Supplementary Data

Supplemental Table S1. Study without a control group

Author, year, country	Study Design	Participants' characteristics (*n*, gender, age, type of AANMD)	Intervention features	Study length	Study outcomes (end of study compared to baseline)	Summary of Study
Strauss *et al.* (2010) USA	Pre-post-intervention study	*n* = 15, 18±12 months Type of AANMD: Maple Syrup Urine Disease (MSUD)	Medical formula enriched with selenium, zinc, alpha-linolenic acid, and a group of amino acids that compete with BCAA for uptake into the brain	29±7 months	**Biochemical** - Decrease plasma leucine, valine and isoleucine concentrations ($p < 0.05$) - Increase plasma tryptophan, tyrosine, methionine and threonine concentrations ($p < 0.05$) - Increase plasma selenium concentrations ($p < 0.05$) - Increase plasma fatty acids (AA, EPA, DHA, total omega-3&6) concentrations ($p < 0.001$) **Clinical** - Decrease rate of brain uptake of isoleucine and valine ($p < 0.05$) - Increase rate of brain uptake of tryptophan, methionine and threonine ($p < 0.05$)	Medical food fortified with essential nutrients such as fatty acids, vitamins and minerals as well as a specific amino acids composition significantly improve metabolic control as evidenced by decreasing plasma leucine, valine and isoleucine concentrations, selenium concentrations, increases plasma fatty acid concentration and decreases rate of brain uptakes of branched-chain amino acids substrates and increases rate of uptake of inhibitive amino acid among MSUD children.
Acosta *et al.* (2005) USA	Pre-post-intervention study	*n* = 17, age= 0.22 – 38.84 months Type of AANMD: Urea cycle defects (UCD)	Medical food (Cyclinex-1 Amino Acid-Modified Medical Food with Iron)	6 months	**Anthropometry** - Improve weight ($p = 0.01$) and length ($p = 0.04$) **Biochemical** - Decrease number of subjects with plasma albumin (-17%) and transthyretin (-22.5%) concentrations lower than reference range[1] -	Medical food with when used with intact protein and adequate energy, enhances growth and improves protein status among UCD patients
Yannicelli *et al.* (2003) USA	Pre-post-intervention study	*n* = 16 (10 girls 6 boys), age = 0.03-3.00 years Type of AANMD: Methylmalonic or Propionic acidemia (MMA or PA)	Medical food (Propimex-1 Amino Acid-Modified Medical Food with Iron)	6 months	**Anthropometry** - Improve weight (+23%), length and (+8%), head circumferences (+11%) percentiles[2] **Biochemical** - Decrease number of subjects with plasma glycine (-22%) and isoleucine (-25%) concentrations exceeded reference range[1]	Medical food improves growth, metabolic control, and indices of protein and vitamin status among MMA and PA patients during a 6-month period.

					- Increase number of subjects with plasma methionine (+15%), threonine (+40%), valine (+35%) meet minimum reference range - Increase number of subjects with plasma albumin (+14%), retinol binding protein (+6%), retinol (+46%), and α-Tocopherol (+8%) meet minimum reference range	
MacDonald *et al.* (2011) UK	Open-label, pilot intervention study	*n* = 9 (3 boys 6 girls), 5-16-year-old Type of AANMD: Phenylketonuria (PKU)	Infant protein substitute with prebiotics (PKU Anamix Infant: Nutricia)	7.14 – 19.43 weeks	**Biochemical** - No significant difference in phenylalanine and tyrosine level **Clinical** - Decrease stool pH level ($p < 0.05$)	Infant formula contains prebiotics can support good phenylalanine control and might lower stool pH value.
Zaki *et al* 2016 Egypt	Prospective, self-controlled, small-scale clinical trial	*n* = 10 (6 boys 4 girls). 4-16-year-old Type of AANMD: Phenylketonuria (PKU)	**Phase 1:** 50% GMP + 50% AAF **Phase 2:** 100% AAF	9 weeks	**Biochemical** - There was no significant difference in phenylalanine, urea, creatinine, albumin, ALT, AST and Hb	The introduction of GMP protein substitute does not affect the metabolic control, renal and liver profile among PKU patients in this study.

[1]Result reported as changes in percentage of subjects with biochemical parameters lower than/ exceed reference range at baseline and study end, no statistically test was reported.
[2]Results were reported as improvement in weight and height percentile, no statistically test was reported.
AANM: Amino acid and nitrogen metabolism; BCAA: Branched-chain amino acid; NS: Not significant UK: United Kingdom; USA: United States America; AA: Arachidonic Acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic Acid; GMP: Glycomacropeptide; AAF: Amino-acid formula; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; Hb: Haemoglobin.

Supplemental Table S2. Study with control group (2 groups)

Author, year, country	Study Design	Participants' characteristics (*n*, gender, age, types of AANMD)	Intervention features	Study length	Study outcomes (treatment group *vs*. control group)	Summary of Study
Strauss *et al.* (2011) USA	Non-randomized prospective interventional study	**T** *n* = 12 (6 girls 6 boys), 30 months (8 - 61 months) **C** *n* = 25 (characteristics not mentioned) Type of AANMD: Glutaric Aciduria Type 1 (GAT1)	**Treatment:** Medical formula with low lysine (0 mg) and fortified with arginine (90 mg), reduced tryptophan (5mg), fortified with omega-6 and omega-3 polyunsaturated fatty acids (PUFAs) **Control:** Protein-restricted diet and L-carnitine	2 years	**<u>Anthropometry</u>** - Increase head circumference index ($p = 0.01$) **<u>Biochemical</u>** - Increase plasma leucine, tryptophan, arginine, isoleucine, valine, methionine, threonine and citrulline concentrations ($p < 0.05$) - Decrease plasma lysine, glycine concentrations and lysine/arginine ratio ($p < 0.05$) - Increase plasma DHA, total n-6 and n-3 fatty acids level ($p < 0.05$) **<u>Clinical</u>** - Increase rate of brain uptake of leucine, arginine, isoleucine and methionine ($p < 0.05$) - Decrease rate of brain uptake of phenylalanine, lysine, histidine and glutamine ($p < 0.05$) **<u>Dietary</u>** - Increases total protein, natural protein and arginine intake ($p < 0.0001$) - Decreases total lysine (p=0.0006) and tryptophan ($p < 0.0001$) intake	Medical formula fortified with arginine and improves growth, metabolic control, increases plasma fatty acid concentration and limiting the rate of uptake of offensive amino acid (lysine) into brain, as well as increases total protein and arginine intake among GAT1 patients.
Kolker *et al.* (2012) Germany	Non-randomized prospective interventional study	**T:** *n* = 26 **C:** *n* = 8 Total: *n* = 34 (21 girls 13 boys), 7.43 years (0.7–10.9 years) Type of AANMD: Glutaric Aciduria Type 1 (GAT1)	**Treatment:** Medical formula with low lysine (0 mg) and **fortified with arginine (90 mg**), and reduced tryptophan **Control:** Medical formula with low lysine (0 mg) but normal **arginine (59 mg)**, and reduced tryptophan	1 year	**<u>Biochemical</u>** - No significant difference in plasma lysine/arginine ratio **<u>Clinical</u>** - No significant difference in frequency of dystonia and gross motor milestones **<u>Dietary</u>** - Increase total dietary arginine intake ($p < 0.05$) - Decrease total lysine-to-arginine ratio ($p < 0.001$)	Lysine-free, tryptophan-reduced and arginine-fortified medical food significantly increases arginine intake and decreases dietary lysine-to-arginine ratios in GA-I patients.
Gokmen-Ozel *et al.* (2011)	Randomised, controlled,	3-10-year-old	**Treatment:**	14 days	**<u>Anthropometry</u>** - No significant in weight change	CHO/ protein-equivalent ratio can be reduced

UK	crossover study	*n* = 14, 12 boys, 2 girls, 6.3 years (3 - 9.7 years). Type of AANMD: PKU	Low CHO protein substitute with a median CHO/Protein-equivalent ratio 0.5:1 **Control:** Control protein substitutes with a median CHO/Protein-equivalent ratio 1:1		**Biochemical** - No significant change in plasma phenylalanine concentration **Dietary** - Increase energy intake from protein substitute ($p < 0.05$)	to 0.5:1 without any loss of phenylalanine control or causes significant in weight changes.
Agostoni *et al*., 2001 Italy	Double-blind, placebo-controlled trial	**T:** n=10 (5 boys 5girls), 10±7 years **C:** *n* = 10 (6 boys 4 girls), 10±5 years Type of AANMD: PKU	**Treatment:** Dietary LCPUFA supplement providing 0.3–0.5% of the daily energy requirements as LCPUFA **Control:** Placebo capsule (Olive oil supplement)	12 months	**Biochemical** - Higher weight (%) of DHA and total omega-3 in plasma phospholipids ($p = 0.002$) in treatment group	Dietary supplement with a balanced LCPUFA mixture increases the levels of plasma DHA pools among PKU children.
Beblo *et al*., 2001 Germany	Non-randomized open clinical trial	**T:** *n* = 36 (17 boys 19 girls), 6.3±0.6 years **C:** *n* = 30 (15 boys 15 girls), 6.6±0.5 years Type of AANMD: PKU	**Treatment:** Fish oil capsules with 500 mg of salmon oil (35% of omega-3 fatty acids: 18% of eicosapentaenoic, 12% DHA) **Control:** No supplement was given to the healthy children	3 months	**Biochemical** - No significant change in plasma phenylalanine concentration **Clinical** - Increase length of visual evoked potential (VEP) latencies at pattern size 5' ($p = 0.013$) and 10' ($p = 0.014$)	DHA supplementation improves visual development among PKU children without affecting phenylalanine concentrations.
Agostoni *et al*., 2006 Italy	Prospective, double-blind, randomized study	**T:** *n* = 21 (8 boys 13 girls), 18±5.9 days **C:** *n* = 21 (12 boys 9 girls), 20±6.9 days Type of AANMD: PKU	**Treatment:** LC-PUFA-supplemented formula containing levels of DHA [0.3g/100g fatty acids] and AA [0.7g/100g fatty acids] **Control:** Standard phenylalanine-free infant formula)	20 weeks	**Biochemical** - Decline in DHA and total n-3 fatty acids are lower among treatment group ($p < 0.05$) **Clinical** - No significant difference in Bayley test scores for both mental and physical development	Phenylalanine free infant formula with LC-PUFA in infants with PKU prevents the decline in DHA status among infant with PKU.
Koletzko *et al*. (2007) Germany	Randomized, double-blind controlled trial	**T:** *n* = 10 (7 boys 3girls), 2.1±0.9 weeks	**Treatment:** Phenylalanine free amino acid mixture (for breastfed infant) OR	12 months	**Biochemical** - Plasma $C_{20:4n}$-6 (AA) and $C_{22:6}$n-6 (DHA) significantly higher in treatment group at 12th month *(p-value not reported)*	Formula supplemented with

		C: *n* = 11 (6 boys 5 girls), 2.0±0.4 weeks Type of AANMD: PKU	phenylalanine containing formula with LCPUFA **Control:** Phenylalanine free amino acid mixture (for breastfed infant) / phenylalanine containing formula without LCPUFA		**Dietary** - Dietary $C_{20:4n}$-6 (AA) and $C_{22:6}$n-6 (DHA) significantly higher in treatment group at 12th month ($p < 0.05$)	LCPUFA enhances plasma DHA and AA's concentration as well as dietary intake of DHA and AA.
Giovannini *et al.* (2014) Italy	Randomized controlled trial	**T:** *n* = 10 (7 boys 3girls), 2.1±0.9 weeks **C:** *n* = 11 (6 boys 5 girls) 2.0±0.4 weeks Type of AANMD: PKU	**Treatment:** Prolonged-release phenylalanine free protein substitute (overall release time: 3 hours) **Control:** Conventional substitute (duration of action shorter than treatment~2hours)	30 days	**Biochemical** - Increase plasma transthyretin concentrations ($p = 0.017$) - Decrease plasma phenylalanine concentration ($p = 0.01$)	Prolonged released protein substitute improves protein status and metabolic control among PKU children.
MacDonald *et al.* (2006) UK	Randomised, crossover, prospective study	*n* = 25 (14 girls and 11 boys), 6 years (2–10 years) Type of AANMD: PKU	**Treatment:** 2g/kg/BW/day of protein equivalent from protein substitute **Control:** 1.2 g/kg/BW/day of protein equivalent from protein substitute	14 days	**Biochemical** - Control group had bigger increase in phenylalanine concentration ($p < 0.001$)	Lower dose of protein substitute significantly increases blood phenylalanine concentrations.
Cleary *et al.* (2006) UK & French	Randomized controlled trial	**T:** *n* = 44 (7 boys 3 girls), 2.1±0.9 weeks **C:** *n* = 20 (6 boys 5 girls) 2.0±0.4 weeks Type of AANMD: PKU	**Treatment:** EFA-supplemented phenylalanine free formula containing levels of Linoleic Acid [17.2g/100g fatty acids] and α-Linolenic Acid [4.5g/100g fatty acids] **Control:** Fat-free protein substitute	20 weeks	**Biochemical** (% of PUFA in erythrocyte membrane phospholipids) - Higher weight (%) of DHA and total omega-3 in plasma phospholipids ($p = 0.002$) in treatment group ($p = 0.04$) **Dietary** - Higher fat intake ($p < 0.001$), Linoleic acid (18:2n-6) ($p = 0.002$), Linolenic acid (18:3n-6) ($p < 0.001$) and 18:2n-6: 18:3n-6 ratio ($p = 0.004$) in plasma phospholipids in treatment group	EFA-supplemented formula improves DHA status and increases total fat, linoleic acid and α-linolenic acid intake.
Boblo *et al.* (2007) Germany	Non-randomized open clinical trial	**T:** *n* = 24 (17 males 19 females), 1-11-year-old **C:**	**Treatment:** 500mg fish oil capsule providing 18% EPA & 12% DHA (2-10 capsules/day according to body weight) **Control:**	3 months	**Biochemical** - Increase plasma $18:2_n6$, AA, $22:5_n6$, EPA, $22:5_n3$, DHA and total n-6 PUFA in treatment group ($p < 0.001$) **Clinical** - Increase motor development index ($p = 0.011$) in treatment group ($p < 0.001$)	Fish oil (Omega-3) supplements significantly improves body coordination and fine motor skills as well as plasma fatty acids among PKU children.

		n = 30 healthy children (15 boys 15 girls), 6.6 ± 0.5 years Type of AANMD: PKU	No supplement was given to healthy children			
Daly 2017 UK	Non-randomized, prospective, pilot study	T: *n* = 12, 6–16 years C: *n* = 9, 6–14 years Total: *n* = 22 (13 boys, nine girls), 6–16 years Type of AANMD: PKU	**Treatment:** CGMP-AA protein substitute **Control:** Phe-free L-amino acid	26 weeks	**Anthropometry** - No significant difference in weight and height **Biochemical** - Increase in phenylalanine concentration and phenylalanine: tyrosine ratio (Phe: Tyr ratio) in treatment group ($p = 0.02$) - Decrease in tyrosine concentration ($p = 0.03$) **Dietary** - No significant difference in total energy, protein, CHO and fat intake	CGMP-AA protein substitute increases blood phenylalanine concentration and Phe: Tyr ratio, which might have an impact in long-term metabolic control.
Daly 2019 UK	Non-randomized, prospective, pilot study	T: *n* = 31 C: *n* = 19 Total: *n* = 50 (28 boys, 22 girls); Age: 9.2 years (5–16 years) Type of AANMD: PKU	**Treatment:** CGMP-AA2 protein substitute **Control:** Phe-free L-amino acid	12 months	**Anthropometry** - Increase weight and BMI in treatment group ($p < 0.0001$) **Biochemical** - Increase in phenylalanine concentration and phenylalanine: tyrosine ratio (Phe: Tyr ratio) in treatment group ($p < 0.001$) - Higher whole blood selenium ($p = 0.0002$) and selenium in treatment group ($p = 0.0007$)	CGMP-AA protein substitute increases blood phenylalanine concentration and Phe: Tyr ratio as well as whole blood and plasma selenium, hence it should be used cautiously among PKU children.

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AANM: Amino acid and nitrogen metabolism; NS: Not significant; PKU: Phenylketonuria; Phe: Phenylalanine; UK: United Kingdom; USA: United States America; AA: Arachidonic Acid; EPA: Eicosapentaenoic acid; DHA: Docosahexaenoic Acid; VEP: Visual Evoked Potential; CGMP: Casein Glycomacropeptide; BMI: Body mass index; CRP: C-Reactive Protein; MCV: Mean corpuscular volume; RBP: Retinol binding protein.

Supplemental Table S3. Study Involve three or more different groups

Author, year, country	Study Design	Participants' characteristics (*n*, gender, age, types of AANMD)	Intervention features	Study length	Study outcomes (Treatment group *vs.* control group)	Summary of Study
Demmelmair *et al*., 2018, Germany	Double blind Randomized controlled trial	*n* = 109, gender not reported, 5-13 years Type of AANMD: PKU	**R1:** 0mg DHA supplementation **R2:** > 0 to < 1.9 mg DHA supplementation **R3:** ≥ 1.9 to 7 mg DHA supplementation	6 months	**Biochemical** - Subjects received intervention in regime 3 had highest plasma DHA concentration ($p < 0.001$) compared to other groups **Clinical** - No significant difference in length of VEP, RPM-score and LOS T-score	DHA supplement significantly improves plasma DHA level but not neurological function.
Daly *et al*., 2020, UK	Non-randomized, longitudinal study	R1: *n* = 19, age =11.1 R2: *n* = 16, age = 7.3 R3: *n* = 13, age = 9.2 Total: n=50 (28 boys, 22 girls) Type of AANMD: PKU	**R1:** Liquid phenylalanine-free AA formula **R2:** CGMP50 (combination of CGMP + AA) **R3:** CGMP100 (all substitute from CGMP)	3 years	**Anthropometry** - No significant difference in weight and BMI **Biochemical** - Subjects received intervention in regime 1 & 2 had increased phenylalanine level at 36th month (*no comparison between group)* **Dietary** - No significant difference in total energy intake	CGMP -AA does not slow down weight gain and not lead to lower energy intake.
Daly *et al*. (2019) UK	Randomized crossover, controlled trial	*n* =19 (12 girls, 7 boys), 6-16 years Type of AANMD: PKU	**R1:** CGMP-AA formula + No dietary phenylalanine adjustment **R2:** CGMP-AA formula + Dietary phenylalanine adjustment **R3:** Conventional phenylalanine-free L-AA + No dietary phenylalanine adjustment	14 days	**Biochemical** - Subjects received intervention in regime 1 had higher plasma phenylalanine concentration compared to R2 and R3 ($p < 0.0001$), R2 is higher than R3 ($p < 0.0009$) - Subjects received intervention in R1 and 2 had higher plasma tyrosine concentration compared to R3 ($p = 0.002$)	CGMP-AA protein substitute increases blood phenylalanine and tyrosine concentrations, hence it should be used cautiously among PKU children.

MacDonald *et al.* (2003) UK	Randomized, crossover study	Protocol A, B, C *n* = 13 (3 boys 10 girls) Protocol A, B, D *n* = 3 (1 boy 2 girls) Total: *n* = 16 (12 girls 4 boys), 4 years (1-11 years) Type of AANMD: PKU	**Protocol A:** Protein substitute was administered in **three** equal, divided doses over a **10 h period**. **Protocol B:** Protein substitute was administered in **three** equal, divided doses over a **14 h period** **Protocol C:** Protein substitute was administered in **four** equal divided doses over a **14 h period**. **Protocol D:** Protein substitute was administered in **six** equal divided doses over a **14 h period**.	**A, B & C:** 7 days **D:** 3 days	**<u>Biochemical</u>** - Subjects assigned to protocol D had smallest changes in phenylalanine concentration compared to A and B at 4, 8 and 16 hours ($p < 0.02$) **<u>Dietary</u>** - No significant difference in total energy and phenylalanine intake	Frequent administration of protein substitute day and night significantly reduces phenylalanine fluctuation similar to normal physiological pattern seen in non-PKU individuals

AANM: Amino acid and nitrogen metabolism; PKU: Phenylketonuria; UK: United Kingdom; DHA: Docosahexaenoic Acid; TG: Triglycerides; LDL: Low-density-lipoprotein; HDL: High-density lipoprotein; VEP: Visual evoked potential; RPM: Raven's Progressive Matrices; LOS: Lincoln-Oseretzky Motor Development.