

Dietary protein intake variability in individuals with phenylketonuria: Analysis of baseline PRISM data

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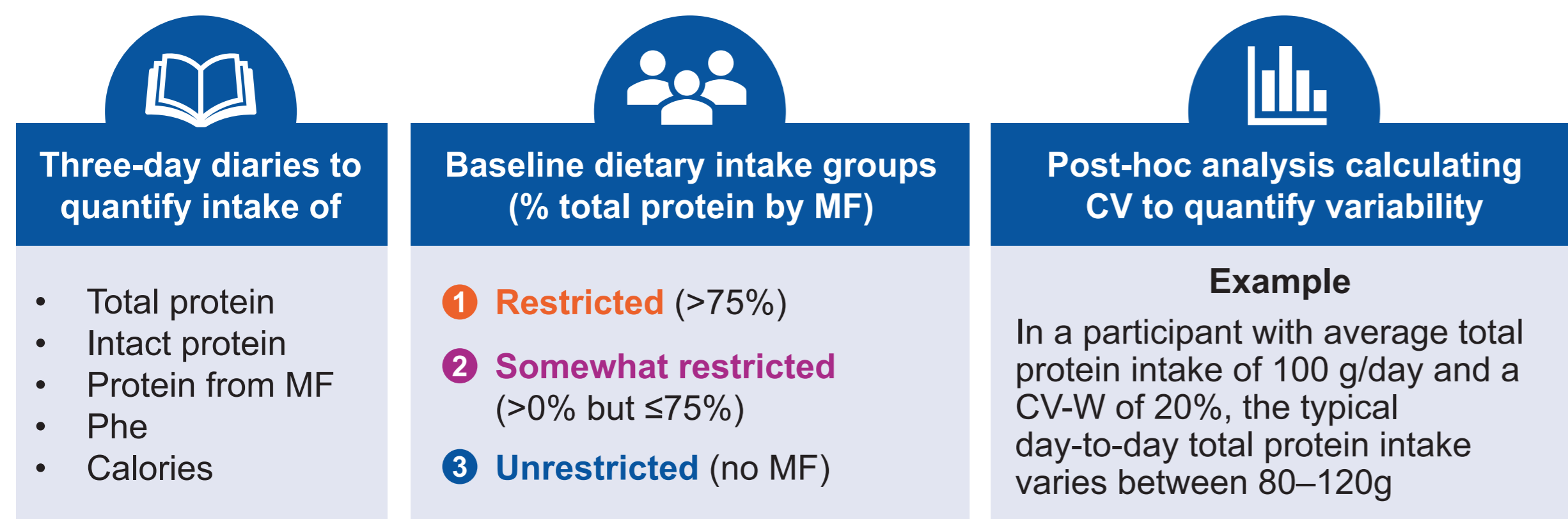
Background & Objective

- Phenylketonuria (PKU) is an autosomal recessive condition characterized by chronic elevation of phenylalanine (Phe) in the blood, requiring lifelong management¹
- Dietary Phe restriction has historically been used to control blood Phe by limiting intact protein intake, with required protein needs supplied by specialized medical food²
- However, diet directly impacts biomarkers used to assess drug efficacy (eg, Phe) in clinical trials for inborn errors of metabolism (IEMs), thereby complicating the interpretation of the drug's effect on disease outcomes³
- Therefore, the Food and Drug Administration (FDA) provides guidance on maintaining diet stability and defining allowable deviations in protein intake in clinical trials⁴
- Currently, the GMDI working group is reviewing literature and working to publish best practice recommendations for implementing FDA guidance on diet stability
- The objective of this analysis is to describe the day-to-day variability of dietary protein intake within and between individuals with PKU from a large phase 3 program at study entry

Methods

- PRISM (NCT01819727, NCT01889862, NCT03694353) was a phase 3 clinical trial program designed to evaluate the safety and efficacy of pegvaliase, enrolling participants with PKU and elevated blood Phe, irrespective of their degree of dietary Phe restriction⁵
- Three-day diet diaries were collected at baseline and throughout the study to quantify protein intake (Figure 1). Participants were to maintain a stable dietary intake (within ± 10% of baseline) unless instructed differently by the research dietitian or principal investigator
- Participants were categorized into 3 groups according to their baseline dietary intake, which was defined by the proportion of total protein contributed by medical food (MF) (Figure 1)
- In this post-hoc analysis, both within- and between-subject coefficients of variation (CV) were calculated for each dietary parameter to quantify variability in baseline dietary intake

Figure 1. Overview of methods



Results

- Baseline diet diaries were collected for a total of 250 participants (Figure 2)
- Overall, the mean (± SD) age of participants was 29.1 (± 8.7) years, and mean (± SD) BMI was 28.4 (± 6.7) kg/m². Participants were predominantly non-Hispanic and white
- Demographics and baseline characteristics are shown in Table 1

Figure 2. Diet of participants with baseline diet diary

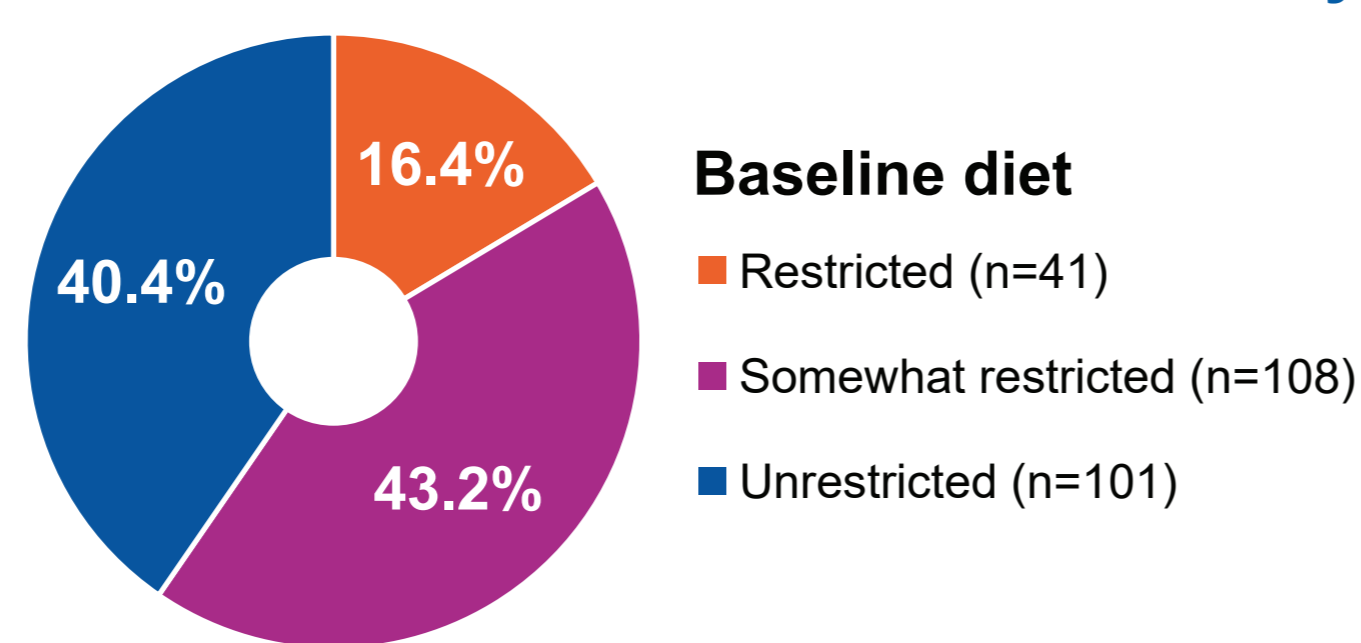
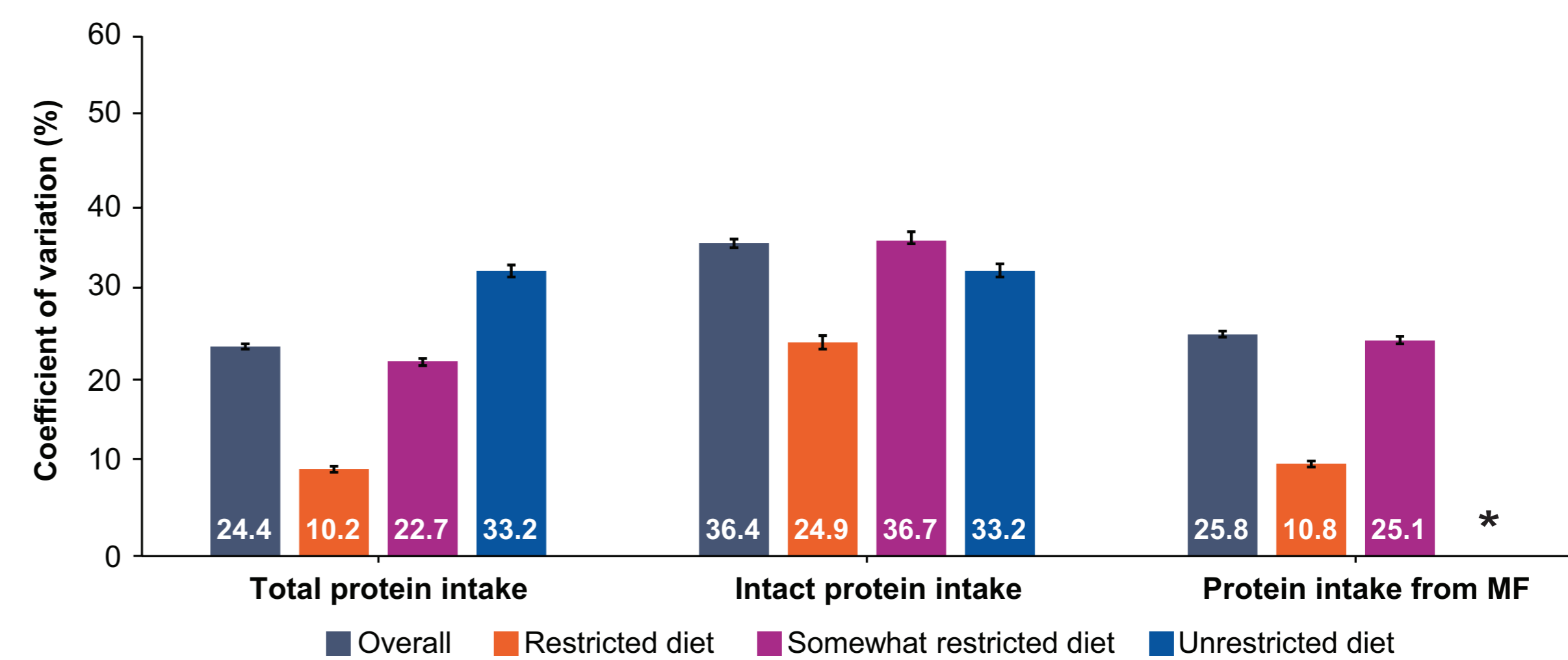


Table 1. Baseline demographics

Baseline diet	Restricted n=41	Somewhat restricted n=108	Unrestricted n=101
General characteristics			
Age, y, mean ± SD	26 ± 9.4	28.6 ± 8.3	30.9 ± 8.4
Age range, y, min-max	16–51	16–55	16–52
Gender, n (%)			
Female	23 (56.1)	47 (43.5)	53 (52.5)
Male	18 (43.9)	61 (56.5)	48 (47.5)
BMI, kg/m ² , mean ± SD	26.3 ± 6.3	27.8 ± 6.4	30 ± 7.0
Dietary intake, mean ± SD			
Average total protein, g/day	76.6 ± 20.4	69.6 ± 34.8	53.0 ± 31.0
Average intact protein, g/day	14.3 ± 5.7	32.9 ± 20.5	53.0 ± 31.0
Average MF protein, g/day	62.3 ± 16.0	36.7 ± 22.9	0.0 ± 0.0
Average Phe, mg/day	658 ± 285.3	1394.6 ± 746.6	2374.9 ± 1356.8
Average kcal/day	1707.5 ± 481.5	1913.1 ± 762.4	1844.4 ± 699.3

- Average within-subject CV (CV-W) was lowest in participants with the most restricted diets for both total (10.2%) and intact protein (24.9%) intake (Figure 3)
- The CV-W was highest for total protein intake in participants with an unrestricted diet (33.2%), while the CV-W of intact protein intake was higher in participants with a somewhat restricted diet (36.7%)

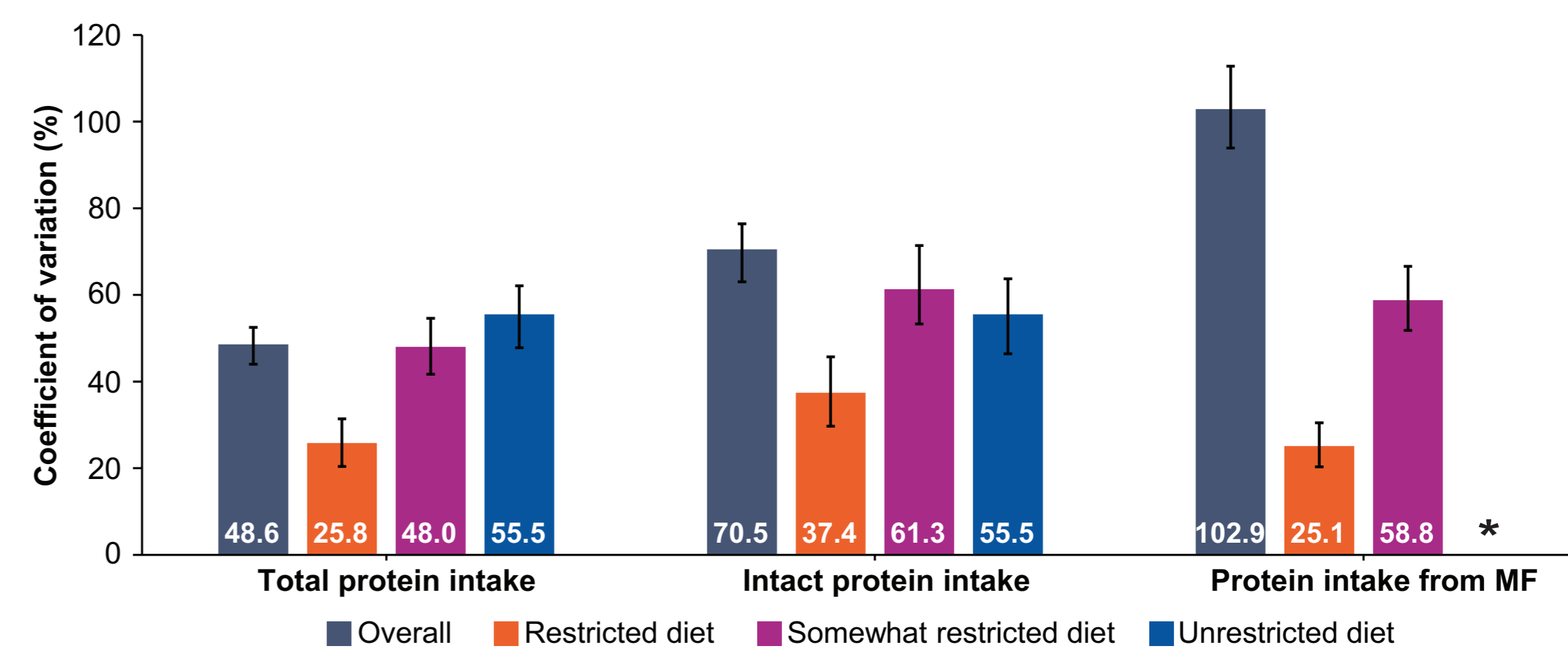
Figure 3. Average within-subject CV (CV-W) by baseline diet group



* CV-W is not applicable for protein intake from MF in the unrestricted diet group, as patients in this group consume no MF. Error bars represent 95% confidence intervals

- Average between-subject CV (CV-B) was lowest in participants with the most restricted diets for both total (25.8%) and intact protein intake (37.4%) (Figure 4)
- The CV-B was highest for total protein intake in participants with an unrestricted diet (55.5%), while the CV-B of intact protein intake was higher in participants with a somewhat restricted diet (61.3%)

Figure 4. Average between-subject CV (CV-B) by baseline diet group



* CV-B is not applicable for protein intake from MF in the unrestricted diet group, as patients in this group consume no MF. Error bars represent 95% confidence intervals

Conclusions

- Analysis of this large data set provides insight into the variability of protein intake in individuals with PKU (age 16–55 years old)
- Day-to-day within-subject CV was highest among individuals with an unrestricted diet, followed by those with a somewhat restricted diet
- Between-subject CV followed similar trends, with generally higher variability than within-subject CV across all groups
- In participants with an unrestricted diet, the observed variability in both within-and between-subject CV is driven solely by their intake of intact protein
- Future research should explore strategies to reduce the burden of dietary intake capture while improving accuracy in clinical trials, including novel approaches such as food photography and other cell phone/app-based reporting tools

Practice Implications

- This analysis provides a reference for protein intake variability within and between individuals with PKU (16–55 years), with varying degrees of protein restriction, which may be used to determine appropriate allowable variation and assist in the evaluation of alternative and novel strategies to collect dietary intake information in the clinical trial setting

References

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Disclosures

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Abbreviations

BMI: body mass index; CI: confidence interval; CV: coefficient of variation; CV-B: between-subject coefficient of variation; CV-W: within-subject coefficient of variation; FDA: Food and Drug Administration; GMDI: Genetic Metabolic Dietitians International; IEM: inborn errors of metabolism; MF: medical food; Phe: phenylalanine; PKU: phenylketonuria; SD: standard deviation

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