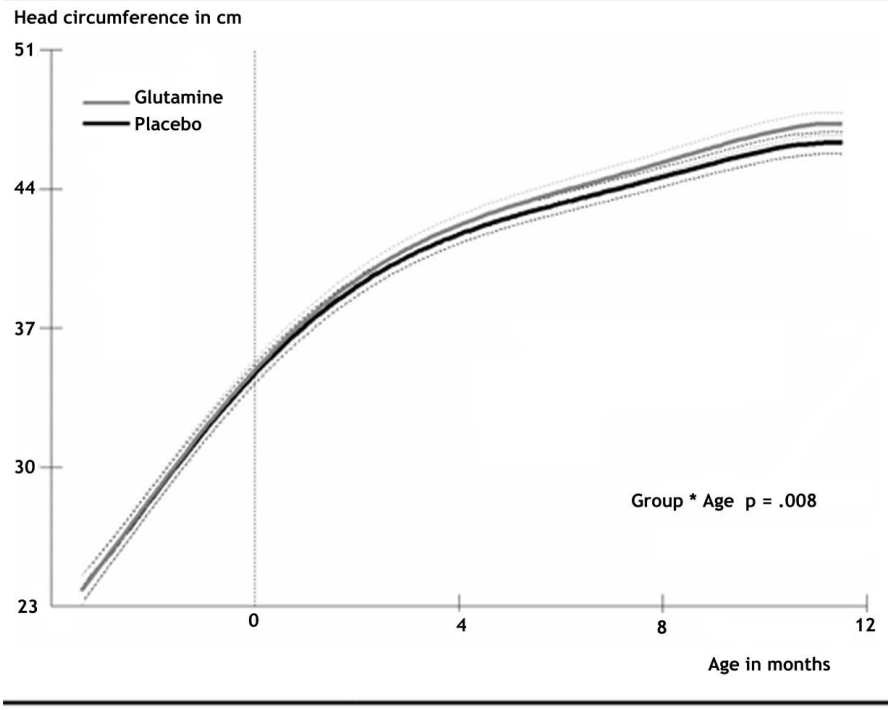

Figure 2. Growth trajectories for body weight and length for the first four years of life

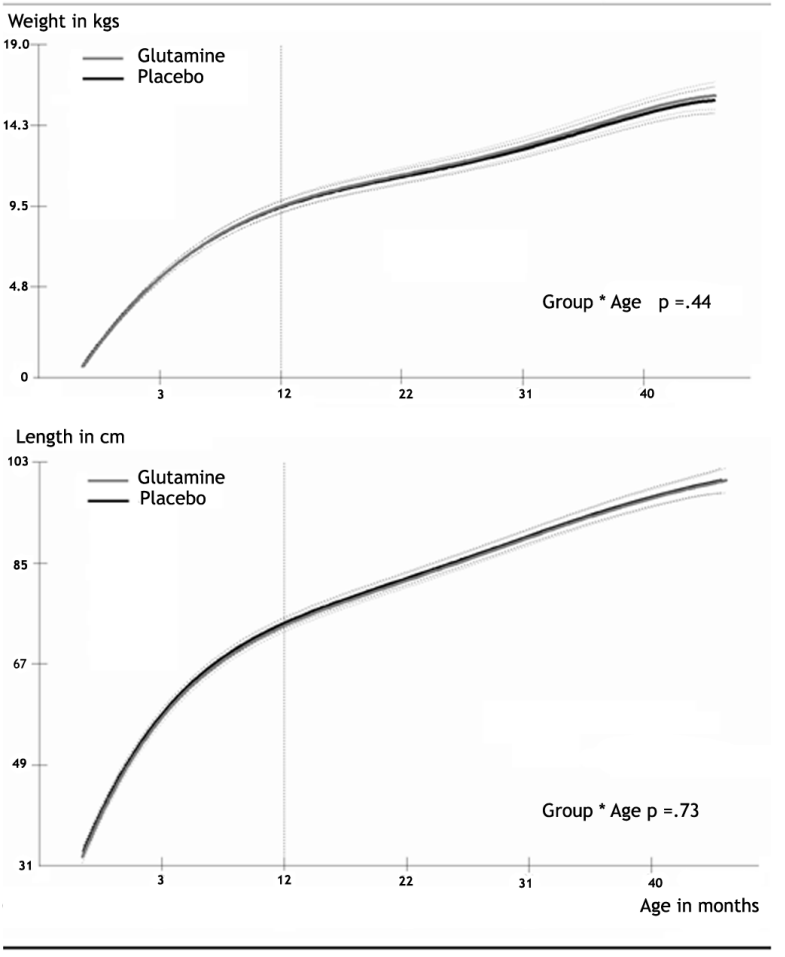

Table 3. Outcomes of multilevel modeling for growth trajectories of head circumference, weight, and length

			Weight			**Height**			**Head circumference**
	Coefficient	SE	p	Coefficient	SE	p	Coefficient	SE	p
Fixed effects									
Constant	9.49	164.3	**<.001**	75.72	0.52	**<.001**	34.70	0.25	**<.001**
Age	3.28	77.9	**<.001**	13.44	0.28	**<.001**	33.16	0.57	**<.001**
Age^2	-1.93	93.7	**<.001**	-6.21	0.37	**<.001**	-35.79	1.54	**<.001**
Age^3	0.99	41.4	**<.001**	5.13	0.16	**<.001**	-22.12	9.07	**.02**
Age^4	-0.07	40.5	.07	-1.80	0.19	**<.001**	86.06	17.00	**<.001**
Age^5	-0.03	12.9	**.03**	0.21	0.06	**<.001**	-50.08	9.29	**<.001**
Treatment group	-0.06	105.4	.60	-0.55	0.68	.42	0.20	0.36	.58
Treatment group*Age	0.08	0.1	.44	0.12	0.33	.73	0.83	0.31	**.008**

Note. Bold numbers pertain to a significant p-value (p<.05). SE = Standard Error.

Discussion

This study shows a significant association between head circumference in the first year of life and brain structure volumes in very preterm children at school age.[15] In addition, there was a significant interaction in growth trajectories of head circumference between groups, demonstrating a larger increase in head circumference growth in the glutamine group compared to the placebo group, resulting in a medium to large sized increase of head circumference at the end of the first year of life (*d*=0.74). This finding clearly shows a gradual emergence of differences in the trajectory of brain growth between the glutamine and placebo group, persisting throughout the first year of life. Furthermore, given that we found a specific effect of intervention on increase in head circumference in contrast to growth in weight and length, it is less likely that findings originate from variation among groups in nutritional factors related with growth.

From literature, there are several potential mechanisms which may underpin the suggested beneficial effect of glutamine supplementation on head circumference in the first year of life and brain structure volume as assessed at school age.[16] First, findings from our previous study suggested that a lower incidence of serious neonatal infections in the glutamine group mediated the increase in white matter volume at school age.[5] Interestingly, in the current study we found that a lower incidence of serious neonatal infections was also related with an increase in head circumference in the first year of life. Second, increased head circumference in the glutamine group as compared to the placebo group may also result from a more direct involvement of glutamine in cell proliferation and growth. Although intervention only lasted for 28 days at the beginning of life, It is well-established that glutamine is a major fuel and nucleotide substrate for rapidly proliferating cells,[16] indicating that even a (short) depletion of glutamine availability during catabolic conditions may have a deleterious influence on cell growth and proliferation. Given the abundant myelination and increase in brain volume in the first year after birth, differences in brain structure volumes (i.e. white matter volume) may relate to better glutamine availability during catabolic conditions in the glutamine group as compared to the placebo group, although future studies using larger samples are warranted to confirm findings.

Our findings may suggest that an early postnatal nutritional intervention is related with improved brain growth of very preterm infants in the first year of life, which may

eventually underpin differences in brain structure volumes at school age. In other studies, poor early postnatal (brain) growth has been associated with delayed cortical maturation[17] as well as adverse developmental outcomes in childhood, including poor intellectual functioning and motor outcomes.[18-20] In addition, there is some evidence that a smaller head circumference in the early neonatal period of very preterm children is predictive for poor later development, including poor neurocognitive functioning[6-8] and poor behavioral outcomes as indicated by increased prevalence rates of Attention Deficit Hyperactivity Disorder (ADHD).[21] However, the predictive value of postnatal head circumference on neurocognitive and behavioral development is limited,[6,18] suggesting that other factors influence development at school age which may dilute the potential beneficial effects of an increased head circumference growth in the first year of life in our sample. Indeed, we recently described no differences between the glutamine group and control group on overall measures of motor, cognitive and behavioral development at school age.[22] In general, the relation between brain structure volumes and neurocognitive functioning is largely unclear, although there is some evidence that larger brain structure volumes are moderately associated with improved neurocognitive functioning in very preterm children at various ages[23-27] and also in normally developing children.[9]

The present study has limitations, which need to be taken into account. First, the power of the study was limited due to the number of children that dropped out of the current study. Unfortunately, we were therefore not able to discriminate between growth trajectories of children with or without serious neonatal infections for the glutamine and placebo group, to further elucidate the working mechanism underlying the glutamine effects. Second, data on growth measures were collected using three different sources, eventually leading to some missing values. Nevertheless, by using multilevel modeling, which allows missing data, we maximized power to aggregate growth data of all children into growth trajectories per group. Indeed, power was sufficient to detect any clinically meaningful medium- to large-size effects of group on measures of head circumference.[28] Furthermore, three different data sources may potentially introduce some accuracy differences in growth measurement. However, all measurements were performed using standardized procedures, and no significant differences between both groups were present in either the proportion of data collected per source, the number of available data points per child, nor the age of growth assessment. Finally, we did not have data on the developmental

patterns of head circumference between one and eight years of age. Although the first year of life is the most crucial period of head circumference growth for boys as well as girls,[11] differences in brain growth between the glutamine and placebo group might have been present after this period.

In conclusion, this study shows a positive association between increased head circumference in the first year of life and larger brain structure volumes in very preterm children at school age. In addition, we found evidence for increased head circumference growth in the glutamine group as compared to the placebo group in the first year of life, whereas no group differences were present in the growth trajectories of weight and length. Together, these findings suggest that the differences in brain structure volumes between the glutamine and placebo group at school age may have emerged from a difference in the growth trajectory of the brain during the first year of life. These findings illustrate the necessity for future studies to look into the replication and elucidation of the working mechanism underlying potential glutamine effects in early brain development.

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