Quantifying dietary intake variation in phenylketonuria: implications for clinical trial design

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Introduction

- Dietary intake variation directly influences biochemical markers used to assess drug efficacy.
- In the general population, within-subject dietary intake variation averages ~25%, though this differs by nutrient.[1-4]
- No prior studies have evaluated dietary intake variation in phenylketonuria (PKU).
- It remains unknown if dietary intake variation impacts blood Phenylalanine (Phe).

Objectives

Primary aim:

Assess within– and between–subject variation in dietary intake among females with PKU.

Secondary aims:

1. Compare within-subject dietary intake variation between treatment groups (diet only, sapropterin, or pegvaliase).
2. Assess whether within-subject dietary intake variation is associated with blood Phe.

Methods

Participants

Females diagnosed with PKU (n = 117; ages 12 – 59 years, median = 18 years) who attended the Emory Metabolic Camp between 2013 – 2025.

Dietary assessment method

Three-day diet records were collected immediately prior to the camp, and blood Phe was measured on day 1 to reflect recent dietary intake.

Calculation of dietary intake variation

Within-subject coefficient of variation (CV_w)

$$CV_w = \frac{SD}{mean} * 100$$

Between-subject coefficient of variation (CV_b)

$$CV_b = \frac{SD_b}{group\ mean} * 100$$

Statistical analysis

Kruskal-Wallis and post-hoc Dunn tests were used to test for differences in CV_w between groups. Linear mixed-effects models were used to assess the relationship between CV_w and blood Phe.

Results

Table 1. Median (IQR) daily intakes and blood Phe concentrations by treatment*

	Overall n=117	Diet only n=58	Sapropterin n=51	Pegvaliase n=8
Energy, kcal	1474.8 (1223.9, 1831.6)	1479.6 (1228.0, 1749.8)	1427.6 (1126.8, 1881.7)	1436.0 (1386.4, 1626.9)
Carbohydrate, g	204.5 (170.3, 255.8)	211.8 (175.2, 255.5)	203.3 (164.9, 268.2)	185.3 (161.5, 204.3)
Fat, g	47.1 (35.2, 63.7)	45.0 (35.2, 56.3)	50.1 (35.6, 66.0)	59.8 (39.4, 71.0)
Total pro, g	56.9 (43.1, 69.7)	57.3 (40.8, 68.7)	55.5 (42.6, 66.9)	73.4 (67.6, 86.9)
Intact pro, g	15.1 (9.5, 27.6)	11.5 (8.0, 20.6)	19.7 (11.1, 28.6)	52.8 (29.2, 66.3)
Medical food pro, g	36.0 (10.0, 54.0)	39.5 (20.5, 55.4)	27.0 (1.4, 45.4)	21.7 (0.0, 38.5)
Dietary Phe, mg	622.0 (393.0, 1056.0)	469.0 (345.5, 827.8)	847.0 (448.5, 1202.5)	2562.0 (1303.5, 2874.0)
Blood Phe concentration, µmol/L	529.0 (315.5, 942.3)	709.0 (447.0, 995.0)	391.2 (264.1, 715.0)	197.5 (27.0, 476.0)

*Dietary intakes are presented as median (IQR).

Figure 1. Within- and between-subject CVs by nutrient in the overall cohort

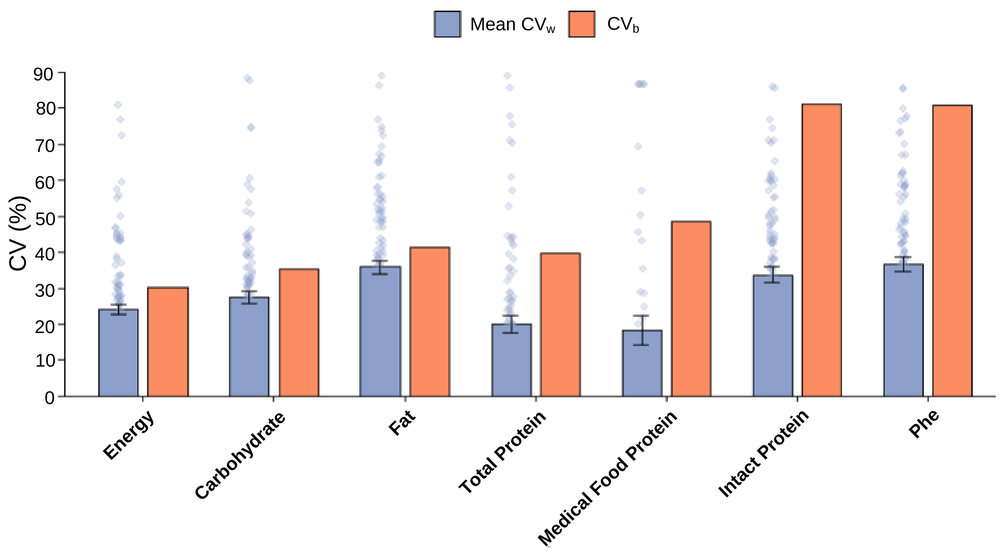
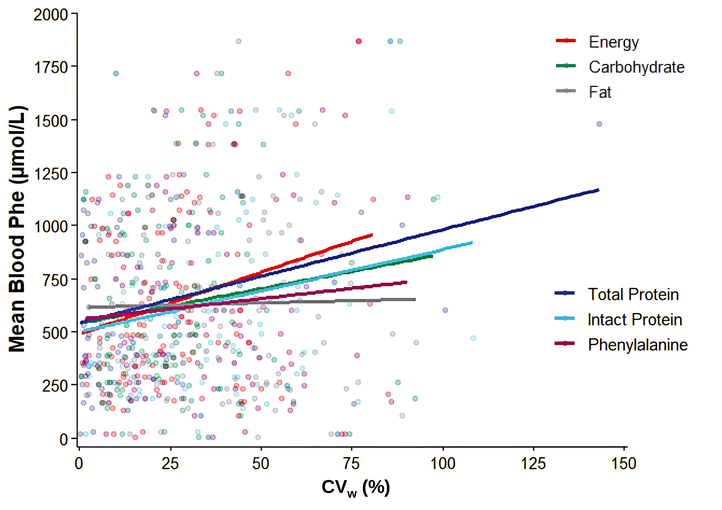


Table 2. Within- and between-subject CVs and their ratios by treatment*

	Overall			Diet only			Sapropterin			Pegvaliase		
	CV_w (%)	CV_b (%)	$\frac{CV_w}{CV_b}$	CV_w (%)	CV_b (%)	$\frac{CV_w}{CV_b}$	CV_w (%)	CV_b (%)	$\frac{CV_w}{CV_b}$	CV_w (%)	CV_b (%)	$\frac{CV_w}{CV_b}$
Energy	24.08 ± 16.17	30.12	0.80	22.60 ± 15.03	29.92	0.76	25.39 ± 17.84	32.4	0.78	26.43 ± 13.65	14.06	1.88
Carbohydrate	27.56 ± 19.29	35.22	0.78	27.14 ± 17.39	32.07	0.85	27.30 ± 21.88	39.74	0.69	32.31 ± 16.07	21.17	1.53
Fat	35.94 ± 20.04	41.34	0.87	32.24 ± 19.43	42.45	0.76	38.46 ± 20.00	39.55	0.97	46.62 ± 20.83	43.94	1.06
Total protein	20.01 ± 24.01	39.76	0.5	17.94 ± 24.14	40.91	0.44	22.49 ± 25.06	39.14	0.57	19.14 ± 15.38	25.3	0.76
Intact protein	**33.77 ± 22.10**	81.08	0.42	**36.28 ± 23.83**	86.39	0.42	**31.91 ± 19.91**	65.7	0.49	**27.42 ± 22.78**	58.95	0.47
Medical food protein	18.32 ± 40.47	48.51	0.38	16.65 ± 36.56	43.86	0.38	19.47 ± 46.02	51.65	0.38	25.95 ± 38.71	72.9	0.36
Dietary Phe	**36.63 ± 20.81**	80.99	0.45	**38.88 ± 21.69**	79.35	0.49	**34.84 ± 19.11**	66.63	0.52	**31.72 ± 25.37**	54.32	0.58

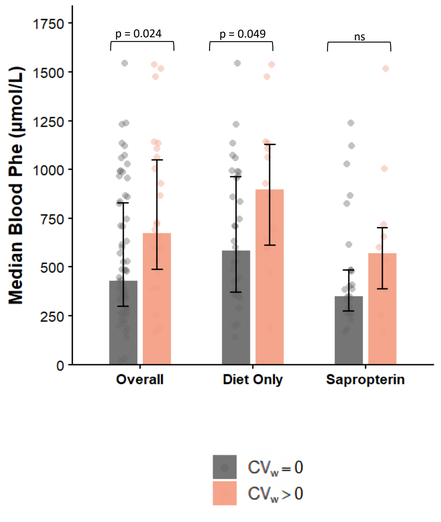
*CV_w are presented as mean ± SD. Kruskal-Wallis tests indicated no significant differences in CV_w between treatment groups.

Figure 2. Higher within-subject variation in energy, total protein, and intact protein intake was associated with higher blood Phe



Energy	Carbohydrate	Fat	Total Protein	Intact Protein	Phe
Adj R^2 = 0.04	Adj R^2 = 0.07	Adj R2 = 0.05	Adj R^2 = 0.10	Adj R^2 = 0.09	Adj R^2 = 0.06
β = 5.92	β = 2.92	β = -0.12	β = 3.64	β = 3.37	β = 2.04
P = 0.012	P = 0.131	P = 0.947	P = 0.021	P = 0.045	P = 0.262

Figure 3. Median blood Phe is higher in individuals with any variation in medical food protein intake in the overall cohort and diet only group



Conclusion

- Dietary intake variation was substantial in PKU and was nutrient dependent.
- Within-subject variation was not significantly different between treatment groups.
- Greater variability in energy and total, intact, and medical food protein was associated with higher blood Phe, highlighting the potential for dietary variation to confound drug efficacy assessment.
- Standardizing and monitoring dietary intake variation in PKU clinical trials is recommended to improve dietary consistency and reduce confounding.

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