

Development and Validation of a Simple Equation to Evaluate Dietary Protein Intake Using the Blood Urea Nitrogen/Serum Creatinine Ratio in Patients With Stage 3 Chronic Kidney Disease

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Abstract

Background: A simple, effective and convenient method to assess dietary protein intake (DPI) for chronic kidney disease (CKD) patients is urgently needed in clinical practice. We developed a simple equation to evaluate DPI in patients with stage 3 CKD with the blood urea nitrogen (BUN)/serum creatinine (SCr) ratio (BUN/SCr).

Methods: In a prospective cohort of 136 inpatients with stage 3 CKD from 2 centres, we developed estimation equations based on BUN/SCr and the spot urinary urea nitrogen (UUN)/urinary creatinine (UCr) ratio (UUN/UCr) in combination with sex and body mass index (BMI). These equations were then internally and externally validated.

Results: The following candidate parameters were derived from univariate regression analysis for 5 established models: sex, BMI, BUN/SCr, UUN and UUN/UCr. Sex and BMI were included in all models after variable evaluation using multiple regression analysis. UUN, UUN/UCr and BUN/SCr were included in model 3, model 4 and model 5, respectively. Both internal validation and external validation indicated that model 5 resulted in the lowest values of bias and root mean square error and the highest P_{30} compared with model 3 and model 4. Therefore, the model 5 equation, $DPI = -5.18 (-14.49 \text{ if the patient is female}) + 1.89 \times BMI + 1.38 \times BUN/SCr$, was selected because of the higher correlation [$r = 0.498$ (95% confidence interval 0.163, 0.719)] and the smaller distribution of the difference between the predicted and measured protein intakes than those of the other models.

Conclusion: The DPI equation developed using BUN/SCr, sex and BMI may be used to estimate protein intake for patients with stage 3 CKD.

Trial registration

Chinese Clinical Trial Registry Center (ChiCTR-ROC-17011363). Registered in 11 May 2017, Retrospectively registered, <http://www.chictr.org.cn/index.aspx>

Background

Dietary interventions, including dietary protein intake (DPI) restriction, can slow chronic kidney disease (CKD) progression and the onset of symptoms in the early stages and may delay the need for kidney replacement therapy in advanced stages [1-3]. In clinical practice, the DPI target of 0.6-0.8 g/kg/day is frequently recommended to patients with CKD regardless of aetiology [4]. While clinical judgement, patient preference, and adherence are key points in the application and practical implementation of dietary protein restriction, regular, simple, and easy monitoring of DPI is essential for ongoing nutritional education, improvements in compliance and the evaluation of the potential risk of protein-energy wasting in patients on a low-protein diet (LPD) [4]. Clinically, several methods, such as 24-hour dietary recall, diet records and diaries (with or without dietary interviews), urea dynamic calculated protein intake, and food frequency questionnaires, have been used to assess DPI for patients with CKD [5, 6]. However, the accuracy of these methods is inevitably affected by factors such as patient memory, understanding, and cooperation and investigator communication skills. Twenty-four-hour urine collection to measure urinary urea nitrogen (UUN) is a reliable method to estimate DPI. Maroni's formula is thus the most used tool for evaluating DPI in many clinical trials [7-9]. However, the collection of 24-hour urine samples is not convenient for outpatients. Furthermore, due to the decline in renal function and the decrease in urine volume and the secretion of urinary urea nitrogen in advanced CKD, the accuracy and feasibility of Maroni's formula are questioned. Therefore, a simple, effective and convenient method to assess DPI for CKD patients is urgently needed.

A previous study has shown that the random UUN/urinary creatinine (UCr) ratio (UUN/UCr) can be used as an indicator of protein intake [10]. Another study has also shown that the blood urea nitrogen (BUN)/serum creatinine (SCr) ratio (BUN/SCr) exhibited a good linear relationship with DPI ($r=0.94$) and concluded that BUN/SCr may be used as an assessment of protein intake in patients with stable end-stage renal disease [11]. Considering the differences in the excretion rates of creatinine and urea nitrogen in urine in patients at different stages of CKD, we prospectively enrolled patients with stage 3 CKD to develop a simple equation to assess DPI using BUN/SCr and spot UUN/UCr.

Methods

Study population

We screened 148 hospitalized patients with stage 3 CKD in the Division of Nephrology of Guangdong Provincial People's Hospital and the Division of Nephrology of the First Affiliated Hospital of Wenzhou Medical University from March 2017 to November 2018. CKD was diagnosed by the National Kidney Foundation (NKF) Kidney Disease Outcomes Quality Initiative (K/DOQI) clinical practice guidelines [12]. Stage 3 of CKD is defined as an estimated glomerular filtration rate (eGFR) greater than or equal to 30 ml/min/1.73 m² and less than 60

ml/min/1.73 m². eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[13]. Patients aged <18 or >70 years; patients with acute kidney injury, malnutrition, hypovolemia, gastrointestinal bleeding, malignant tumours, intestinal absorption dysfunction, infection, serum albumin < 30 g/L, or 24-h urinary protein > 3.5 g/day; patients receiving corticosteroids; and patients unwilling to receive an LPD were excluded from the study. Patients with missing values or poor diet compliance were also excluded. The remaining 136 patients completed the LPD programme. Ninety-six patients were randomized into 2 groups to obtain a developmental dataset to develop DPI estimation models and an internal validation dataset to validate the DPI estimation models, and 40 patients were used as an external validation cohort to validate the DPI estimation models.

LPD prescription

The nutritional status of all the enrolled patients was assessed by dietitians before and after a 7-day personalized LPD programme. Patients were prescribed a protein intake of 0.6~0.8 g/kg/day, an energy intake of 30~35 kcal/kg/day, a salt intake of 5~6 g/day, a phosphorus intake of 800~1000 mg/day, and a calcium intake less than 1500 mg (including meals and drugs) [2, 14, 15]. Cooks prepared the food for each individual patient following the dietitians' prescriptions.

Data collection

Patient demographic characteristics and biochemical parameters, including name, age, sex, body mass index (BMI), BUN, SCr, serum albumin, C-reactive protein (CRP), spot UUN and UCr, haemoglobin, 24-h UUN (24hUUN), 24-h urinary protein and causes of renal disease, were collected. These parameters were examined before and after a 7-day LPD. Dietary protein intake was calculated using Maroni's formula [8]: DPI (g/day)=6.25×(0.031×Body weight in kg)24hUUN (g/day).

Statistical analysis

The data analysis was conducted following a procedure of data description, model building and model validation. First, n/n, the median (interquartile range) or the mean ± the standard deviation were used as appropriate to describe variables. Characteristics that were compared between the training group and the testing group were analysed with the chi-square test, Mann-Whitney U test or t test. Second, regression models were built with measured DPI as the dependent variable and demographic variables and blood and urine indexes as independent variables. For each independent variable, we bootstrapped the univariate linear regression coefficient 1000 times within the training dataset to obtain the mean and 95% confidence interval (CI), and we selected those variables whose 95% CI did not include 0 as candidates for multiple regression. The three candidate variable groups were defined as follows: one group contained only demographic variables and blood test indexes, one group contained only demographic variables and urine test indexes, and the last group contained demographic variables and both blood and urine indexes. Then, multiple regression models were built based on each candidate variable group, and statistical inferences were made on the basis of coefficients by bootstrapping in the same way as in the univariate model. The number of variables was reduced in a backward pattern by removing variables with a 95% CI that included 0 until all coefficients were statistically significant. If there was collinearity in a model, the backward model selection procedure was restarted with all subgroups of non-collinear candidate variables instead. Third, the final models from the training dataset were applied to the test dataset, and Pearson's correlation coefficient and the difference between the predicted DPI and the measured DPI was calculated. Statistical analysis was conducted using R statistical software (R Development Core Team; <http://R-project.org>). P < 0.05 was considered statistically significant.

Results

Baseline characteristics

As shown in Figure 1, we screened 148 inpatients with stage 3 CKD. Twelve patients dropped out for the reasons depicted within the figure, and 136 patients successfully completed the experiment. Sixty-four patients were enrolled in the developmental dataset, 32 patients were enrolled in the internal validation dataset and 40 patients were enrolled in the external validation dataset.

The demographic and biochemical characteristics of the enrolled patients are summarized in Table 1. There was no statistically significant difference between the patients in the developmental dataset and those in the internal validation dataset. Significant differences in sex, albumin, BUN, BUN/SCr, UUN, UCr and UUN/UCr were found between the developmental and internal validation datasets combined and the external validation dataset.

Development and validation of models

With a univariate regression analysis, we selected the following candidate parameters for the equation evaluation models: sex, BMI, BUN/SCr, UUN and UUN/UCr ($p < 0.05$) (Table 2). Five models were developed, as shown in Table 5. Sex and BMI were included in all 5 models after variable evaluation using the multiple regression models ($p < 0.01$). For each individual, model 1 included BUN/SCr and UUN/UCr, and model 2 included BUN/SCr and spot UUN. However, UUN/UCr and spot UUN were not significant ($p > 0.05$) in model 1 and model 2; therefore, they were not considered in the final models. Model 3 included sex, BMI and spot UUN. Model 4 included sex, BMI and UUN/UCr. Model 5 included sex, BMI and BUN/SCr. Spot UUN, UUN/UCr and BUN/SCr were statistically significant in the 3 models. Finally, model 3, model 4 and model 5 were chosen as candidate models for further validation.

Then, we compared the ability of candidate models to predict DPI. In the internal validation dataset, model 5 showed the highest correlation between the predicted DPI and the measured DPI, $r = 0.489$ (95% CI 0.163,0.719); followed by model 3, $r = 0.396$ (95% CI 0.049,0.658); and model 4, $r = 0.437$ (95% CI 0.098,0.685). Furthermore, model 3, model 4 and model 5 showed correlations [$r = 0.811$ (95% CI 0.668, 0.896); 0.844 (95% CI 0.722, 0.915); 0.786 (95% CI 0.628, 0.882), respectively] between the predicted DPI and the measured DPI in the external validation dataset (Figure 2).

Both internal validation and external validation indicated that the model 5 equation yielded the lowest median difference (bias) and root mean square error (RMSE) and the highest P_{30} compared with model 3 and model 4 (Table 4).

We compared the performances of the three equations (Table 4) for predicting DPI. The adjusted R^2 values were 0.408, 0.425 and 0.436 in models 3, 4 and 5, respectively, and the maximum R^2 value was shown in model 5 (Table 2).

Therefore, the model 5 equation showed the best performance and was accepted to estimate the DPI for patients with stage 3 CKD. The equation was as follows:

$$\text{DPI (g/day)} = -5.18 \text{ (-14.49 if the patient is female)} + 1.89 \times \text{BMI} + 1.38 \times \text{BUN/SCr}$$

(BMI, kg/m^2 ; BUN, mg/dl; SCr mg/dl).

Discussion

LPD is frequently recommended for adults with moderate to advanced CKD regardless of aetiology [16-18]. In clinical practice, the safety of and adherence to an LPD are not regularly evaluated because the current methods to assess DPI are not convenient or reliable for patients or clinicians. Thus, a simple and convenient equation to estimate DPI is needed to follow and instruct CKD patients who are required to undergo dietary protein restriction. In this prospective study, we showed that UUN/UCr, BUN/SCr, UUN, sex, and BMI exhibited strong relationships with the DPI values calculated by Maroni's formula in patients with stage 3 CKD. We developed 5 equations to predict DPI using various combinations of these indexes, and we validated an equation incorporating the variables sex, BMI and BUN/SCr to estimate DPI in patients with stage 3 CKD.

The most accurate technique for measuring nitrogen intake is the analysis of a duplicate diet in a metabolic unit. Previously, 24-h pooled urine and spot UUN concentrations were demonstrated to reflect dietary protein intake to some extent, and these variables are applicable to estimate DPI in patients regardless of renal function [19]. One study showed that the estimation of 24hUUN from a nocturnal spot sample is too inaccurate for routine clinical practice [20]. The concentration of urea nitrogen is definitely affected by renal function, including GFR, and the secretion and absorption of tubular epithelial cells. Another study suggested that UUN/UCr can be used to accurately calculate urinary urea excretion for the previous 24-h period [19]. Creatinine and/or potassium adjustment may be helpful to reduce errors in the measurement of UUN, but this method is still questionable if the patient's daily urine volume is less than 1500 ml.

In contrast, the BUN level reflected protein intake [19] if conditions such as malnutrition, hypovolemia, gastrointestinal bleeding, malignant tumours, intestinal absorption dysfunction, or infection were excluded. BUN/SCr is relatively reliable for reflecting the accumulation of urea nitrogen in patients regardless of renal function, and it is easy to collect samples for BUN/SCr analysis. Because BUN/SCr varies physiologically with renal function, age, sex and BMI, the available demographic and renal function data should be considered when BUN/SCr is used to estimate DPI.

Several strengths of this study are to be noted. First, we applied a prospective cohort design. Subjects were enrolled from two centres, and all of them were inpatients. Second, all the patients were limited to a specific population of patients with stage 3 CKD who presented relatively stable urine volume, which enabled the collection of 24-h pooled urine to perform the analyses because UUN excretion will decrease as renal function decreases [21]. Third, the application of internal and external validations ensures that our estimated DPI equation is reliable. Finally, with the available demographic data, such as sex and BMI, and the results of urea nitrogen and SCr, which can

be obtained using the same serum sample, the current estimated DPI equation would be more convenient for use in outpatients in clinical practice.

There were several limitations in this study. First, we focused only on patients with stage 3 CKD in this study, and the prediction equation was not tested in patients with stage 4~5 CKD. Whether the established equation is suitable for patients with stage 4~5 CKD needs to be further verified. In addition, we used the bootstrap method to develop models due to the small sample size, and there was selection bias in the models. Finally, instead of the most accurate technique for measuring nitrogen intake by the analysis of a duplicate diet in a metabolic unit, we used Maroni's formula, which had obvious limitations itself, to calculate the DPI. Thus, a longitudinal observation of the relation between DPI and BUN/SCr needs to be performed in a larger sample.

Conclusions

This study provides a new equation to estimate DPI using easily obtained parameters such as BUN/SCr, sex and BMI. The new equation may be widely used in clinical practice to monitor DPI and evaluate the nutrition status of patients with stage 3 CKD.

Abbreviations

BMI: body mass index; BUN: blood urea nitrogen; BUN/SCr: blood urea nitrogen/serum creatinine; CI, confidence interval; CRP: C-reactive protein; DPI, dietary protein intake; eGFR: estimated glomerular filtration rate; IQR, interquartile range; SCr: serum creatinine; UCr: urinary creatine; UUN: urinary urea nitrogen; UUN/UCr: urinary urea nitrogen/ urinary creatine.

Declarations

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Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Authors' contributions

YHW, ZJC, JL and WJW analyzed the data, edited all tables, prepared all figures, and wrote the manuscript. WJW, YHW and JTX designed the study. ZL and DW made LPD prescription and completed patients diet education. QLL, YFZ and SGZ gave various opinions in their interpretations of the study results. SL, TTL, XQQ, CFQ and SCL collected the data. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved. All authors have read and approved the manuscript.

Ethics approval and consent

This study was approved by the medical ethics committee of Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences and the First Affiliated Hospital of Wenzhou Medical University and conducted according to the principles of the Declaration of Helsinki. Informed consent was obtained from every patient as specified in the recommendations of the International Committee of Medical Journal Editors (ICMJE).

Consent for publication

The authors agree to publication of this article in BMC Nephrology.

Competing interests

The authors declare that they have no competing interests.

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Tables

Table 1. Demographic and biochemical characteristics of enrolled patients.

	Developmental dataset (n=64)	Internal validation dataset (n=32)	External validation dataset (n=40)	P*
Sex (male/female)	48/16	25/7	16/24	<0.001
Age (years)	48.2±12.3	49.4±12.1	50.1±9.1	0.452
BMI	24.1±3.1	24±2.3	23.3±3.1	0.187
eGFR (ml/min.1.73 m ²)	47.9±13.3	44.6±12.1	44.5±8.3	0.217
Cause of renal disease n (%)				0.123
Glomerulonephritis	36 (56.3)	22 (68.8)	26 (65.0)	
Diabetes	12 (18.8)	4 (12.5)	2 (5.0)	
Hypertension	8 (12.5)	3 (9.4)	3 (7.5)	
Others	8 (12.5)	3 (9.4)	9 (22.5)	
Albumin (g/L)	38.3±4.2	38.4±4.1	42.1±3.1	<0.001
CRP (mg/L)	2.7 (2.8)	2.3 (1.9)	2.7 (2.1)	0.439
Haemoglobin (g/L)	128.1±20.3	127.9±15.3	126.1±17.3	0.561
SCr (mg/dl)	1.6 (0.4)	1.7 (0.7)	1.5 (0.5)	0.124
BUN (mg/dl)	17.7 (6.1)	18.5 (8.1)	20.9 (8.4)	0.005
BUN/SCr	11.2±2.6	11.4±1.9	14±3.5	<0.001
UCr (mg/dl)	98.4 (79.9)	92.8 (87.1)	129.6 (84.1)	<0.001
UUN (mg/dl)	394.8 (319.2)	456.4 (251.3)	569.4 (119.8)	<0.001
UUN/UCr	4.4±1.2	4.7±1.0	4.5±1.6	0.96
Proteinuria (g/24 h)	0.7 (1.5)	1 (0.9)	0.9 (0.2)	0.841
Protein intake (g/day)	52.1±11.8	54±10.8	51.7±9.8	0.615
Protein intake/weight (g/kg/day)	0.8 (0.2)	0.8 (0.2)	0.9 (0.2)	0.02
Values are the mean ± the standard deviation, the median (IQR) or n/n.				
*For comparison of the combined development and internal validation dataset vs. the external validating dataset.				
BMI, body mass index; eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; SCr, serum creatinine; BUN, blood urea nitrogen; UCr, urinary creatinine; UUN, urinary urea nitrogen; BUN/SCr, blood urea nitrogen/serum creatinine ratio; UUN/UCr urinary urea nitrogen/urinary creatinine ratio; IQR, interquartile range.				

Table 2. Dietary protein intake estimation model

Variables	Univariate regression model		Model 1		Model 2		Model 3		Model 4		Model 5	
	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p	coef (95% CI)	p
Intercept			-5.59 (-23.74, 11.78)	0.484	-5.89 (-22.92, 11.20)	0.448	0.85 (-15.87, 16.47)	0.901	3.16 (-13.61, 18.12)	0.643	-5.18 (-21.10, 11.92)	0.537
Female	-8.82 (-14.32, -3.68)	<0.001	-14.18 (-19.03, -9.34)	<0.001	-12.85 (-17.60, 8.05)	<0.001	-11.07 (-15.98, -6.25)	<0.001	-12.67 (-18.01, -7.54)	<0.001	-14.49 (-19.94, -9.62)	<0.001
BMI	1.53 (0.84, 2.22)	0.002	1.7 (0.98, 2.45)	0.002	1.9 (1.30, 2.49)	0.002	1.97 (1.35, 2.62)	0.002	1.74 (0.98, 2.58)	0.002	1.89 (1.36, 2.52)	0.002
BUN/SCr	1.11 (0.14, 2.27)	0.018	1.11 (0.33, 2.00)	0.01	0.96 (0.09, 1.92)	0.028					1.38 (0.57, 2.28)	0.002
UUN (mg/dl)	0.02 (0.004, 0.03)	0.012			0.01 (-0.001, 0.02)	0.076	0.01 (0.005, 0.02)	0.008				
UUN/UCr	3.03 (0.90, 5.07)	0.012	1.62 (-0.31, 3.50)	0.096					2.09 (0.04, 4.10)	0.046		
Age (years)	0.11 (-0.15, 0.33)	0.318										
eGFR	0.2 (-0.04, 0.45)	0.096										
SCr (mg/dl)	-3.83 (-15.4, 7.39)	0.531										
BUN (mg/dl)	0.35 (-0.27, 1.02)	0.296										
UCr (mg/dl)	0.03 (-0.01, 0.07)	0.146										

Adjusted R² Model 1: 0.464, Model 2: 0.47, Model 3: 0.428, Model 4: 0.405, Model 5: 0.436

CI, confidence interval; BMI, body mass index; BUN/SCr, blood urea nitrogen/serum creatinine ratio; UUN, urinary urea nitrogen; UUN/UCr, urinary urea nitrogen/urinary creatinine ratio; eGFR, estimated glomerular filtration rate; SCr, serum creatinine; BUN, blood urea nitrogen; UCr, urinary creatinine.

Table 3. Dietary protein intake equation

Model	Equation
1	DPI= -5.59 (-14.18 if female) +1.70×BMI+1.11×BUN/SCr+1.62×UUN/UCr
2	DPI= -5.89 (-12.85 if female) + 1.90×BMI+ 0.96×BUN/SCr+ 0.01×UUN
3	DPI= 0.85 (-11.07 if female) +1.97×BMI+0.01×UUN
4	DPI= 3.16 (-12.76 if female) +1.74×BMI+ 2.09×UUN/UCr
5	DPI= -5.18 (-14.49 if female) +1.89×BMI+1.38×BUN/SCr

DPI, dietary protein intake (g/24 h); BMI, body mass index; SCr, serum creatinine; BUN, blood urea nitrogen; UCr, urinary creatinine; UUN, urinary urea nitrogen; BUN/SCr, blood urea nitrogen/serum creatinine ratio; UUN/UCr, urinary urea nitrogen/urinary creatinine ratio.

Table 4. Comparison of the equations developed for estimating DPI in internal validation and external validation datasets

		Median difference (95% CI)		Interquartile range for difference (95% CI)		Root mean square error (95% CI)		P ₃₀ (95% CI)	
Internal validation	Model 3	-3.99	(-6.26, 3.40)	12.80	(6.56, 20.64)	10.88	(8.33, 13.28)	0.55	(0.36, 0.72)
	Model 4	-3.67	(-6.25, 4.01)	14.44	(8.26, 17.33)	10.00	(7.68, 12.34)	0.65	(0.45, 0.80)
	Model 5	-2.73	(-6.98, 4.50)	13.58	(7.50, 17.22)	9.64	(7.36, 11.90)	0.71	(0.52, 0.85)
External validation	Model 3	-3.38	(-6.02, -1.58)	7.24	(4.79, 10.40)	6.76	(5.16, 8.20)	0.70	(0.53, 0.83)
	Model 4	-7.02	(-8.02, -4.96)	5.95	(3.17, 9.43)	7.94	(6.51, 9.43)	0.63	(0.46, 0.77)
	Model 5	-2.76	(-4.44, -1.15)	7.35	(3.62, 10.34)	6.45	(4.98, 7.86)	0.78	(0.61, 0.89)
<p>DPI, dietary protein intake.</p> <p>Median difference refers to the estimated DPI minus the measured DPI.</p> <p>Interquartile range refers to the 25th-75th percentile.</p> <p>P₃₀ refers to the percentage of DPI estimates that are within 30% of the measured DPI.</p>									

Figures

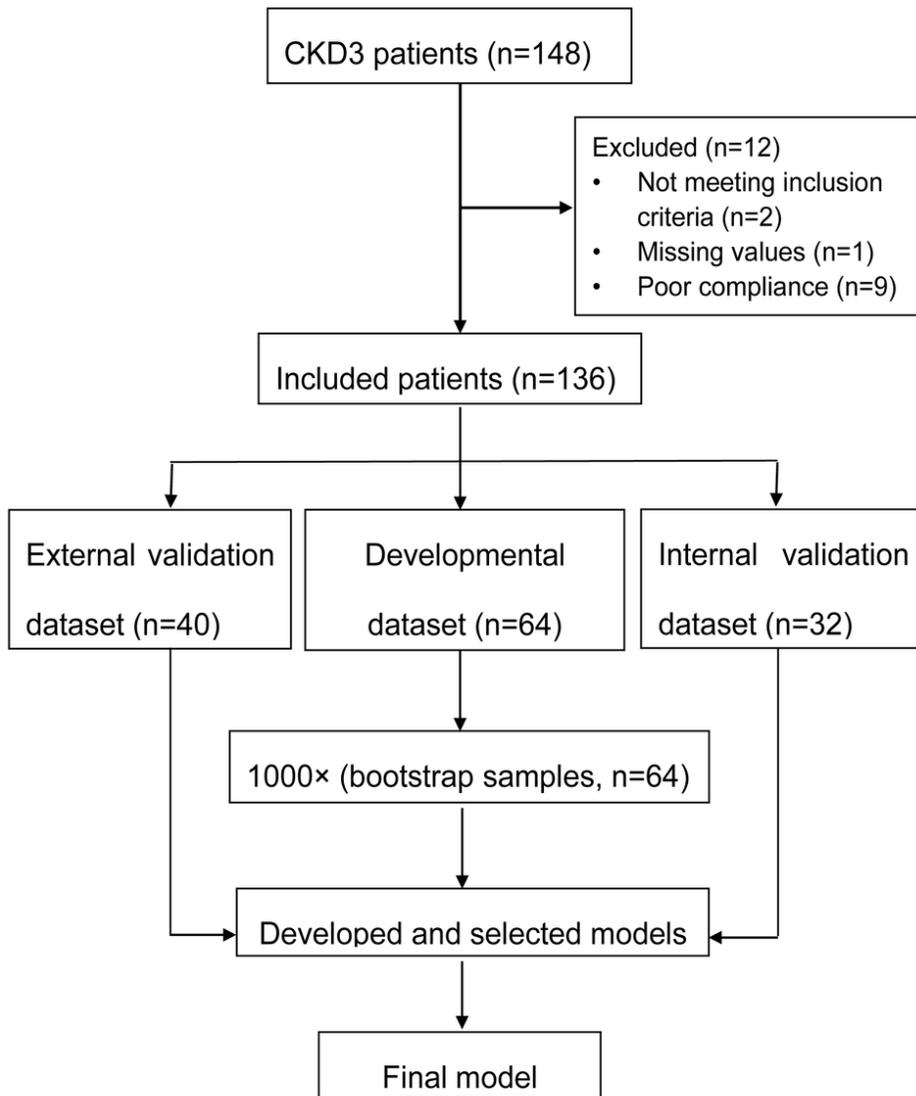


Figure 1

Flowchart of the enrolment process and participants included in the final analysis.

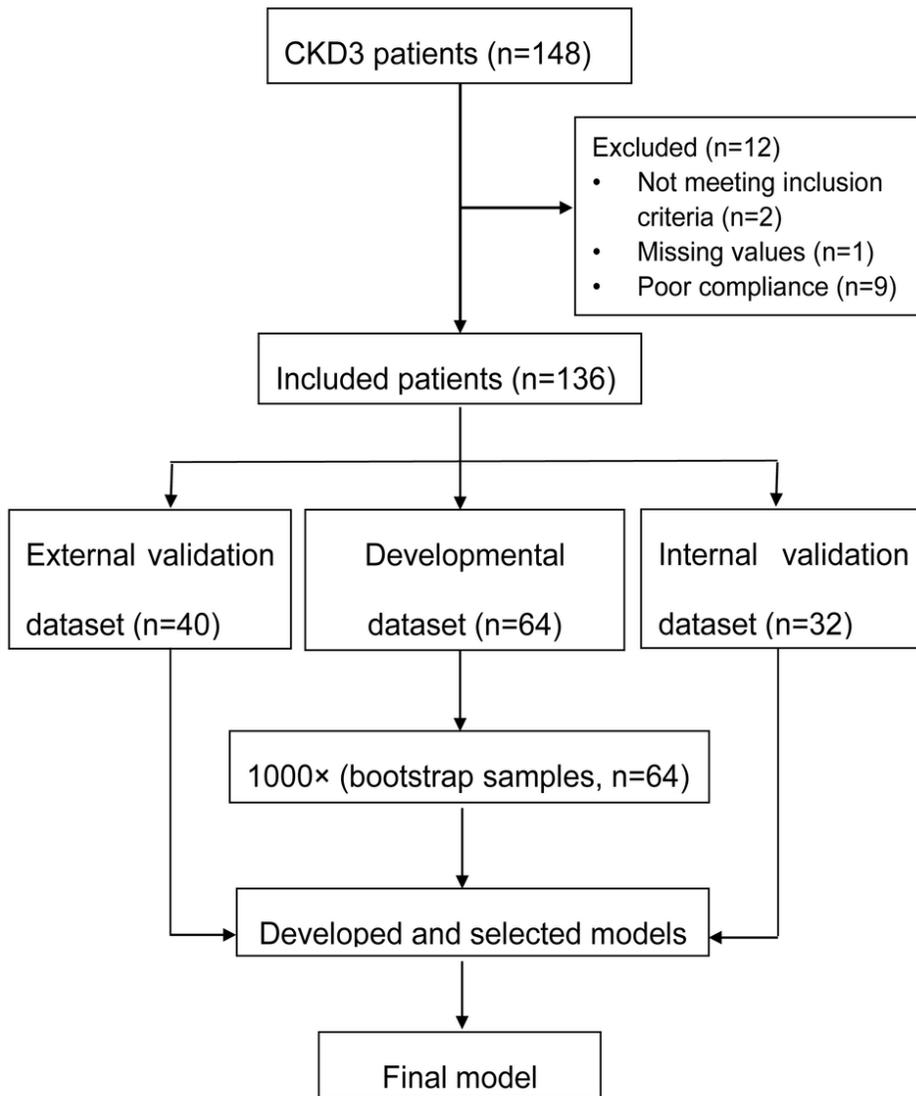


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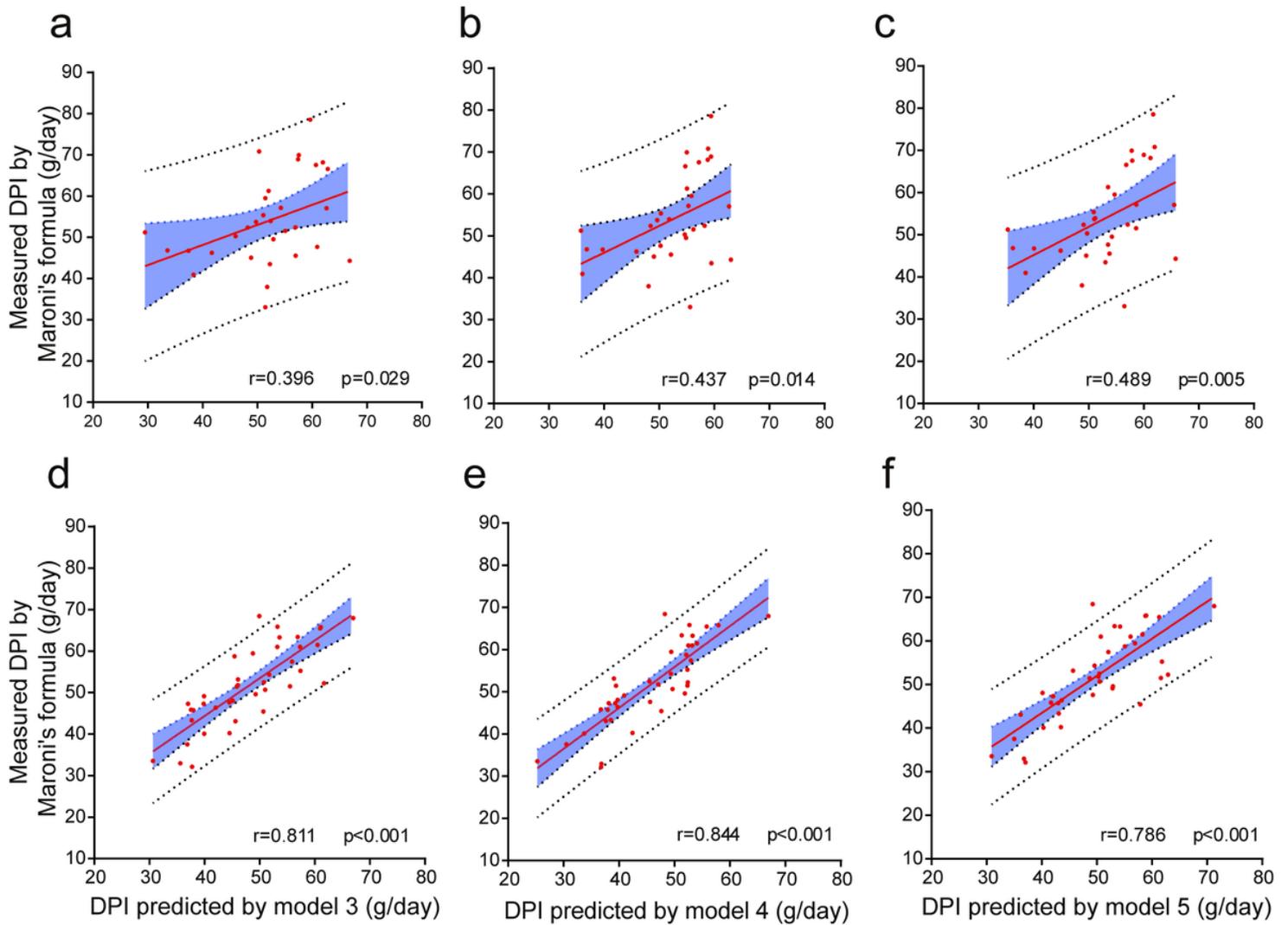


Figure 2

Relations of predicted dietary protein intake (DPI) with measured DPI in validation datasets. a, b, c: internal validation datasets; d, e, f: external validation datasets a, b and c showed the correlations between DPI predicted by model 3, model 4, model 5 and measured DPI by Maroni's formula in internal validation datasets. d, e and f showed the correlations between DPI predicted by model 3, model 4, model 5 and measured DPI by Maroni's formula in external validation datasets. The blue area is the 95% confidence interval of predicted DPI. The dotted lines show the 95% prediction interval of predicted DPI.

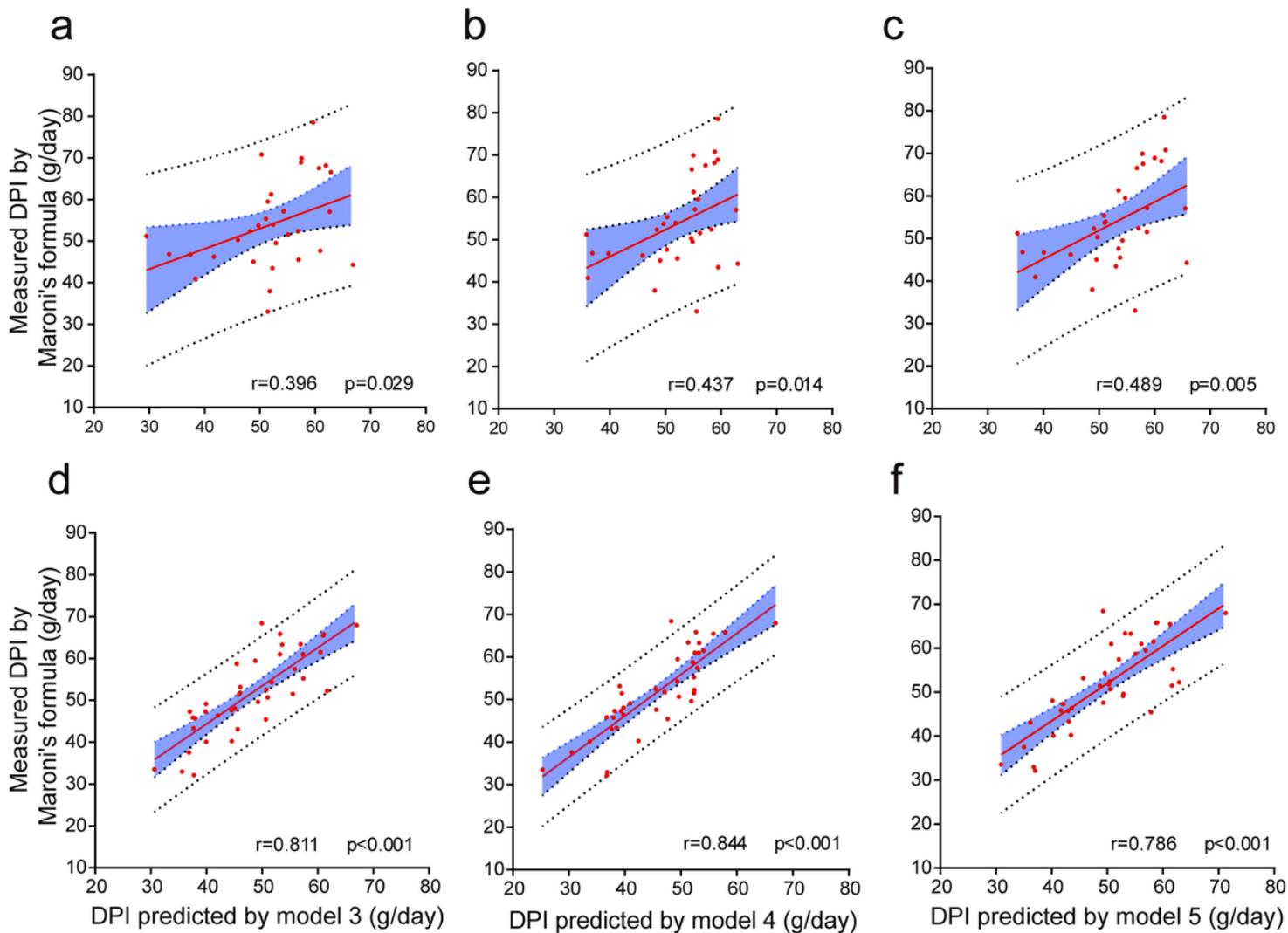


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