

# Longitudinal Study of Body Composition and Metabolic Factors in Adults with Phenylketonuria Treated with Pegvaliase

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## Background

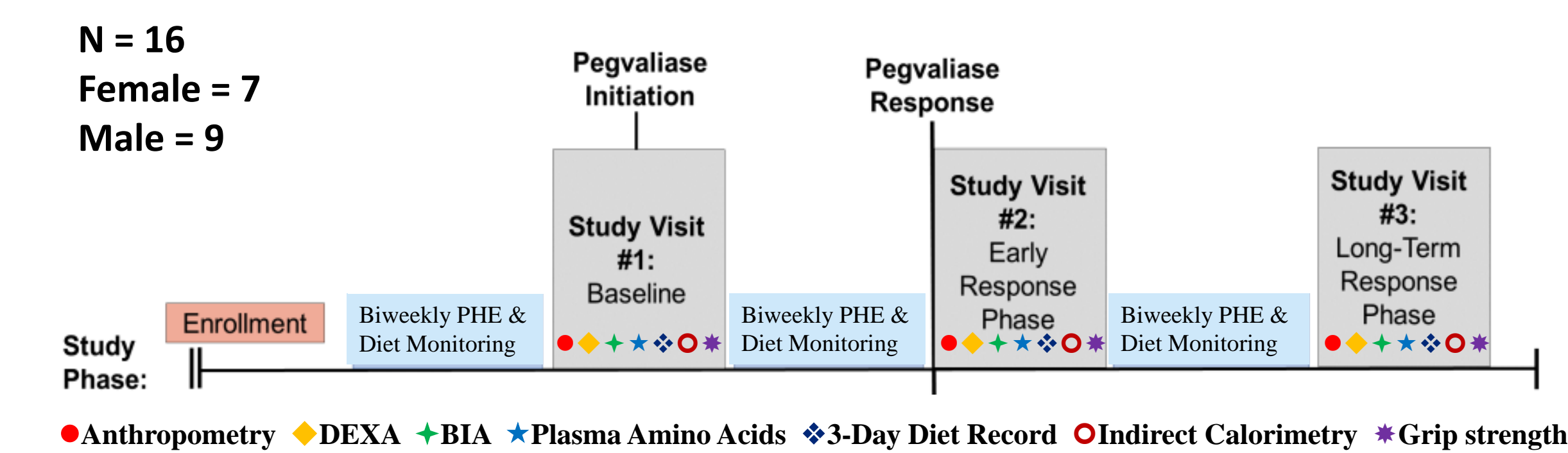
- PKU requires lifelong protein restriction, impacting body composition and lean mass.
- Pegvaliase enables normalization of dietary protein intake in adults with PKU.
- Its effects on body composition; however, remain incompletely characterized.
- This interim analysis compares baseline with one-year post-response data and provides an early longitudinal view of body composition change after pegvaliase response.

## Objectives

- Evaluate how total and intact protein intake, plasma phenylalanine (Phe), physical activity, and sex relate to lean mass, adiposity, and other body composition outcomes one year after pegvaliase response.
- Hypothesis:** Adults with PKU treated with pegvaliase will increase protein tolerance, maintain or improve blood Phe control, and show favorable body composition changes.

## Methods

Figure 1. Study Protocol Design



### Measurements of Interest:

#### Body composition (DEXA)

- Fat-Free Mass Index (FFMI)
- Fat Mass Index (FMI)
- Android/Gynoid (A/G) fat ratio

#### Diet analysis (Metabolic pro)

- Protein intake

#### Biomarker

- Plasma Phenylalanine (Plasma Amino acid)

#### Physical activity

- Physical activity assessed using adapted BodyStat questionnaire and categorized into low, moderate, and high activity levels

#### Statistical analysis

- Paired comparisons were used to assess changes from baseline to post-response
- Linear mixed-effects models evaluated predictors of FFMI over time
- Models adjusted for protein intake and physical activity to assess independent effects

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## Results

Figure 3. Sex-Specific Changes in Diet Protein Intake, Plasma Phe, and Body Composition After Pegvaliase Response

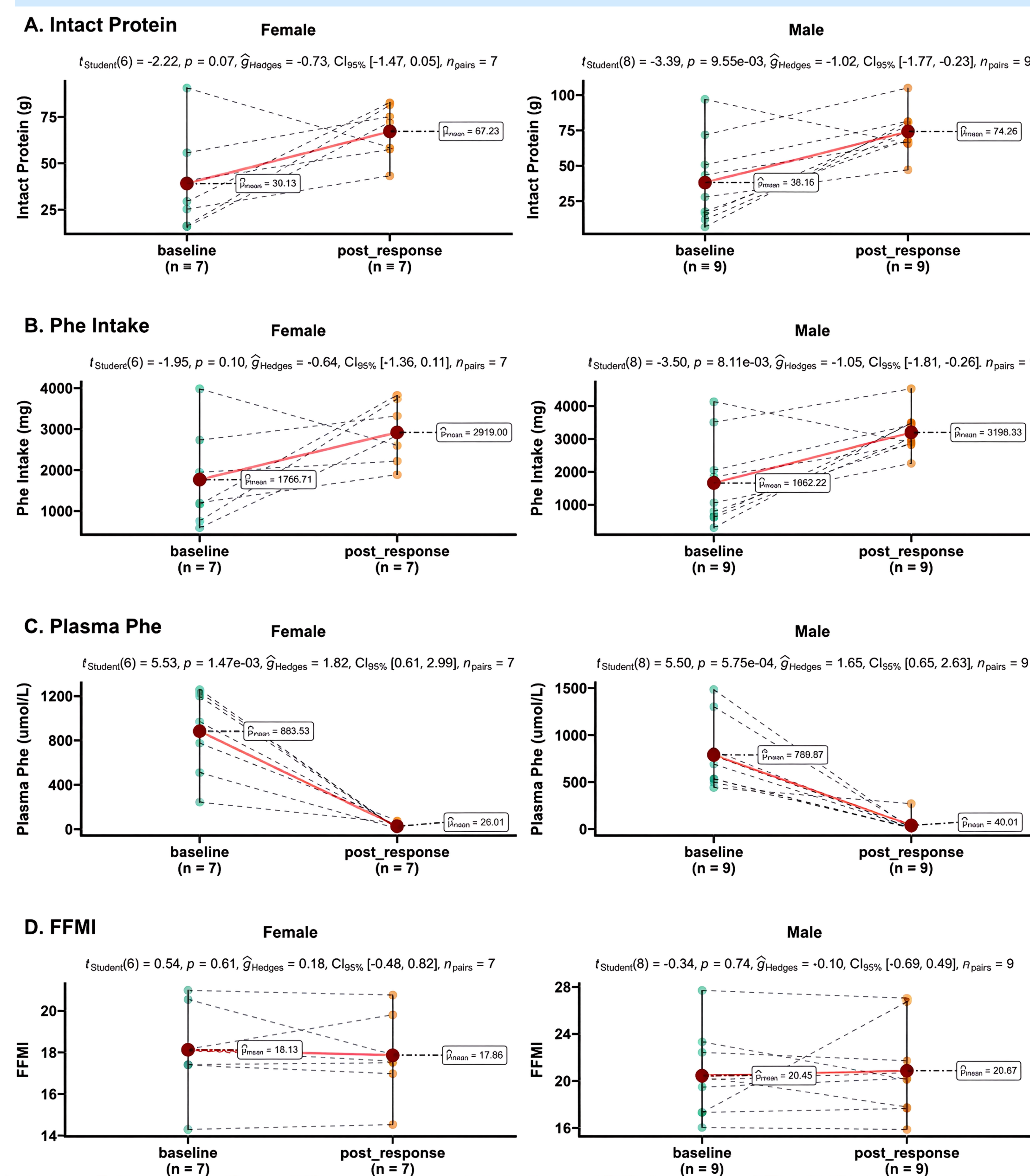


Figure 4. Dietary Factors, Not Plasma Phe Alone, Are Associated with FFMI

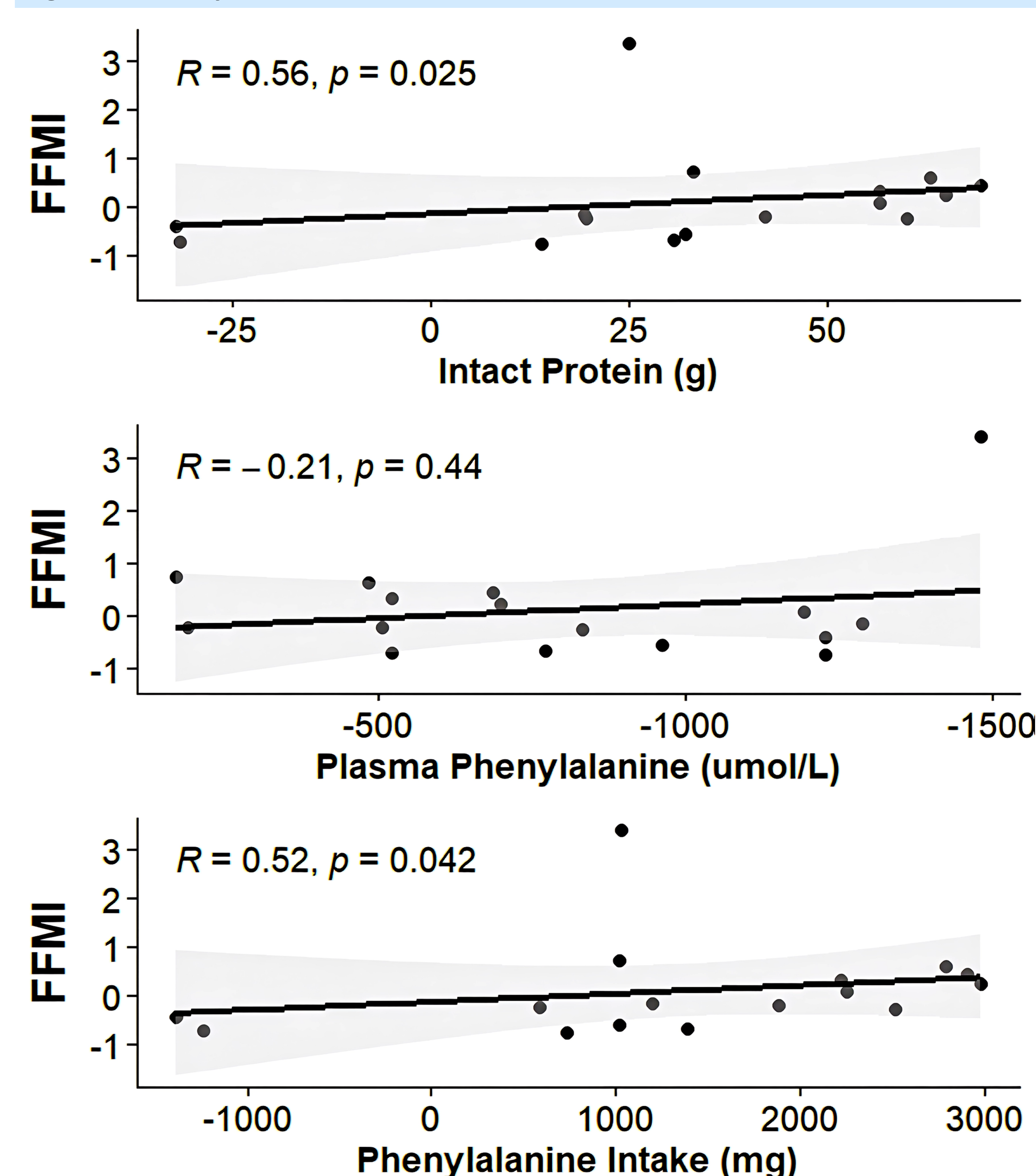


Table 1. Protein intake increased substantially without weight gain, accompanied by improved FFMI and favorable fat distribution, with distinct sex-specific mechanisms

Changes in Body Composition and Metabolic Measures (Baseline → One-Year Post Response)

Measure	Overall Change	Females	Males
Protein Intake	↑↑↑ 84%*	↑↑↑ 72%*	↑↑↑ 95%*
Weight	No change	Stable	Stable
FFMI (kg/m <sup>2</sup> )	↑ +0.34 Improved	Stable (↓ FM)	↑ +0.3†
Fat Mass (FMI)	↓ Trend	↓↓	↑ slightly
A/G Ratio	↓ Reduced (Improved distribution)	↓ Reduced (Significant improvement)*	No significant change
Plasma Phe	↓↓↓*	↓↓↓*	↓↓↓*

Magnitude suffixes indicate change intensity: ↑/↓ (≤1%), ↑↑/↓↓ (≤5%), ↑↑↑/↓↓↓ (≤50%)

\* Statistical significance defined as p-value < 0.05.

† Clinically significant and consistent with non-PKU literature on protein intake and body composition.

### Determinants of FFMI (Multivariate Model)

Predictor	Direction of association	p-value
Protein intake ↑	↑ Higher FFMI	0.016
Physical activity ↑	↑ Higher FFMI	0.010
Lower Phenylalanine	↓ Phe → Higher FFMI	0.007

Context-dependent; not independently associated with FFMI in multivariable model

- Intact protein intake increased by 84% after pegvaliase response ( $p < 0.001$ ) without weight gain.
- Higher FFMI was associated with greater intact protein intake ( $p = 0.016$ ), medium activity ( $p = 0.010$ ), and lower plasma Phe in the multivariable model ( $p = 0.007$ ).
- Phe alone was not significantly correlated with FFMI. Its effect depends on protein intake and physical activity (multivariable model)
- Sex-stratified trends were favorable: females showed improved fat distribution, while males showed modest net FFMI-mass accrual.

## Conclusions

- Pegvaliase-associated dietary normalization was accompanied by a favorable shift in body composition.
- Leads to clinically meaningful body composition remodeling, even in severe PKU
- Demonstrates that metabolic control alone is insufficient → Optimal outcomes require alignment of diet, activity, and Phe reduction
- These findings support the importance of protein intake and metabolic control for lean-mass preservation in adults with PKU.

**Optimizing body composition in PKU requires more than metabolic control—it requires diet and lifestyle alignment**