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FEEDING IMPAIRMENTS ASSOCIATED WITH PLASMA STEROLS IN SMITH-LEMLI-OPITZ SYNDROME

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Abstract

Objective—To quantitatively evaluate feeding impairment in children with Smith-Lemli-Opitz Syndrome (SLOS) and to correlate feeding impairment with clinical and biochemical indices of disease severity.

Study design—Subjects were 26 children with SLOS, 0.4 to 19 years age. Clinical severity was measured using an existing scoring system. We created a tool to quantitatively evaluate feeding. Plasma sterol concentrations were measured, and statistical associations (correlations) with feeding scores were calculated.

Results—Oral hypo- or hypersensitivity, adverse behaviors, and risk for dysphagia were seen in ~65% of children with SLOS; 13/26 children experienced failure-to-thrive (FTT), and 10/26 required gastrostomy. 7DHC concentrations, as a measure of severity, correlated with Total Feeding Score and the Oral Function subcategory score ($p<.001$), less so with Oral Structure, adverse behaviors or dysphagia. Correlations with cholesterol concentrations were not statistically

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significant. 7DHC > 0.24 mmol/L or Chol < 1.95 mmol/L is predictive of gastrostomy use. Feeding impairments may improve with age.

Conclusions—Feeding impairment is common and complex in patients with SLOS. Findings confirm that oral sensitivities, adverse feeding behaviors and risk of oral phase dysphagia are amenable to quantitative evaluation and analysis. Feeding difficulties in children with SLOS are correlated with plasma sterol concentrations, suggesting a link between the biochemical severity in SLOS and feeding function. These findings expand the behavioral phenotype of SLOS and begin to provide insights into the biologic causes of feeding difficulties.

Keywords

Dysphagia; Feeding Impairment; Sterols; 7-Dehydrocholesterol; Cholesterol; Gastrostomy; Behavioral Phenotype; Smith-Lemli-Opitz Syndrome

Smith-Lemli-Opitz syndrome (SLOS) is the most common metabolic disorder of cholesterol synthesis. Affected individuals manifest multiple malformations and variable intellectual disability (1). SLOS is an autosomal recessive disorder with defective *DHCR7* enzyme activity in the last step of cholesterol synthesis (2, 3). Plasma cholesterol is low or low-normal, and the cholesterol precursor 7-dehydrocholesterol (7DHC) is elevated. The broad and variable spectrum of phenotype and neurodevelopmental disability are correlated with cholesterol and 7DHC concentrations (4). A distinctive behavioral phenotype has been described consisting of aggression, resistance, irritability, and hyperactivity (5); Autism Spectrum Disorder is very common (6). The severity of cholesterol synthesis defect correlates significantly with challenging behaviors (7).

Although several clinical characteristics of SLOS relate to feeding difficulties, this has not been comprehensively studied. These difficulties are, in part, biologically based: orofacial anomalies and gastrointestinal anomalies are seen (8). Clinical course in infancy is often characterized by oral sensorimotor impairments, abnormal suck, feeding aversions, swallowing difficulties, and vomiting. Oral tactile defensiveness and failure to developmentally progress to more complex textures are also often part of the clinical spectrum (8). The frequency of dysphagia and gastroesophageal reflux has not been reported. Failure-to-thrive (FTT) may be the presenting problem. These anatomical, neurological, developmental and sensory feeding difficulties are potentially exacerbated by the behavioral phenotype.

Our goal was to quantitatively document the frequency of feeding difficulties and to describe the feeding impairments in a cohort of children with SLOS. We hypothesized that impaired feeding in SLOS is frequent and characterized predominantly by oral sensitivity, negative feeding behaviors, and dysphagia. Additionally, we hypothesized that the feeding problems in SLOS are biologically based, correlate with biochemical severity, and improve with age. Finally, we proposed to expand the behavioral phenotype of SLOS by objectively quantifying the feeding patterns exhibited by these children.

METHODS

Children with SLOS (n=26) were evaluated for feeding disorders (Table I). SLOS diagnosis was confirmed by elevated 7DHC, and/or gene sequencing of *DHCR7* mutations. The children were admitted to the Clinical and Translational Research Center at Oregon Health & Science University (OHSU) for up to 1-week visits as part of a natural history study. The OHSU Institutional Review Board approved these studies, and written informed consent was obtained. Each child was evaluated 1–8 times at 6–12 month intervals as long as they were participants in this ongoing natural history study. Phenotype, neurodevelopmental status, history of internal organ structure and current function, orofacial structure, and clinical feeding status of these children were recorded. Feeding evaluation was a two-hour encounter by a team composed of a developmental pediatrician, speech-language pathologist, occupational therapist, and registered dietician. Anthropomorphic measurements were obtained, and BMI calculated to discern failure-to-thrive (FTT). A Pediatric Neurodevelopmental exam, including feeding history and oropharyngeal exam, was performed. Five specific pediatric questions queried the presence of dysphagia, gastroesophageal reflux (GER), aspiration, oral feeding, and requirement for gastrostomy tube feeding; these were assigned a scale score for severity 0–2, “0” being normal, “2” being most severely affected.

An established SLOS Anatomical Severity Score was used as an index of severity of individual cases (8, 9). It rates anatomy of ten organ systems using a scale score for severity 0–2, “0” being normal, “2” being most severely affected; normalized total scores range 0–100. This Score ranks cleft lip, palate and uvula but does not address feeding, oral function or dysphagia.

Feeding assessment was carried out in a comprehensive fashion (10–12) following American Speech-Language-Hearing Association (ASHA) guidelines (13). The mouth was visualized simultaneously by the Developmental Pediatrician, Speech-Language Pathologist, and Occupational Therapist. The soft palate was palpated, and deformities such as surgical scars, cleft soft or hard palate, or bifid uvula, were recorded. Imaging, bronchoscopy or ENT evaluations were not performed.

Because of a lack of data collection tools covering the full age range and breadth of pediatric feeding impairments with which to quantitatively document components of the feeding evaluation for statistical analysis (14–23), we created an Oral Sensorimotor and Feeding Data Collection Tool© (Oregon Health & Science University, Nancy L Sinden, MS, and Christine D Brown, OT).

The purpose of this tool is to gather data on oral sensorimotor functioning. It is composed of 29 items in 3 sub-categories of oral structure, oral function, and “other” (feeding behavior, risk of pharyngeal dysphagia and risk of esophageal dysphagia) (Figure 1; available at www.jpeds.com). Items were rated on a scale of 0–3, “0” being normal, “3” being most severely affected; total scores range 0–87. Though not statistically validated, we used this as a tool in this pilot study to quantify clinical observations. In evaluation of each child the

speech-language pathologist and the occupational therapist came to consensus on each item score. Total composite and sub-category scores were calculated.

Subjects were generally receiving a diet supplemented with cholesterol. Plasma cholesterol level stabilizes after 3–4 weeks of a new diet (24). For one of their multiple admissions, 20 subjects came for evaluations after a 3-week diet of very little (essentially zero) cholesterol intake. Plasma sterol concentrations while receiving the cholesterol-free diet were used as an estimate of biochemical severity. Six families declined participation in the cholesterol-free diet; for these we used the plasma concentrations that resulted in the highest ratio of 7DHC/Cholesterol as the best estimate of biochemical severity. We also measured sterol concentrations at each study admission. Sterol measurements were performed as previously described(7).

Statistical analyses

Results are presented as mean ± SD with confidence intervals. Substratification analyses were performed using 2-tailed Student's *t*-tests or Wilcoxon Rank Sum test and were applied where appropriate to compare the difference between two groups: orally fed vs. gastrostomy fed. Mixed-effects model was applied to examine statistical association as a measure of correlation between measures of interest. This model is particularly useful in longitudinal studies where multiple evaluations (eg, feeding scores) of the same patient are performed over time and associated with a single measure (eg, plasma 7DHC or cholesterol concentrations). Discriminant analysis with one-record-leave-out cross validation of 7DHC concentrations vs. route of feeding was carried out to identify cut-off plasma sterol concentrations indicating need for gastrostomy; further logistic regression analysis was performed to predict the outcome; sensitivity and specificity of the cut-off (using area under the curve) were calculated. As is customary, a p value < 0.05 indicated statistical significance; trends toward significance were considered for associations with p values 0.05 to 0.10.

RESULTS

The age range, sex, and SLOS Anatomical Severity scores of subjects are stated in Table I. The Anatomical Severity Scores ranged from 0 to 40 (average 18.3). Seventeen of the children were below the 3rd percentile on measurement of weight for age, weight-for-length, and/or BMI, and 13 of these (6 boys and 7 girls) were even below the 1st percentile and met criteria for FTT.

No patient experienced cholestatic liver, renal or severe cardiac dysfunction. Bile acid production is likely normal in these patients with mild to moderate Anatomical Severity Scores (less than 50) (25). Palate structure was clinically scored with our data collection tool; all cleft soft and hard palates had been repaired prior to these evaluations. In these patients there is no statistical association between internal organ anatomy or function, and plasma sterol levels (data not shown).

Comparison of orally fed children with those fed by gastrostomy was done using the Student t-test (Table I). Those who required gastrostomy had statistically significantly higher (more

severe) SLOS Anatomical Severity Score, lower plasma cholesterol concentrations and higher 7DHC concentrations.

Feeding scores (composite and subcategory scores) are also shown in Table I. Particular characteristics described in the feeding tool stood out. 18/26 exhibited oral sensitivity. 9/26 exhibited negative behaviors that affected eating. 13/26 children experienced Failure-to-Thrive (FTT).

Mean Total Feeding and 3 Sub-Categories scores are significantly different in orally fed compared with tube-fed children (Table I). Of 16 orally fed, 8 (50%) showed oral sensitivity, 4 demonstrated negative feeding behaviors, and 1 (6%) was at risk for dysphagia. 10/26 required gastrostomy feedings to provide some or all of their nutrition. All 10 tube-fed exhibited oral sensitivities; 5 demonstrated negative behaviors, and 9 had risk of dysphagia to the extent of eating refusal and/or FTT which necessitated gastrostomy nutrition for all or a portion of their nutrition.

Associations between feeding scores and plasma sterol concentrations

Plasma cholesterol concentrations were >100 mg/dL (normal) in only 7/26. 7DHC was elevated in 24/26, and borderline-elevated in two diagnosed by genetic studies. Most aspects of oral feeding are statistically associated with plasma sterol concentrations (Table II). Overall, scale scores are associated (correlated) with 7DHC and inversely associated with cholesterol concentrations as markers of biochemical severity. Only sensory issues and cholesterol are not significantly associated. The strongest associations are between 7DHC and feeding scores, whereas associations between cholesterol and feeding scores are weaker. Further, associations between 7DHC and Oral Function scores and particularly its subtest the Oral Motor Function score ($p<.001$) are stronger with greater effect than those between 7DHC and Oral Structure and “Other” scores. Sub-stratification analysis demonstrates association is stronger in 5 of 6 categories on the feeding measures except Oral Structure in tube fed but only for 7DHC. These are shaded on Figure 1 (online) showing the evaluation tool to emphasize strongest associations. Cholesterol association with Oral Structure has a very weak effect (−0.06).

There is no association between the Total Feeding Score and the current concentration of 7DHC ($p= 0.722$). There does not appear to be a direct affect from current 7DHC concentrations on current feeding abilities.

Discriminant Analysis yielded thresholds for gastrostomy (0.24 mmol/L for 7DHC, and 1.95 mmol/L for cholesterol) from which we calculated predictive values. Further analysis with logistic regression analysis using these thresholds found: if 7DHC > 0.245 mmol/L or Chol < 1.95 mmol/L, a child has a 67% chance of eventually requiring a gastrostomy tube. The correct specified positive predictive value is 77%, sensitivity 80%, specificity 75%. The measure of accuracy for the combination of these two threshold tests is 85% (ROC area under the curve.)

We further investigated the relationship between feeding impairment and sterols, adjusting for age. This was stimulated by our clinical impression that oral feeding improved in some

patients. Statistical analysis showed that age was indeed a significant predictor of feeding skills and did not change the statistical significance of the relationship between feeding and sterols (data not shown). Age is a significant factor in the association between feeding impairment and 7DHC (Total Feeding Score, effect size: −1.00, CI −1.96, −0.05, p=0.04; Oral Motor score: −0.36, CI −0.61, −0.11, p=0.006), but not in the association with cholesterol concentration.

Associations of Pediatric feeding queries to sterol concentrations

Associations between the total of five specific Pediatric history questions scores are significant with both 7DHC ($p<0.001$) and cholesterol ($p<0.001$) (Table III). The total of these history scale scores is also strongly associated with the Total Feeding score on our feeding evaluation scoring tool ($p<0.001$), corroborating the use of the Oral Sensorimotor and Feeding Data Collection Tool©. Four of the five specific Pediatric history questions are found to be associated with plasma sterol concentrations, except aspiration; again, strongest associations are with 7DHC concentrations.

DISCUSSION

It was our clinical impression that many children with SLOS have feeding difficulties and negative feeding behaviors. These seemed more severe than in children with other static neurodevelopmental disabilities with otherwise comparable motor and cognitive function. This was a quantitative study of feeding impairment in these children with SLOS.

There are limitations of this study, one of which is the relatively small sample size. Validity of the statistical analysis of orally vs. gastrostomy fed using a two-independent sample Student t-test might be questioned; we therefore also performed the Wilcoxon rank sum test, and the results are consistent and hence confirmatory. Specific imaging or probes for diagnosis of tracheal aspiration or gastroesophageal reflux were not carried out; family's report of diagnosis, history of suggestive symptoms or clinical observation were used to make these specific categorical diagnoses. Ours is a study of the natural history of SLOS; interventions, therapies or treatments were not analyzed although dietary cholesterol supplementation was nearly universal. It would have been corroborative to compare feeding scores generated by the Oral Sensorimotor and Feeding Data Collection Tool© with a gold standard for feeding impairment, but no such standard exists; the strength of associations of plasma sterols with feeding scores as well as with Pediatric feeding history do, however, support the use of the tool.

Cholesterol deficiency potentially affects the structure and function of all organs because of its ubiquitous presence in cell membranes, major role in synaptogenesis, role in hedgehog signaling, as well as essential role as precursor to sterol hormones and bile acids. Deficiency of cholesterol, accumulation of precursor dehydrocholesterols or a combination of both may underlie the pathology.

Feeding difficulties in children with SLOS are correlated with plasma sterol concentrations, suggesting a link between the biochemical severity and feeding ability but less so to orofacial structure. The strongest associations are between 7DHC and Total Feeding Score,

the category of Oral Function, and particularly subcategory of Oral Motor Function. Statistical associations with cholesterol are not as strong. This intimates that 7DHC has specific impact on feeding, cholesterol abnormalities less so.

Biochemical severity is more strongly associated with Oral Function than Oral Structure. It would seem intuitive that cholesterol deficiency would directly impact embryologic development and therefore structure. Sterols are important in synapse formation in the brain; aberrations of sterols may impact nervous system function, thereby affecting feeding. Indeed, Porter has proposed that sterols play a major role in CNS function; intellectual disability and behavioral phenotype in SLOS may be due to the cholesterol deficit in the CNS (4). Our findings of a stronger statistical association of plasma sterols to feeding function than structure support the view that the impact of abnormal plasma sterols is more on neurological function than on orofacial formation.

More specifically, it has been suggested that the malformations found in SLOS may result from accumulation of non-cholesterol sterols (26). 7DHC has been shown to be very reactive toward free radical oxidation, and some of the oxidative products have been shown to be extraordinarily toxic to cells (27). Our findings of weaker statistical associations with cholesterol intimate that 7DHC may have more specific toxic effects. More severely affected children will likely have high concentration of 7DHC in early development; these high concentrations may have long-term consequences on later function.

We wondered whether lowering 7DHC after infancy might improve feeding impairment. We found no association between current concentrations and Total Feeding score, suggesting current 7DHC concentrations may not have a direct effect on current feeding skills. If this is the case, interventions to reduce 7DHC levels after infancy may not be therapeutic for feeding impairment; this warrants further study.

Those children with the most severe SLOS as indicated by plasma sterol concentrations are expected to have the highest risk of feeding impairment. At the time of diagnosis of SLOS the concentrations of plasma 7DHC and cholesterol can alert caretakers to predict difficulties, assiduously monitor growth and feeding, and have a low clinical threshold to supplement nutrition and institute feeding therapies or even foresee the need for gastrostomy.

Despite these findings, we noted some children have clinically improved with age. One subject was unexpectedly able to wean off gastrostomy, despite otherwise static developmental status. These statistical associations, adjusted for age, were strongest between plasma 7DHC concentrations versus Total Feeding Scores and Oral Function. These findings remind clinicians that improvements in feeding ability are possible over long term and may be fostered by nutritional supplementation as well as intense oral feeding therapy focusing on oral skills, tolerances, and feeding behaviors.

We quantified the Pediatric Neurodevelopmental exam based on five questions specific to feeding history. Abnormal plasma sterol concentrations are statistically associated with four of the five questions. This serves as another confirmation of the association of feeding impairment with plasma sterol concentrations.

Finally, feeding evaluations in other neurodevelopmental conditions have not been quantitatively compared with date. The Oral Sensorimotor and Feeding Data Collection Tool©. might be used to quantitatively compare feeding in typically and variably developing children of all ages, as well as for longitudinal quantitative monitoring for clinical management in any child with neurodevelopmental dysphagia. Validation of the Oral Sensorimotor and Feeding Data Collection Tool© will be carried out and reported.

Feeding impairment is common and complex in SLOS. This study describes feeding difficulties including related behavioral problems seen in at least 65% of children with SLOS. These findings expand the behavioral phenotype of Smith-Lemli-Opitz Syndrome and begin to provide insights into the biologic causes of feeding difficulties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

BMI	Body Mass Index
Chol	cholesterol
7DHC	7-dehydrocholesterol
DHCR7	7-Dehydrocholesterol Reductase
FTT	Failure-to-Thrive
GER	Gastroesophageal Reflux
SLOS	Smith-Lemli-Opitz Syndrome

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Table 1

Characteristics of Subjects and Mean Feeding Scores

Orally fed			plasma sterols[§]					MEAN			
subject	sex	Anatomical Severity Score[*]	cholesterol mmol/L	7DHC mmol/L	visits #	age first visit[†] yr	age last visit yr	TOTAL FEEDING SCORE	ORAL STRUCTUE SCORE	ORAL FUNCTION SCORE	OTHER SCORE
1	M	20	0.64	0.187	2	0.9	1.7	33.5	6.0	27.0	0.5
2	F	5	2.20	0.242	5	1.0	5.9	35.2	7.0	25.4	2.8
3	M	20	0.62	0.283	2	1.1	1.6	40.0	7.5	29.0	3.5
4	M	15	3.42	0.052	2	2.5	5.9	34.5	2.5	31.0	1.0
5	M	20	2.87	0.003	1	2.6	4.3	10.5	3.5	6.0	1.0
6	M	5	3.39	0.242	1	3.9	3.9	33.0	8.0	23.0	2.0
7	M	5	3.67	0.005	2	4.4	7.2	24.0	4.5	18.0	1.5
8	F	17	3.13	0.003	1	5.8	5.8	2.0	0.0	2.0	0.0
9	M	6	2.46	0.125	1	5.9	5.9	17.0	1.0	15.0	1.0
10	M	17	1.97	0.244	2	7.6	12.0	3.5	2.0	1.5	0.0
11	F	10	2.64	0.060	3	9.1	12.5	5.7	1.3	3.7	0.7
12	F	10	2.46	0.122	4	9.3	12.4	8.0	3.7	4.3	0.0
13	F	10	2.17	0.130	4	10.2	13.2	9.3	4.3	4.3	0.7
14	F	17	2.82	0.208	3	11.3	14.4	6.7	2.7	3.3	0.7
15	M	20	0.80	0.328	1	11.6	11.6	33.0	3.0	29.0	1.0
16	M	6	2.72	0.354	1	19.4	19.4	10.0	1.0	5.0	4.0
mean		12.69	2.37	0.162		6.66		19.12	3.63	14.23	1.27
sd		6.13	0.96	0.116		5.02		13.67	2.45	11.51	1.21
G-Tube fed											
17	F	40	0.16	0.270	2	0.4	1.1	52.0	12.0	36.0	4.0
18	M	38	0.51	0.356	3	0.6	1.7	50.7	9.0	35.3	6.3
19	M	40	0.21	0.270	2	0.6	1.2	58.5	10.5	41.0	7.0
20	M	35	1.22	0.359	8	0.7	5.3	62.7	8.8	47.2	6.7
21	F	25	1.91	0.473	3	1.1	3.1	67.3	8.7	52.0	6.7
22	F	11	2.41	0.174	1	2.1	2.3	35.0	7.0	26.0	2.0
23	M	30	1.45	0.244	3	5.4	7.4	60.0	11.3	42.3	6.3

Orally fed			plasma sterols[§]					MEAN			
subject	sex	Anatomical Severity Score[*]	cholesterol mmol/L	7DHC mmol/L	visits #	age first visit[†] yr	age last visit yr	TOTAL FEEDING SCORE	ORAL STRUCTUE SCORE	ORAL FUNCTION SCORE	OTHER SCORE
24	M	11	2.28	0.343	8	5.8	10.8	61.0	5.8	47.0	8.2
25	F	17	1.22	0.247	2	8.2	12.2	42.0	5.5	33.0	3.5
26	F	33	2.28	0.343	2	13.2	15.7	52.5	9.0	37.5	6.0
mean		28.00	1.36	0.31		3.80		54.17	8.77	39.73	5.67
SD		11.42	0.86	0.08		4.30		9.89	2.17	7.74	1.88
t-test		p=0.002	p=0.011	p=0.001				p<0.0001	p<0.0001	p<0.0001	p<0.0001
							95%CI	(−44.62,−25.4)	(−7.05,−3.22)	(−33.32,−17.71)	(−5.84,−2.95)
Wilcoxon Rank Sum test								p<0.0001	p<0.0003	p<0.0001	p<0.0001
							95%CI	(−48.70,−25.00)	(−7.50,−3.00)	(−35.00,−16.00)	(−35.00,−16.00)

[*](Kelley, R. I., Hennekam, R. C. The Smith-Lemli-Opitz syndrome 2000. 37:321.)

[§]Plasma sterols as marker of biochemical severity

[†]age at first feeding evaluation visit

Table 2

Association of feeding scores with sterol concentrations

Dependent variable (Y)	Independent variables (X)	Effect size (Coefficient estimate)	P-value of Effect size	95% CIs for the effect size
• Total Feeding Score	• 7DHC	• 2.98	• <0.001	• (1.64, 4.32)
	• Cholesterol	• −0.30	• 0.002	• (−0.48, −0.12)
• Oral Structure	• 7DHC	• 0.41	• 0.001	• (0.17, 0.64)
	• Cholesterol	• −0.06	• <0.001	• (−0.08, −0.03)
• Oral Function	• 7DHC	• 2.60	• <0.001	• (1.44, 3.76)
	• Cholesterol	• −0.25	• 0.004	• (−0.41, −0.09)
• Oral Sensory	• 7DHC	• 0.25	• 0.016	• (0.05, 0.46)
	• Cholesterol	• −0.02	• 0.099	• (−0.050, 0.004)
• Oral Motor	• 7DHC	• 0.75	• <0.001	• (0.47, 1.02)
	• Cholesterol	• −0.07	• 0.001	• (−0.11, −0.03)
• Other and Outcomes	• 7DHC	• 1.66	• <0.001	• (0.88, 2.44)
	• Cholesterol	• −0.15	• 0.007	• (−0.26, −0.05)

Table 3

Association of items from Pediatric history with sterol concentrations

Dependent variable (Y)	Independent variables (X)	Effect size (Coefficient estimate)	P-value of Effect size	95% CIs for the effect size
• Total score Pediatric history (5 items)	• 7DHC	• 0.47	• <0.001	• (0.24, 0.70)
	• Cholesterol	• −0.05	• <0.001	• (−0.082, −0.024)
	• Total Feeding Score	• 0.12	• <0.001	• (0.087, 0.144)
• Dysphagia	• 7DHC	• 0.33	• <0.001	• (0.13, 0.53)
	• Cholesterol	• −0.03	• 0.046	• (−0.0565, −0.0005)
• Gastroesophogeal Reflux	• 7DHC	• 0.25	• 0.003	• (0.08, 0.41)
	• Cholesterol	• −0.02	• 0.036	• (−0.041, −0.001)
• G-tube feeding	• 7DHC	• 0.64	• <0.001	• (0.28, 0.99)
	• Cholesterol	• −0.04	• 0.031	• (−0.067, −0.003)
• Oral feeding	• 7DHC	• 0.31	• 0.003	• (0.11, 0.52)
	• Cholesterol	• −0.02	• 0.053	• (−0.0502, 0.0003)
• Head Circumference SS	• 7DHC	• 0.28	• 0.002	• (0.10, 0.45)
	• Cholesterol	• −0.022	• 0.024	• (−0.041, −0.003)