

Supplementary Table S1. Actual dietary intakes of PKU patients in early childhood (0-3 years of age).

Reference	N	Age	Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Acosta et al., 1998	20	1 mo	Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	33	2 mo	571 (23)		221 (14)		51 (4)		9.2 (0.75)		14.0 (0.7)	
	31	3 mo	584 (20)		250 (13)		47 (2)		9.2(0.75)		14.5 (0.6)	
	34	4 mo	626 (22)		270 (11)		44 (2)		10.4 (0.60)		16.1 (0.6)	
	34	5 mo	681 (24)		264 (15)		38 (2)		12.5 (0.75)		18.1 (0.7)	
	33	5 mo	718 (26)		265 (15)		34 (2)		14.0 (0.75)		19.6 (0.7)	
	32	6 mo	572 (24)		254 (13)		31 (2)		14.6 (0.75)		20.0 (0.7)	
	35	Total	660 (18)		255 (10)		40 (1)		11.9 (0.60)		17.3 (0.6)	
Aldámiz-Echevarría et al., 2014	N/A	0-2y	N/A		N/A		Median (IQR) 28.2 (20.8-36.2)		Median (IQR) 0.8 (0.5-1.0)		Median (IQR) 1.4 (1.0-1.7)	
Aldámiz-Echevarría et al., 2015 ^a	<u>BH4</u>	<u>BH4</u>			Mean (SD)		Mean (SD)		Mean (SD)		Mean (SD)	
	22	1 y			37.1 (19.1)		1.4 (1.1)		0.9 (0.6)		2.2 (1.7)	
	<u>Diet</u>	<u>Diet</u>	N/A		N/A		N/A		N/A		N/A	
	44	1 y			Mean (SD) 28.2 (14.1)		Mean (SD) 0.6 (0.2)		Mean (SD) 1.5 (0.5)		Mean (SD) 2.2 (0.5)	
		2 y			25.8 (17.0)		0.6 (0.3)		1.6 (0.8)		2.1 (0.7)	
Alm et al., 1986	16	1 y			Mean (SD) 43.4 (16.1) Median(range) 38.5 (30-80)							
			N/A		N/A		N/A		N/A		N/A	
	17	2 y			Mean (SD) >39.7 (24.8) Median(range) 27 (16 to >80)							
Hoeksma et al., 2005		6 mo					N/A		N/A		N/A	
	NP=117	1 y					Mean (SD) 1.22 (0.53)		Mean (SD) 1.46 (0.58)		Mean (SD) 2.70 (0.50)	
	PS=135	2 y	N/A		N/A		1.03 (0.41)		1.28 (0.38)		2.36 (0.51)	
	TP=133	3 y					0.97 (0.46)		1.26 (0.34)		2.25 (0.56)	
		Total					0.93 (0.51)		1.22 (0.42)		2.20 (0.65)	
							0.99 (0.34)		1.29 (0.28)		2.33 (0.42)	

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Reference	N	Age	Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			kcal/day	kcal/kg/day	mg/day	mg/kg/day	g/day	g/kg/day	g/day	g/kg/day	g/day	g/kg/day
Evans et al., 2019 ^b			<i>Mean (SD)</i>	<i>Mean (SD)</i>			<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
	7 to 11	4 mo	686 (146.8)	95.6 (22.9)			5.6 (1.5)	0.78 (0.16)	13.9 (5.0)	2.0 (0.8)	17.5 (4.2)	2.5 (0.6)
	7 to 20	5 mo	735 (160.1)	100.1 (22.0)			6.6 (1.5)	0.87 (0.16)	18.7 (4.9)	2.6 (0.8)	21.0 (5.1)	2.9 (0.7)
	19	6 mo	717 (129.0)	89.4 (16.2)			5.4 (1.8)	0.69 (0.23)	18.9 (5.3)	2.4 (0.6)	24.3 (5.4)	3.1 (0.6)
	20	7 mo	805 (176.5)	95.0 (18.1)			5.6 (1.8)	0.66 (0.189)	21.7 (5.3)	2.6 (0.5)	27.3 (5.5)	3.3 (0.5)
	20	8 mo	871 (217.3)	97.4 (23.3)			6.3 (1.6)	0.72 (0.17)	23.4 (4.6)	2.7 (0.5)	29.7 (5.2)	3.4 (0.6)
	19 to 20	9 mo	958 (226.5)	99.1 (38.7)			6.3 (1.8)	0.69 (0.19)	25.7 (3.5)	2.8 (0.4)	32.0 (4.1)	3.5 (0.4)
	18 to 19	10 mo	1018 (315.8)	99.9 (38.7)			7.1 (2.1)	0.75 (0.22)	26.7 (4.9)	2.8 (0.4)	33.8 (6.1)	3.5 (0.6)
	16 to 17	11 mo	985 (243.0)	97.0 (22.9)			7.6 (2.6)	0.77 (0.28)	27.2 (5.3)	2.7 (0.5)	34.9 (6.5)	3.5 (0.6)
	17 to 19	12 mo	1004 (271.5)	101.9 (23.0)			7.0 (2.8)	0.69 (0.30)	27.0 (5.6)	2.7 (0.4)	33.9 (6.6)	3.3 (0.6)
	18 to 20	15 mo	1176 (246.1)	102.1 (33.8)			7.9 (2.6)	0.72 (0.26)	31.3 (6.7)	2.9 (0.5)	39.3 (7.4)	3.6 (0.6)
	20	18 mo	1184 (306.9)	100.0 (28.0)			8.0 (2.7)	0.68 (0.23)	33.5 (7.1)	2.8 (0.6)	41.4 (7.9)	3.5 (0.7)
	19	24 mo	1321 (369.2)	100.4 (30.5)			9.0 (2.8)	0.69 (0.21)	36.0 (5.4)	2.7 (0.4)	45.0 (5.3)	3.4 (0.4)
			<i>Median (range)</i>	<i>Median (range)</i>	N/A		<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>
	7 to 11	4 mo	661 (369-913)	98.3 (58-130)			5.2 (4.4-8.9)	0.70 (0.6-1.1)	14.0 (5.5-23.9)	2.1 (0.8-3.7)	16.9 (10.2-23.9)	2.5 (1.5-3.7)
	7 to 20	5 mo	689 (482-1083)	94.6 (64-141)			6.1 (5.6-10.0)	0.83 (0.7-1.2)	18.0 (6.1-28.4)	2.5 (0.8-4.2)	21.9 (12.0-32.5)	2.9 (1.5-4.2)
	19	6 mo	699 (529-1021)	88.1 (62-133)			5.2 (3.2-9.8)	0.65 (0.4-1.3)	19.6 (10.9-28.1)	2.4 (1.3-3.5)	24.1 (16.5-37.1)	3.0 (1.8-4.1)
	20	7 mo	784 (583-1187)	93.1 (62-127)			5.1 (3.2-10.3)	0.62 (0.4-1.1)	21.0 (11.5-30.3)	2.7 (1.4-3.4)	26.1 (20.5-39.9)	3.3 (2.3-4.3)
20	8 mo	813 (644-1376)	90.4 (59-146)			6.1 (4.5-11.7)	0.66 (0.5-1.2)	23.0 (15.0-32.2)	2.7 (1.6-3.3)	28.8 (21.3-43.9)	3.4 (2.3-4.5)	
19 to 20	9 mo	928 (593-1502)	101.5 (11-153)			6.0 (4.2-10.7)	0.61 (0.5-1.1)	25.1 (19.8-31.8)	2.9 (2.2-3.3)	30.2 (27.1-42.5)	3.5 (2.7-4.4)	
18 to 19	10 mo	1003 (611-1910)	98.5 (60-172)			7.2 (4.2-13.7)	0.75 (0.4-1.4)	26.6 (17.2-35.1)	2.9 (2.0-3.3)	32.7 (22.3-45.5)	3.6 (2.5-4.5)	
16 to 17	11 mo	934 (703-1613)	98.3 (61-138)			7.0 (4.3-15.5)	0.71 (0.4-1.6)	26.5 (18.5-38.0)	2.7 (2.0-3.8)	32.8 (28.4-53.5)	3.4 (2.7-5.4)	
17 to 19	12 mo	952 (621-1756)	106.2 (62-150)			6.1 (4.3-15.5)	0.65 (0.4-1.5)	27.0 (18.6-37.7)	2.7 (2.0-3.7)	33.3 (24.7-53.2)	3.4 (2.6-5.2)	
18 to 20	15 mo	1132 (768-1644)	103.6 (72-153)			7.5 (3.0-15.5)	0.69 (0.3-1.4)	31.8 (20.2-43.7)	2.8 (2.1-4.0)	38.8 (26.8-59.2)	3.4 (2.7-5.4)	
20	18 mo	1161 (596-2014)	96.8 (55-167)			7.6 (5.3-17.5)	0.63 (0.4-1.4)	32.1 (24.6-51.7)	2.7 (1.9-4.2)	40.0 (33.5-61.1)	3.3 (2.3-5.0)	
19	24 mo	1667 (682-1912)	90.3 (54-166)			8.4 (6.0-18.0)	0.66 (0.4-1.3)	36.4 (25.0-46.2)	2.7 (1.9-3.5)	43.4 (34.9-56.8)	3.4 (2.3-4.0)	
Kindt et al., 1983	15	4 mo										<i>Median (range)</i>
	15	6 mo										2.6 (2.1-3.1)
	16	9 mo										2.1 (1.7-2.8)
	16	12 mo	N/A		N/A		N/A		N/A		N/A	2.0 (1.6-2.6)
	16	1.5 y										1.8 (1.5-2.7)
	16	2 y										1.7 (1.3-2.5)
	11	2.5 y										1.6 (1.2-2.4)
												1.6 (1.2-2.3)

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Reference	N	Age	Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
	11	3 y										1.6 (1.2-2.1)
Ponzone et al., 2008	22	2 mo	N/A		<i>Mean (SD)</i> 284.1 (53.8)	N/A	N/A		N/A		N/A	
					<i>Median (range)</i> 280 (220-390)							
Rohde et al., 2015			N/A		<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	N/A		N/A	
	20	1 y			267.0 (59.8)	25.0 (5.1)	6.7 (1.5)	0.6 (0.1)				
	13	2 y			311.9 (166.9)	22.6 (10.8)	7.8 (4.2)	0.6 (0.3)				
	13	3 y			288.8 (96.4)	19.4 (5.5)	7.2 (2.4)	0.5 (0.1)				
	46	0-3 y			285.9 (108.5)	22.7 (7.4)	7.1 (2.7)	0.6 (0.2)				
					<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>				
	20	1 y			250 (190-450)	24.6 (16.9-33.7)	6.3 (4.8-11.3)	0.6 (0.4-0.8)				
	13	2 y			270 (160-800)	19.2 (12.9-54.4)	6.8 (4.0-20.0)	0.5 (0.3-1.4)				
	13	3 y			260 (180-550)	18.2 (13.4-34.4)	6.5 (4.5-13.8)	0.5 (0.3-0.9)				
	46	0-3 y			255 (160-800)	20.4 (12.9-54.4)	6.4 (4.0-20.0)	0.5 (0.3-1.4)				
Thiele et al., 2017			N/A		N/A	N/A	N/A	<i>Mean (SD)</i>	N/A	<i>Mean (SD)</i>	N/A	<i>Mean (SD)</i>
	82	1 y						0.7 (0.2)		1.6 (0.4)		2.3 (0.4)
	90	2 y						0.5 (0.1)		1.6 (0.4)		2.1 (0.4)
	83	3 y						0.5 (0.1)		1.6 (0.7)		2.0 (0.5)

Abbreviations: PKU, phenylketonuria; N, number of patients in the age group; mo, months; y, years; SD, standard deviation; N/A, not available; IQR, inter quartile range; BH4, tetrahydrobiopterin; NP, natural protein; TP, total protein; PS, protein equivalent from protein substitute.

^a Data of BH4 group refers to the baseline intakes of patients who were treated with BH4; diet group includes the baseline and follow-up data of patients who were treated with a phenylalanine restricted diet.

^b The sample size was shown as a range where the number of included patients was different for energy and protein intakes (e.g. due to missing data, loss to follow-up, etc.)

Supplementary Table S2. Actual dietary intakes of PKU patients in late childhood (4-10 years of age).

Reference	N	Age	Dietary intakes									
			Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Aldámiz-Echevarría et al., 2013 ^a	36	BH4 ₁ 5 y				<i>Median (IQR)</i> 29.9 (18.3-52.3)			<i>Median (IQR)</i> 0.9 (0.7-1.2)		<i>Median (IQR)</i> 1.8 (1.0-3.6)	
	10	BH4 ₂ 5 y				<i>Median (IQR)</i> 30.8 (24.6-54.8)			<i>Median (IQR)</i> 0.7 (0.5-1.2)		<i>Median (IQR)</i> 1.7 (1.3-2.2)	
	72	Diet ₁ 5 y	N/A		N/A	<i>Median (IQR)</i> 19.2 (9.3-31.6)	N/A		N/A	<i>Median (IQR)</i> 1.3 (1.0-1.8)	N/A	<i>Median (IQR)</i> 2.0 (1.3-2.4)
		7 y				12.9 (7.9-20.3)			<i>Median (IQR)</i> 1.2 (0.9-1.8)		<i>Median (IQR)</i> 1.4 (1.0-2.4)	
	20	Diet ₂ 5 y				<i>Median (IQR)</i> 9.9 (8.2-21.8)			<i>Median (IQR)</i> 1.5 (1.0-1.7)		<i>Median (IQR)</i> 2.0 (1.6-2.4)	
		10 y				10.9 (8.8-13.7)			<i>Median (IQR)</i> 1.1 (0.8-1.3)		<i>Median (IQR)</i> 1.6 (1.2-1.9)	
Aldámiz-Echevarría et al., 2014	N/A	2-9 y	N/A		N/A	<i>Median (IQR)</i> 15.5 (10.9-20.4)	N/A		N/A	<i>Median (IQR)</i> 1.3 (1.0-1.7)	N/A	<i>Median (IQR)</i> 1.8 (1.4-2.3)
Daly et al., 2019	18	10 y	N/A		N/A		<i>Median (range)</i> 5 (3-30)	N/A	<i>Median (range)</i> 60 (40-80)	N/A	N/A	
Dobbelaere et al., 2003 ^b	20 Phe=15	4.5 y	<i>Mean</i> 1264	<i>Mean (SD)</i> 86 (20)	<i>Mean (SD)</i> 391 (182.8)	<i>Mean (SD)</i> 27 (8.2)	N/A		N/A		<i>Mean</i> 24.5	<i>Mean (SD)</i> 1.67 (0.23)
				<i>Range</i> 61-128	<i>Median (range)</i> 348 (204-768)	<i>Median (range)</i> 26.6 (18.5-42.4)						<i>Range</i> 1.2-2.1
Evans et al., 2017	32	9 y	N/A		N/A		N/A	<i>Median (range)</i> 0.5 (0.18-0.8)	N/A	<i>Median (range)</i> 1.54 (0.8-2.7)	N/A	<i>Median (range)</i> 2.05 (1.0-3.5)
Giovannini et al., 2014	55	9 y	<i>Mean (SD)</i> 1762 (399)	<i>Mean (SD)</i> 60 (4.3)	<i>Mean</i> 398	N/A	<i>Mean</i> 13.2	<i>Mean (SD)</i> 0.5 (0.3)	N/A	<i>Mean (SD)</i> 0.15 (0.47)	<i>Mean</i> 54.2	<i>Mean</i> 1.95

Supplementary Table S2. Actual dietary intakes of PKU patients in late childhood (4-10 years of age)

Reference	N	Age	Dietary intakes									
			Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Gökmen-Özel et al., 2011	14	6 y	<i>Median (range)</i> 1728 (857-3781)	<i>Median (range)</i> 72 (36-160)	<i>Median (range)</i> 390 (190-1310)	<i>Median (range)</i> 17.1 (8-55.5)	<i>Median (range)</i> 7.8 (3.8-26.2)	<i>Median (range)</i> 0.32 (0.2-1.1)	<i>Median (range)</i> 58.1 (37.8-74.5)	<i>Median (range)</i> 2.4 (1.35-3.0)	<i>Median (range)</i> 66.2 (41.6-100.7)	<i>Median (range)</i> 2.78 (1.55-3.99)
Huemer et al., 2007	34	9-10y	N/A	N/A	N/A	N/A	<i>Mean (SD)</i> 0.3 (0.2)	N/A	<i>Mean (SD)</i> 0.9 (0.2)	<i>Mean (SD)</i> 33.7 (10.3)	<i>Mean (SD)</i> 1.2 (0.3)	
							<i>Median (range)</i> 0.24 (0.1-1.1)		<i>Median (range)</i> 0.84 (0.6-1.4)	<i>Median (range)</i> 32.5 (11.3-32.5)	<i>Median (range)</i> 1.1 (0.8-2.4)	
Kindt et al., 1983	10	3.5 y	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	<i>Median (range)</i> 1.5 (1.23-2.0)	
	7	4 y									<i>Median (range)</i> 1.7 (1.5-1.9)	
	7	5 y									<i>Median (range)</i> 1.6 (1.36-1.7)	
	3	6 y									<i>Median (range)</i> 1.5 (1.5-1.5)	
MacDonald et al., 2006	25	6 y	N/A	N/A	<i>Mean (SD)</i> 485 (180)	<i>Mean (SD)</i> 9.7 (3.6)	<i>Mean (SD)</i> 59.4 (9.3)	N/A	N/A	N/A		
					<i>Median (range)</i> 450 (250-1050)	<i>Median (range)</i> 9 (5-21)	<i>Median (range)</i> 60 (40-80)					
Rocha et al., 2012 & 2013	2	4 y	N/A	N/A	N/A	N/A	<i>Mean (SD)</i> 21.30 (13.15)	<i>Mean (SD)</i> 1.13 (0.57)	<i>Mean (SD)</i> 24.51 (0.72)	<i>Mean (SD)</i> 1.36 (0.22)	<i>Mean (SD)</i> 45.81 (12.43)	<i>Mean (SD)</i> 2.49 (0.34)
	4	5 y					<i>Mean (SD)</i> 13.73 (4.89)	<i>Mean (SD)</i> 0.69 (0.17)	<i>Mean (SD)</i> 30.18 (5.69)	<i>Mean (SD)</i> 1.58 (0.47)	<i>Mean (SD)</i> 43.91 (6.18)	<i>Mean (SD)</i> 2.27 (0.47)
	2	6 y					<i>Mean (SD)</i> 31.20 (8.49)	<i>Mean (SD)</i> 1.15 (0.57)	<i>Mean (SD)</i> 33.80 (15.83)	<i>Mean (SD)</i> 1.13 (0.27)	<i>Mean (SD)</i> 65.00 (7.35)	<i>Mean (SD)</i> 2.28 (0.30)
	6	7 y					<i>Mean (SD)</i> 25.02 (11.22)	<i>Mean (SD)</i> 0.94 (0.32)	<i>Mean (SD)</i> 25.52 (6.38)	<i>Mean (SD)</i> 1.04 (0.41)	<i>Mean (SD)</i> 50.53 (7.05)	<i>Mean (SD)</i> 1.99 (0.29)
	5	8 y					<i>Mean (SD)</i> 27.14 (13.07)	<i>Mean (SD)</i> 1.18 (0.71)	<i>Mean (SD)</i> 34.50 (9.23)	<i>Mean (SD)</i> 1.39 (0.26)	<i>Mean (SD)</i> 61.64 (7.71)	<i>Mean (SD)</i> 2.57 (0.57)
	4	9 y					<i>Mean (SD)</i> 24.60 (4.98)	<i>Mean (SD)</i> 0.93 (0.47)	<i>Mean (SD)</i> 27.13 (11.45)	<i>Mean (SD)</i> 0.95 (0.32)	<i>Mean (SD)</i> 51.73 (10.77)	<i>Mean (SD)</i> 1.88 (0.58)
	7	10 y					<i>Mean (SD)</i> 27.64 (12.08)	<i>Mean (SD)</i> 0.88 (0.42)	<i>Mean (SD)</i> 42.30 (7.78)	<i>Mean (SD)</i> 1.34 (0.27)	<i>Mean (SD)</i> 69.94 (8.74)	<i>Mean (SD)</i> 2.22 (0.34)
	30	4-10 y					<i>Mean (SD)</i> 24.87 (10.55)	<i>Mean (SD)</i> 1.00 (0.49)	<i>Mean (SD)</i> 31.61 (10.52)	<i>Mean (SD)</i> 1.24 (0.37)	<i>Mean (SD)</i> 56.49 (12.16)	<i>Mean (SD)</i> 2.24 (0.47)

Supplementary Table S2. Actual dietary intakes of PKU patients in late childhood (4-10 years of age).

Reference	N	Age	Dietary intakes									
			Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
						<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	
	2	4 y:					21.3 (12.0-30.6)	1.13 (0.73-1.53)	24.5 (24.0-25.0)	1.36 (1.44-1.82)	45.8 (37-54.6)	2.49 (2.24-2.73)
	4	5 y:					11.6 (10.7-21.0)	0.68 (0.49-0.91)	30.4 (24.0-36.0)	1.44 (1.40-2.70)	46.6 (34.7-47.8)	2.12 (1.88-2.94)
	2	6 y:					31.2 (25.2-37.2)	1.15 (0.74-1.55)	33.8 (22.6-45.0)	1.13 (1.13-1.59)	65.0 (59.8-70.2)	2.28 (2.06-2.49)
	6	7 y:					21.9 (14.2-38.8)	0.79 (0.68-1.36)	25.5 (18.0-36.0)	1.03 (0.75-1.80)	51.9 (41.6-56.9)	2.01 (1.48-2.35)
	5	8 y:					26.9 (14.8-45.9)	1.12 (0.51-2.24)	34.5 (20.0-45.0)	1.50 (1.17-1.95)	65.9 (48.8-67.5)	2.75 (1.91-3.21)
	4	9 y:					23.0 (20.7-31.8)	0.71 (0.67-1.63)	25.5 (17.9-42.1)	0.97 (0.65-1.58)	50.5 (39.9-66.0)	1.86 (1.21-2.58)
	7	10 y:					20.8 (14.6-44.1)	0.62 (0.55-1.48)	41.7 (30.0-55.0)	1.28 (1.24-2.05)	72.9 (55.6-82.6)	2.22 (1.81-2.75)
	30	4-10 y:					22.0 (10.7-45.9)	0.74 (0.49-2.24)	30.0 (12.5-55.0)	1.32 (0.54-2.25)	56.5 (34.7-82.6)	2.1 (1.21-3.21)
Rohde et al., 2012 & 2014a	14	<i>Initial</i> 6 y	<i>Mean (SD)</i> 1384 (231)		<i>Mean (SD)</i> 335 (72)						<i>Mean (SD)</i> 41 (15)	
					<i>Range</i> 270-480							
	19	<i>FU₁</i> 5.5 y	N/A		<i>Mean (SD)</i> 422 (95)						<i>Mean (SD)</i> 44 (16)	
				N/A	<i>Median (range)</i> 408 (282-713)	N/A	N/A		N/A		<i>Median (range)</i> 42 (22-83)	N/A
	16	<i>FU₂</i> 6 y	N/A		<i>Mean (SD)</i> 413 (101)						<i>Mean (SD)</i> 46 (16)	
					<i>Median (range)</i> 410 (259-695)						<i>Median (range)</i> 45 (27-78)	
Rohde et al., 2015	14	4 y			<i>Mean (SD)</i> 307.5 (68.8)	<i>Mean (SD)</i> 19.0 (4.3)	<i>Mean (SD)</i> 7.7 (1.7)	<i>Mean (SD)</i> 0.5 (1.1)				
	9	5 y			328.3 (87.3)	17.6 (6.2)	8.2 (2.2)	0.4 (0.2)				
	9	6 y			368.9 (186.9)	15.8 (8.3)	9.2 (4.7)	0.4 (0.2)				
	5	7 y	N/A		304.0 (61.9)	13.2 (3.7)	7.6 (1.5)	0.3 (0.1)	N/A		N/A	
	13	8 y			405.0 (150.0)	14.6 (6.9)	10.1 (3.7)	0.4 (0.2)				
	12	9 y			360.4 (94.1)	11.4 (2.8)	9.0 (2.4)	0.3 (0.1)				
	11	10 y			410.0 (133.5)	11.8 (3.4)	10.3 (3.3)	0.3 (0.1)				

Supplementary Table S2. Actual dietary intakes of PKU patients in late childhood (4-10 years of age).

Reference	N	Age	Dietary intakes									
			Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
	73	4-10 y			358.9 (122.5)	14.9 (5.9)	9.0 (3.1)	0.4 (0.2)				
					<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>				
	14	4 y			300 (220-450)	18.6 (12.9-27.8)	7.5 (5.5-11.3)	0.5 (0.3-0.7)				
	9	5 y			300 (240-540)	15.8 (12.2-32.7)	7.5 (6.0-13.5)	0.4 (0.3-0.8)				
	9	6 y			310 (180-700)	12.0 (7.4-33.2)	7.8 (4.5-17.5)	0.3 (0.2-0.8)				
	5	7 y			320 (200-350)	15.2 (7.7-16.4)	8.0 (5.0-8.8)	0.4 (0.2-0.4)				
	13	8 y			350 (240-800)	11.9 (8.8-34.2)	8.8 (6.0-20.0)	0.3 (0.2-0.9)				
	12	9 y			305 (290-600)	10.4 (7.6-15.9)	7.6 (7.3-15.0)	0.3 (0.2-0.4)				
	11	10 y			380 (250-750)	11.2 (7.4-18.0)	9.5 (6.3-18.8)	0.3 (0.2-0.5)				
	73	4-10 y			320 (180-800)	14.0 (7.4-34.2)	8.0 (4.5-20.0)	0.4 (0.2-0.9)				
Schulpis et al., 2013	30	5 y	<i>Mean (SD)</i> 2020 (400)	N/A	N/A		<i>Mean (SD)</i> 9 (1.2)	N/A	N/A		<i>Mean (SD)</i> 70 (18)	N/A
							<i>Mean (SD)</i>		<i>Mean (SD)</i>		<i>Mean (SD)</i>	
	86	4 y					0.4 (0.1)		1.5 (0.4)		1.9 (0.4)	
	83	5 y					0.4 (0.1)		1.4 (0.3)		1.8 (0.4)	
Thiele et al., 2017	86	6 y	N/A		N/A		0.3 (0.1)	N/A	1.4 (0.3)		1.7 (0.4)	
	82	7 y					0.3 (0.1)		1.3 (0.3)	N/A	1.6 (0.3)	
	78	8 y					0.3 (0.1)		1.2 (0.2)		1.5 (0.3)	
	79	9 y					0.3 (0.1)		1.1 (0.3)		1.4 (0.3)	
	75	10 y					0.2 (0.1)		1.0 (0.3)		1.2 (0.3)	
Trefz et al., 2009	39	7 y	N/A		<i>Mean (SD)</i> 480.5 (43.1)	<i>Mean (SD)</i> 16.6 (0.4)	N/A		N/A		N/A	

Abbreviations: PKU, phenylketonuria; N, number of patients in the age group; y, years; SD, standard deviation; N/A, not available; IQR, inter quartile range; BH4, tetrahydrobiopterin; Phe, phenylalanine; FU, follow-up.

^a BH4₁ and BH4₂ groups refer to baseline data (i.e. pre-BH4 treatment) of patients who were followed for 2 y and 5 y, respectively. Diet₁ and Diet₂ groups refer to baseline and follow up data (at 2 y and 5y) of patients who were treated with Phe-restricted diet only.

^b Data on dietary Phe intake was available for 15 patients.

Supplementary Table S3. Actual dietary intakes of PKU patients during adolescence (11-18 years of age).

Reference	N	Age	Dietary intakes									
			Energy	Phenylalanine	Natural protein		Protein equivalent from protein substitute		Total protein			
			<i>kcal/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	
Aldámiz-Echevarría et al., 2014	N/A	9-12 y 12-18 y	N/A	N/A	<i>Median (IQR)</i> 8.6 (7.0-11.3) 7.6 (5.4-10.3)	N/A	<i>Median (IQR)</i> 0.3 (0.2-0.5) 0.3 (0.2-0.5)	N/A	<i>Median (IQR)</i> 1.2 (0.9-1.4) 1.0 (0.7-1.3)	N/A	<i>Median (IQR)</i> 1.2 (1.0-1.7) 1.1 (1.0-1.4)	
Alm et al., 1986	18	12y	N/A	N/A	<i>Mean (SD)</i> >47.3 (30.1) <i>Median (range)</i> 25 (20 to >80)	N/A		N/A		N/A		
Daly et al., 2017 ^a	21 21 21	11 y 11.5 y Total	<i>Range</i> 1624-1689 1630-1690 N/A	N/A		<i>Range</i> 9.0-10.8 9.8-10 <i>Median (range)</i> 5 (3-30)	N/A	N/A N/A <i>Median (range)</i> 60 (60-80)	N/A	N/A	N/A	
Pinto et al., 2019	40	17 y	<i>Median (IQR)</i> 2365 (2202-2575) 43.5 kcal/kg/day	<i>Median</i> 1900	<i>Median (IQR)</i> 35 (20.9-53.1)	<i>Median (IQR)</i> 35 (24-70.3)	<i>Median (IQR)</i> 0.7 (0.42-1.06)	<i>Median (IQR)</i> 44.8 (24-55)	<i>Median (IQR)</i> 0.82 (0.48-1.04)	N/A		
Rocha et al., 2012 & 2013	8	11 y				<i>Mean (SD)</i> 31.41 (13.29)	<i>Mean (SD)</i> 0.75 (0.33)	<i>Mean (SD)</i> 52.45 (16.04)	<i>Mean (SD)</i> 1.27 (0.46)	<i>Mean (SD)</i> 83.87 (18.0)	<i>Mean (SD)</i> 2.03 (0.60)	
	2	12 y				19.35 (3.89)	0.34 (0.01)	66.61 (11.61)	1.17 (0.07)	85.96 (15.5)	1.50 (0.08)	
	3	13 y				30.47 (15.10)	0.72 (0.46)	55.94 (7.70)	1.22 (0.17)	86.40 (8.37)	1.94 (0.57)	
	1	14 y				37.80 (0.00)	0.65 (0.00)	38.51 (0.00)	0.66 (0.00)	76.31 (0.00)	1.30 (0.00)	
	6	15 y				22.32 (6.16)	0.41 (0.10)	53.31 (19.49)	0.99 (0.37)	75.63 (16.9)	1.39 (0.30)	
	7	16 y				29.15 (14.30)	0.46 (0.23)	54.44 (19.45)	0.84 (0.27)	83.59 (20.9)	1.30 (0.31)	
	2	17 y	N/A	N/A		22.60 (3.82)	0.41 (0.05)	71.10 (12.40)	1.30 (0.16)	93.70 (16.2)	1.71 (0.22)	
	3	18 y				18.77 (2.87)	0.29 (0.03)	65.62 (3.44)	1.03 (0.08)	84.38 (3.31)	1.32 (0.05)	
	32	11-18 y				26.83 (11.34)	0.53 (0.28)	56.23 (15.89)	1.07 (0.35)	83.06 (15.7)	1.60 (0.49)	
						<i>Median (range)</i> 28.0 (16.5-57.4)	<i>Median(range)</i> 0.69 (0.40-1.30)	<i>Median (range)</i> 53.81 (19.6-74.3)	<i>Median(range)</i> 1.24 (0.49-2.17)	<i>Median (range)</i> 80.6 (54.7-113.4)	<i>Median (range)</i> 1.91 (1.14-3.00)	
		8	11 y				19.4 (16.6-22.1)	0.34 (0.33-0.35)	66.61 (58.4-74.8)	1.17 (1.34-1.46)	86.0 (75.0-96.9)	1.50 (1.45-1.56)
		2	12 y				26.0 (18.1-47.3)	0.65 (0.29-1.21)	55.00 (48.7-64.1)	1.25 (1.25-1.65)	82.2 (81.0-96.1)	2.03 (1.34-2.46)

Supplementary Table S3. Actual dietary intakes of PKU patients during adolescence (11-18 years of age).

Reference	N	Age	Dietary intakes								
			Energy	Phenylalanine	Natural protein		Protein equivalent from protein substitute		Total protein		
			<i>kcal/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
	1	14 y				37.8 (-)	0.65 (-)	38.51 (-)	0.66 (-)	76.3 (-)	1.30 (-)
	6	15 y				23.5 (14.3-30.3)	0.39 (0.29-0.55)	59.03 (14.8-68.7)	1.08 (0.32-1.58)	78.6 (45.1-92.6)	1.45 (0.81-1.64)
	7	16 y				26.7 (15.8-56.2)	0.45 (0.21-0.86)	62.79 (17.7-69.7)	0.92 (0.35-1.25)	85.7 (55.1-122.3)	1.22 (0.91-1.88)
	2	17 y				22.6 (19.9-25.3)	0.41 (0.37-0.45)	71.10 (62.3-79.8)	1.30 (1.42-1.70)	93.7 (82.2-105.2)	1.71 (1.56-1.87)
	3	18 y				18.4 (16.1-21.8)	0.28 (0.27-0.33)	65.00 (62.5-69.3)	1.06 (1.12-1.30)	84.3 (81.1-87.7)	1.34 (1.26-1.35)
	32	11-18 y				23.45 (14.3-57.4)	0.45 (0.21-1.30)	61.67 (14.8-79.9)	1.07 (0.27-1.81)	82.2 (45.1-122.3)	1.47 (0.81-3.00)
Rohde et al., 2015				<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>				
	4	11 y		350.0 (147.2)	9.07 (2.20)	8.75 (3.68)	0.23 (0.05)				
	7	12 y		453.6 (148.7)	8.82 (2.86)	11.34 (3.72)	0.22 80.07)				
	11	13 y		387.3 (164.4)	10.8 (5.36)	9.68 (4.11)	0.27 (0.13)				
	2	14 y		595.0 (219.2)	11.13 (1.10)	14.88 (5.48)	0.28 (0.03)				
	6	15 y		501.7 (165.6)	7.92 (2.13)	12.54 (4.14)	0.20 (0.05)				
	30	11-15 y		434.5 (164.8)	9.56 (3.80)	10.86 (4.12)	0.24 (0.09)				
			N/A					N/A		N/A	
				<i>Median (range)</i>	<i>Median (range)</i>	<i>Median (range)</i>	<i>Median(range)</i>				
	4	11 y		325 (200-550)	9.87 (5.83-10.71)	8.13 (5.00-13.75)	0.25 (0.15-0.27)				
	7	12 y		450 (300-750)	8.57 (5.18-12.72)	11.25 (7.5-18.75)	0.21 (0.13-0.32)				
	11	13 y		320 (190-650)	9.47 (4.09-20.97)	8.00 (4.75-16.25)	0.24 (0.10-0.52)				
	2	14 y		595 (440-750)	11.1 (10.35-11.9)	14.9 (11.0-18.75)	0.28 (0.26-0.30)				
	6	15 y		450 (350-750)	7.22 (6.25-11.95)	11.3 (8.75-18.75)	0.18 (0.16-0.30)				
	30	11-15 y		420 (190-750)	9.03 (4.09-20.97)	10.5 (4.75-18.75)	0.23 (0.10-0.52)				
Thiele et al., 2017						<i>Mean (SD)</i>		<i>Mean (SD)</i>		<i>Mean (SD)</i>	
	70	11 y				0.2 (0.1)		1.0 (0.3)		1.2 (0.3)	
	70	12 y				0.2 (0.1)		1.0 (0.3)		1.1 (0.3)	
	67	13 y				0.2 (0.1)		0.9 (0.2)		1.1 (0.3)	
	65	14 y	N/A	N/A		0.2 (0.1)	N/A	0.9 (0.2)	N/A	1.1 (0.2)	
	58	15 y				0.2 (0.1)		0.9 (0.2)		1.0 (0.2)	
	53	16 y				0.2 (0.1)		0.9 (0.2)		1.0 (0.2)	
	53	17 y				0.2 (0.1)		0.8 (0.1)		1.0 (0.2)	
	47	18 y				0.2 (0.1)		0.8 (0.1)		1.0 (0.1)	

Abbreviations: PKU, phenylketonuria; N, number of patients in the age group; y, years; SD, standard deviation; N/A, not available; IQR, inter quartile range.

^a In the original article, there were two study groups based on the type of protein substitute used; 1) GMP group prescribed with glycomacropeptides ; 2) AAM group using amino acid mixtures as the protein substitute. Range on energy (kcal/day) and natural protein intakes refer to the mean range of intakes of both groups.

Supplementary Table S4. Actual dietary intakes of adult PKU patients (>18 years of age).

Reference	N	Age	Dietary Intakes									
			Energy		Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>kcal/day</i>	<i>kcal/kg/day</i>	<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Green et al., 2019	16	29.5 y	<i>Mean (SD)</i> 1813 (445)	<i>Mean</i> 25.5	N/A		<i>Mean (SD)</i> 18.3 (7.7)	<i>Mean</i> 0.3	<i>Mean (SD)</i> 58.6 (10.2)	<i>Mean</i> 0.8	<i>Mean (SD)</i> 76.9 (13.4)	<i>Mean</i> 1.1
Rohde et al., 2014b	41	24 y	<i>Mean (SD)</i> 1967 (593.6)	<i>Mean (SD)</i> 31 (12.3)	<i>Mean (SD)</i> 1424 (711.3)	<i>Mean (SD)</i> 23 (13.1)	<i>Mean (SD)</i> 36 (18.1)	<i>Mean (SD)</i> 0.56 (0.31)	<i>Mean (SD)</i> 41 (16.2)	<i>Mean (SD)</i> 0.64 (0.26)	<i>Mean (SD)</i> 77 (21.6)	<i>Mean (SD)</i> 1.2 (0.36)
			<i>Median (range)</i> 1916 (857-3579)	<i>Median (range)</i> 30 (14-67)	<i>Median (range)</i> 1160 (618-3055)	<i>Median (range)</i> 19 (8-74)	<i>Median (range)</i> 28 (15-80)	<i>Median (range)</i> 0.46 (0.23-1.74)	<i>Median (range)</i> 43 (5-70)	<i>Median (range)</i> 0.62 (0.07-1.24)	<i>Median (range)</i> 79 (30-133)	<i>Median (range)</i> 1.15 (0.42-2.29)
							<i>Mean (SD)</i> 33.62 (24.86)	<i>Mean (SD)</i> 0.54 (0.36)	<i>Mean (SD)</i> 53.6 (19.11)	<i>Mean (SD)</i> 0.89 (0.34)	<i>Mean (SD)</i> 86.7 (1.44)	<i>Mean (SD)</i> 1.44 (0.35)
Rocha et al., 2012 & 2013	25	22 y	N/A		N/A		<i>Median (range)</i> 23.7 (12.6-104.2)	<i>Median (range)</i> 0.42 (0.24-1.77)	<i>Median (range)</i> 57.6 (9.33-89.4)	<i>Median (range)</i> 0.95 (0.17-1.46)	<i>Median (range)</i> 80.4 (38.1-141.4)	<i>Median (range)</i> 1.37 (0.68-2.27)

Abbreviations: PKU, phenylketonuria; N, number of patients in the age group; mo, months; y, years; SD, standard deviation; N/A, not available.

Supplementary Table S5. Dietary prescriptions of the patients with PKU in the included studies.

Reference	N	Age	Dietary prescriptions							
			Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			mg/day	mg/kg/day	g/day	g/kg/day	g/day	g/kg/day	g/day	g/kg/day
Evans et al., 2018	7	3 mo	N/A		Median (range)	Median (range)	Median	Median	Median (range)	Median (range)
	19	4 mo		4 (3-5)	0.6 (0.4-0.8)	12	1.9	16 (15-18)	2.5 (1.8-2.8)	
	24	5 mo		4 (3-8)	0.6 (0.4-1.0)	14	2.2	19 (11-25)	2.7 (1.3-3.7)	
	30	6 mo		4 (3-8)	0.6 (0.4-0.9)	17	2.4	21 (17-27)	2.9 (2.2-4.1)	
	31	7 mo		4 (3-8)	0.5 (0.3-1.0)	20	2.5	23 (13-29)	3.0 (2.1-4.2)	
	31	8 mo		4 (3-8)	0.5 (0.3-1.0)	22	2.8	26 (17-33)	3.2 (2.3-4.2)	
	31	9 mo		4 (3-8)	0.5 (0.3-1.0)	24	2.9	27 (18-34)	3.3 (2.6-4.2)	
	31	10 mo		4 (3-8)	0.5 (0.3-1.0)	25	3.0	29 (21-34)	3.3 (2.7-3.9)	
	31	11 mo		4 (3-8)	0.4 (0.3-1.0)	27	3.0	30 (23-35)	3.3 (2.6-4.0)	
	31	12 mo		4 (3-8)	0.4 (0.3-1.0)	28	3.0	30 (23-40)	3.3 (2.4-4.0)	
	31	13 mo		4 (3-9)	0.4 (0.3-1.0)	30	3.1	31 (23-50)	3.3 (2.4-4.3)	
	31	14 mo		4 (3-8)	0.4 (0.3-1.0)	32	3.2	32 (23-45)	3.3 (2.7-4.2)	
	31	15 mo		4 (3-11)	0.4 (0.3-1.0)	32	3.2	33 (26-47)	3.3 (2.6-4.2)	
	31	16 mo		4 (3-11)	0.4 (0.2-1.0)	34	3.1	34 (26-45)	3.3 (2.6-4.2)	
	31	17 mo		4 (3-11)	0.4 (0.2-1.0)	33	3.2	34 (26-45)	3.2 (2.4-3.7)	
	31	18 mo		4 (3-11)	0.4 (0.2-1.0)	34	3.2	34 (27-45)	3.2 (2.4-3.7)	
	31	19 mo		4 (3-11)	0.4 (0.2-1.0)	35	3.2	35 (29-45)	3.2 (2.4-3.7)	
	30	20 mo		4 (3-11)	0.4 (0.2-1.0)	37	3.3	35 (29-45)	3.2 (2.4-3.7)	
	30	21 mo		4 (3-11)	0.4 (0.2-1.0)	38	3.3	36 (29-46)	3.2 (2.4-3.8)	
	29	22 mo		4 (3-11)	0.4 (0.2-1.0)	37	3.4	37 (29-46)	3.3 (2.5-3.7)	
	29	23 mo		4 (3-11)	0.4 (0.2-1.0)	39	3.4	37 (29-46)	3.2 (2.5-3.7)	
	29	24 mo		4 (3-11)	0.4 (0.2-0.9)	37	3.2	37 (29-46)	3.2 (2.5-3.7)	
	Evers et al., 2018					Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
BH4: 18 ^b		11.2 y			0.41 (0.21)		1.05 (0.47)		1.46 (0.68)	
Diet: 19		13.0 y		9.50 (9.96)	0.35 (0.26)	40.80 (20.91)	0.98 (0.31)	50.30 (30.87)	1.33 (0.57)	
Diet: 17		18.0 y		14.98 (10.00)	0.25 (1.17)	54.30 (16.96)	0.91 (0.29)	69.28 (26.96)	1.16 (1.46)	
				Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	Median (range)	
BH4: 18		11.2 y			0.38 (0.15-0.94)		0.96 (0.18-1.94)		1.34	
Diet: 19		12.0 y			0.28 (0.08-0.98)	40.80 (14.20-85.40)	1.00 (0.43-1.52)	50.30	1.28	
				9.50 (5.20-35.0)	0.19 (0.07-0.63)	60.00 (18.0-80.0)	0.96 (0.31-1.45)	70.50	1.15	

Supplementary Table S5. Dietary prescriptions of the patients with PKU in the included studies.

Reference	N	Age	Dietary prescriptions							
			Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
					10.50 (6.0-35.0)					
Ferguson et al., 1996	12	9-15 y	<i>Mean (SD)</i> 373.3 (40.4) <i>Median (range)</i> 350 (350-420)	N/A		N/A		N/A		N/A
Gökmen-Özel et al., 2011	14	6 y	<i>Mean (range)</i> 250 (150-1500)	<i>Mean (range)</i> 10.4 (6.3-62.5)		N/A		N/A		N/A
Green et al., 2019	16	29.5 y		N/A		N/A	<i>Mean (SD)</i> 59 (9) Median (range) 60 (40-80)	<i>Mean</i> 0.84 Median 0.84		N/A
MacDonald et al., 1996	2	0-1 y			<i>Mean (SD)</i> 5.0 (2.83)					<i>Mean (SD)</i> 3.0 (N/A)
	8	2-5 y			3.8 (0.85)					2.5 (N/A)
	5	6-10 y			6.8 (3.91)					2.0 (N/A)
	4	11 y <	N/A		12.8 (3.77)	N/A		N/A	N/A	1.5 (N/A)
	19	Total			6.6 (4.30)					2.2 (0.5)
		median age: 4y			<i>Median (range)</i> 5.0 (3-17)					<i>Median (range)</i> 2.5 (1.5-3.0)
MacDonald et al., 2003	9	2-5 y			<i>Mean (SD)</i> 5.9 (3.3)					<i>Mean (SD)</i> 2.5 (N/A)
	7	6-11 y			6.3 (1.4)					2.0 (N/A)
	16	Total	N/A		6.1 (2.6)	N/A		N/A	N/A	2.3 (0.3)
		median age: 4.5y			<i>Median (range)</i> 6.0 (3-14)					<i>Median (range)</i> 2.5 (2.0-2.5)

Supplementary Table S5. Dietary prescriptions of the patients with PKU in the included studies.

Reference	N	Age	Dietary prescriptions							
			Phenylalanine		Natural protein		Protein equivalent from protein substitute		Total protein	
			<i>mg/day</i>	<i>mg/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>	<i>g/day</i>	<i>g/kg/day</i>
Wendel et al., 1990	137 ^a	6 mo	<i>Mean (SD)</i>	<i>Mean (SD)</i>						
	138	1 y	251 (46)	34 (7)						
	135	1.5 y	262 (52)	28 (7)						
	137	1.5 y	275 (56)	26 (6)						<i>Mean (SD)</i>
	105	2 y	276 (56)	23 (5)						2.26 (0.47)
	98	2.5 y	N/A	22 (5)						2.17 (0.42)
	98	3 y	N/A	21 (5)	N/A		N/A		N/A	2.20 (0.40)
	96	3.5 y	N/A	19 (5)						2.20 (0.38)
	89	4 y	N/A	18 (5)						N/A
	78	4.5 y	N/A	18 (5)						
	65	5 y	N/A	17 (5)						
	55	5.5 y	N/A	16 (4)						
	52	6 y	N/A	15 (5)						
van Spronsen et al., 2009	58	6 mo	<i>Mean (SD)</i>	<i>Mean (SD)</i>						
	59	6 mo	253 (85)	35 (13)						
	59	1 y	280 (66)	29 (7)						
	57	2 y	316 (106)	26 (9)	N/A		N/A		N/A	
	56	3 y	359 (171)	25 (11)						
	59	5 y	386 (170)	21 (9)						
	N/A	10 y	431 (178)	14 (6)						

Abbreviations: PKU, phenylketonuria; N, number of patients in the age group; mo, months; y, years; SD, standard deviation; N/A, not available. ^a The number of patients for total protein intake at 6 months was 136. ^bThere were two cohorts in this study: 1) sapropterin -treated group (N=21), and 2) diet-only treated group (N=19). Only data at baseline (pre- sapropterin treatment) were included in the analysis in the sapropterin -treated group.