Population-based dose–response curve of glomerular filtration rate to dietary protein intake

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ABSTRACT

Background. Kidney function measured as estimated glomerular filtration rate (eGFR) is a risk factor for mortality and severe diseases. Protein intake up-regulates kidney function. The dose–response curve of eGFR over protein intake is unknown. Urinary urea nitrogen is an objective index of protein intake.

Methods. The study cross-sectionally analysed the relation between overnight urinary urea nitrogen ($_{on}$U-ureaN) and eGFR with and without control for other variables in 4106 adults of the Gubbio population. Analyses were done for serum creatinine (S-cr) also to investigate the independency of results from eGFR calculation.

Results. Higher $_{on}$U-ureaN associated with higher eGFR, and lower S-cr independently of sex and age (simple and partial correlation coefficients >0.100, P < 0.001). Analyses by $_{on}$U-ureaN decile indicated sigmoid curves of eGFR and S-cr over $_{on}$U-ureaN with trend to flatness in the lowest 20% and the highest 20% of $_{on}$U-ureaN (<5.19 and >10.12 mg/h, respectively). Multi-variable spline regression indicated that the relation of eGFR over $_{on}$U-ureaN was non-significant for $_{on}$U-ureaN <5.19 mg/h (coefficient = +0.27, 95% CI = −0.31/+0.84, P = 0.364), positive for $_{on}$U-ureaN in the range 5.19–10.12 mg/h (coefficients = 1.35–1.64, lower 95% CI ≥ +0.48, P ≤ 0.002), and non-significant for $_{on}$U-ureaN >10.12 mg/h (coefficient = +0.05, 95% CI = −0.06/ +0.16, P = 0.394). eGFR differed by ≈8 mL/min × 1.73 m^2 between the lowest and highest 20% of $_{on}$U-ureaN distribution.

Conclusions. Higher protein intake relates to higher eGFR. The relation is sigmoid with eGFR up-regulation for $_{on}$U-ureaN >5.19 mg/h, a threshold approximately corresponding to the recommended daily allowance for protein intake (0.8 g/day per kg of ideal weight).

Keywords: creatinine, dietary protein, eGFR, kidney function, urea

INTRODUCTION

Current guidelines indicate that the estimated glomerular filtration rate (eGFR) is the best overall index of kidney function [1]. Meta-analyses of data collected in about 2 000 000 adults from 46 cohorts across 40 countries/regions all over the world proved that eGFR is a strong and independent risk factor for mortality, cardiovascular disease and renal failure [2, 3]. Dietary protein intake is a pivotal modulator of kidney function and, in particular, of glomerular filtration rate [4–8]. The results of observational and interventional studies consistently showed that the short-term effect of high dietary protein intake is an up-regulation of kidney function measured as true glomerular filtration rate or as eGFR [4–9]. The results of studies about the long-term effects were less consistent and suggested that chronically high protein intake at times associates with fast decline of kidney function over time [4–9]. The contrast between short-term upward effects and long-term downward effects was settled down in the hypothesis that the chronic exposure to high protein intake—that is, to stimuli up-regulating kidney function—favours glomerular damage and faster decline of kidney function over time [4–8].

Research data are missing about the dose–response curve of the short-term effects of protein intake on kidney function. In other words, it is not known if the up-regulation of kidney function is continuous over the whole range of protein intakes or appears only above a certain threshold. Information about this dose–response curve could be important not only in medical practice for the prevention of diet-dependent decline of kidney function but also in epidemiology for definition of the possible role of protein intake as eGFR determinant and as covariate of eGFR-associated risks. The present study reports a population-based, observational, cross-sectional analysis about the shape of the relation of eGFR over an objective

index of protein intake in the hours preceding the assessment of kidney function.

MATERIALS AND METHODS

The Gubbio study is a population-based investigation ongoing in the city of Gubbio, Italy. Study activities include the approval by the local institutional committee and an informed consent. Response rates, time of examinations, characteristics of the Gubbio cohort and study design have previously been reported [10, 11]. The present analysis focuses on adults aged 18 years and over at the second exam. Briefly, the second exam included a timed overnight urine collection initiated after the completion of the evening meal and terminated with the first wake-up void included, that is, a urine collection under fed conditions for analyses about urinary markers of diet [12]; a venous blood sample collected early in the morning after an overnight fast for routine biochemistry; a timed morning urine collection initiated after blood sampling, that is, a urine collection under fasting conditions for analyses about kidney tubule functions [13]; a medical visit for the administration of standardized questionnaires about medical history and life styles, and for measurements of anthropometry and blood pressure.

Variables

Data in analysis included the following: gender and age; overnight urinary excretion of urea nitrogen ($_{on}$U-ureaN) and of sodium, potassium, and creatinine; serum creatinine (S-cr) and urea; body mass index (BMI) calculated as $weight_{kg}/height_{m^2}$; ideal weight calculated as $height_{m^2}$ times 22 taking BMI 22 kg/m^2 as indicative of ideal weight [14]; blood pressure; questionnaires on previous diagnosis of kidney disease(s), and treatments with diet(s) or drug(s); and questionnaires on habitual intake of alcohol, milk or yogurt, and caffeine-containing beverages.

The urinary excretion of urea, urea nitrogen, or total nitrogen in 24-h or partial collections is commonly used as objective markers of protein intake [15] because urea is the final product of dietary protein catabolism, is rapidly excreted in the urine after protein ingestion, and accounts for >80% of urinary total nitrogen [16]. Thus, in the present analysis, $_{on}$U-ureaN reflected the protein intake with the meal preceding the initiation of the overnight urine collection. Overnight urinary sodium and potassium were used as indices of their dietary intake [17]. Overnight urinary creatinine was used as index of creatinine generation, that is, of creatinine release from skeletal muscle plus dietary creatinine intake [18, 19]. The completeness of urine collection was evaluated by comparison of overnight urinary creatinine rate to estimated creatinine excretion rate [20]. S-cr and eGFR calculated by the Chronic Kidney Disease Epidemiology Collaboration research group equation were used as GFR indices [21, 22]. eGFR was defined as low when <60 mL/min × 1.73 m^2. Previous kidney disease was defined as the report of kidney stones, kidney malformation, nephrectomy, glomerular disease, interstitial nephropathy or low kidney function. Diabetes mellitus was defined as serum glucose ≥7 mmol/L (126 mg/100 mL) and/or the regular use of drug(s) for diabetes. Metabolic syndrome was defined by data of waist, blood pressure status, and serum levels of HDLc, triglycerides and glucose [23]. Hypertension was defined as systolic pressure ≥140 mm Hg, and/or diastolic pressure ≥90 mm Hg, and/or the regular use of antihypertensive drug(s). Obesity was defined as BMI ≥30 kg/m^2. Persons were defined apparently healthy when without previous kidney disease(s), low eGFR, obesity, hypertension, diabetes or metabolic syndrome.

S-cr was measured in frozen samples by automated biochemistry (Express Plus; Bayer Diagnostic) using a kinetic alkaline picrate assay with IDMS-traceable standardization [24]. Other variables were measured in fresh samples by automated procedures with quality controls [10, 11].

Statistics

Statistical procedures were for investigation about the relationship of $_{on}$U-ureaN (independent variable) with eGFR and S-cr taken as GFR indices (dependent variables). $_{on}$U-ureaN was expressed as mg/h and normalized per kg of ideal weight as suggested for dietary markers to avoid a systematic bias in persons with non-ideal weight [25, 26]. For example, in an obese person, 1.60 m in height and 80 kg in weight, an intake of 80 g/day of a given nutrient points to an intake of 1.42 g/day per kg of ideal weight but to a 30% lower intake per kg of actual weight (1.00 g/day). The bias is opposite in underweight persons. The 24-h urinary excretion of total nitrogen is requested for calculation of daily protein intake [15]. $_{on}$U-ureaN was used to estimate an approximation of daily protein intake on the basis of the evidence that $_{on}$U-ureaN and 24-h urinary total nitrogen were highly correlated with each other and negligibly different when expressed as mg/h in a subgroup of 200 participants of the Gubbio cohort [9]. The 0.150 multiplier was used for conversion of $_{on}$U-ureaN to g/day estimated protein intake. It resulted from the combination of three conversion factors: the 24× factor for conversion of $_{on}$U-ureaN from mg/h to mg/24 h of urinary nitrogen; the 0.001× factor for conversion of 24-h urinary nitrogen from milligram to gram; the 6.25 factor for conversion of g/24-h urinary nitrogen to g/day protein intake as per standard method [15].

eGFR was taken as main GFR index and dependent variable. S-cr was used to assess the dependency of results on eGFR calculations. The association of $_{on}$U-ureaN with GFR indices was controlled for several possible confounders in multi-variable analyses. The list of covariates in multi-variable models was as follows:

(i) other indices of dietary habits with inclusion of urinary sodium/potassium ratio, reported information about treatments with diet, habitual intake of alcohol, milk or yogurt and caffeine-containing beverages;

(ii) comorbidities with inclusion of previous diagnoses of renal disease and presence/absence of low eGFR, hypertension, diabetes, and metabolic syndrome;

(iii) factors possibly responsible for bias in evaluation of GFR indices with inclusion of urinary creatinine for control of non-normal creatinine generation [18, 19] and the presence/absence of obesity or treatment with inhibitors of

the tubular creatinine secretion for control of non-normal creatinine secretion by the renal tubule [18, 27–29].

The shape of the relationship—that is, the dose–response curve of eGFR and S-cr over $_{on}$U-ureaN—was first investigated by ANOVA along $_{on}$U-ureaN quantiles. The use of quantile was to avoid the bias of comparisons among groups predefined by arbitrary cut-offs and with different number of persons. Linear splines regression analyses were *post hoc* designed with knots selection based on results of quantile analyses. Statistical procedures were performed by SPSS.

RESULTS

Descriptive statistics

Of the 4680 persons with age ≥18 years in the Gubbio population sample, 574 persons were excluded from analyses because of missing data in some variables. Persons with complete data and persons with missing data did not significantly differ for any variable with available data (not shown). Table 1 reports descriptive data for the whole cohort. Overnight urinary creatinine was lower by 20% or more than estimated creatinine excretion rate in 370 individuals (9.0%). $_{on}$U-ureaN differed among age strata but not between sexes (Figure 1). In men and women, the means of $_{on}$U-ureaN were progressively higher from age 18–24 years to age 55–64 years and declined after age 65 years (Figure 1). The estimated daily protein intake averaged above the recommended daily allowance of 0.8 g/day per kg of ideal weight in all age strata of men and women. Figure 2 shows the positive association of $_{on}$U-ureaN with morning serum urea which excluded the possibility that high $_{on}$U-ureaN reflected high renal urea clearance rather than high urea generation.

Correlation analyses of $_{on}$U-ureaN with S-cr and eGFR

Table 2 shows that the correlation coefficients of $_{on}$U-ureaN were consistently negative with S-cr and consistently positive with eGFR in all age strata of men and women. For S-cr, the coefficients were significantly negative in strata with age <55 years among men and with age <75 years among women. For eGFR, the coefficients were significant in strata with age <55 years and in the 65–74-year stratum among men, in strata with age <75 years among women. Age-adjusted partial correlation coefficients for the whole cohort were significantly negative with S-cr and significantly positive with eGFR in men and women. Partial correlation coefficients were −0.162 with S-cr and +0.136 with eGFR (P < 0.001) in multi-variable models for men and women together with adjustment for sex, age, and all other covariates listed in MATERIALS AND METHODS—Statistics (other indices of dietary habits, comorbidities and factors possibly responsible for bias in evaluation of GFR indices). These findings were consistent when multi-variable analyses were re-analysed in the subgroup of 2030 apparently healthy men and women (coefficient = −0.228 with S-cr and +0.192 with eGFR, P < 0.001). Findings were identical with exclusion of the 370 individuals with overnight urinary creatinine

Table 1. Descriptive statistics: prevalence or mean ± SD (IQR)

Number of persons (% of men)	4106 (44.5%)
Age, years	50.4 ± 17.5 (36–65)
Weight, kg	70.2 ± 13.0 (60.5–78.5)
Body mass index, kg/m^2	26.7 ± 4.4 (23.6–29.3)
Ideal weight, kg	57.9 ± 6.8 (52.8–62.8)
S-cr, mg/dL[a]	0.91 ± 0.14 (0.81–0.98)
eGFR, mL/min × 1.73 m^2	86.0 ± 16.9 (74–98)
Serum urea nitrogen, mg/dL	16.9 ± 4.2 (14.0–19.1)
$_{on}$U-ureaN,	
mg/h	462 ± 254 (325–552)
mg/h per kg ideal weight	8.03 ± 4.33 (5.66–9.56)
Estimated protein intake, g/day per kg ideal weight	1.20 ± 0.65 (0.89–1.43)
Urinary creatinine, mg/h[b]	60.2 ± 22.1 (43.8–73.1)
Urinary sodium, mmol/h	6.80 ± 4.18 (3.86–8.70)
Urinary potassium, mmol/h	1.61 ± 0.98 (1.05–1.93)
Urinary sodium/potassium ratio	4.56 ± 3.01 (2.92–5.64)
Reported intake of	
Alcohol, g/day	22.3 ± 30.0 (0–25)
Milk or yogurt, mL/day	77.8 ± 89.5 (0–125)
Caffeine-containing beverages, n/day	1.74 ± 1.35 (1.0–2.4)
On dietary treatment, % (n)	1.9 (78)
With eGFR < 60 mL/min × 1.73 m^2, % (n)	5.8 (240)
With reported kidney disease, % (n)	7.9 (325)
With hypertension, % (n)	35.4 (1454)
with obesity, % (n)	20.5 (842)
With metabolic syndrome, % (n)	19.8 (811)
With diabetes mellitus, % (n)	5.4 (221)
On treatment with creatinine secretion inhibitors, % (n)	5.7 (232)
Apparently healthy, % (n)	49.4 (2030)

[a]Multiplier for conversion from mg/dL to μmol/L = 88.40.
[b]Multiplier for conversion from mg/h to μmol/h = 8.84.

Table 2. Correlation coefficients of $_{on}$U-ureaN per kg of ideal weight with S-cr and eGFR by sex and age

	Coefficient with S-cr		Coefficient with eGFR	
	Men	Women	Men	Women
18–24	−0.272***	−0.224***	+0.244**	+0.249***
25–34	−0.175**	−0.219***	+0.193***	+0.198***
35–44	−0.221***	−0.335***	+0.197***	+0.300***
45–54	−0.260***	−0.176***	+0.229***	+0.177***
55–64	−0.055	−0.218***	+0.040	+0.223***
65–74	−0.073	−0.144**	+0.088	+0.240***
≥75	−0.136°	−0.030	+0.168*	+0.026
All ages[a]	−0.157***	−0.162***	+0.101***	+0.132***

[a]Partial correlation coefficient with adjustment for age.
°P ≤ 0.10.
*P < 0.05.
**P < 0.01.
***P < 0.001.

lower by 20% or more than estimated creatinine excretion rate (not shown).

Shape of relation of $_{on}$U-ureaN with S-cr and eGFR

The plot of mean eGFR over median $_{on}$U-ureaN along $_{on}$U-ureaN deciles indicated a positive sigmoid curve with a trend to flatness in the tails of the $_{on}$U-ureaN distribution, approximately in the two lowest deciles and in the two highest deciles (Figure 3). Findings for the plot of S-cr mirrored the eGFR curve indicating a negative sigmoid curve with trends towards flatness
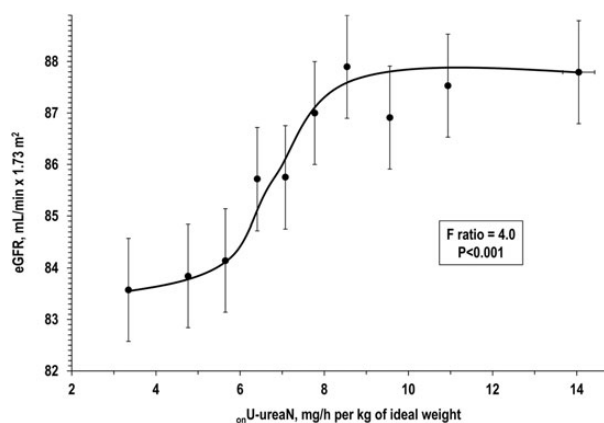
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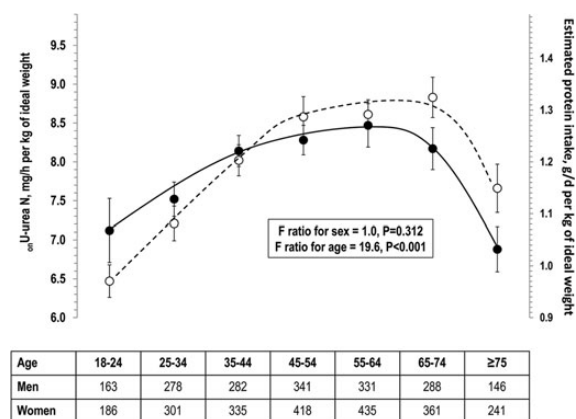
FIGURE 1: Mean ± SE of $_{on}$U-ureaN per kg of ideal weight by age stratum in men (closed circles) and women (open circles). The additional vertical axis on the left gives the corresponding values of estimated protein intake as g/day per kg of ideal weight (conversion factor from $_{on}$U-ureaN = times 0.150). The table at the bottom reports the number of person per age stratum in men and women.
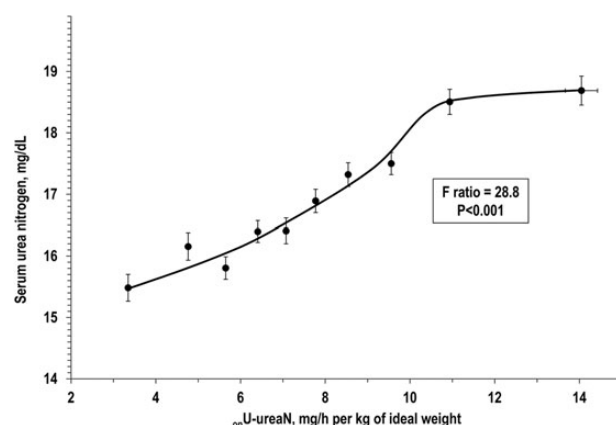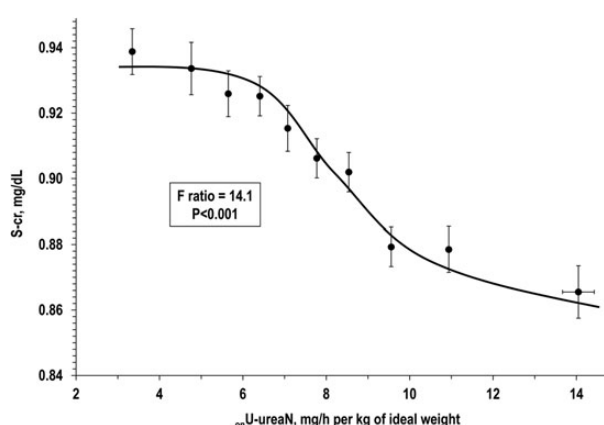

FIGURE 2: Mean ± SE of serum urea nitrogen plotted over median ± SE of $_{on}$U-ureaN per kg of ideal weight in $_{on}$U-ureaN decile (men and women combined). When non-indicated, the SE of $_{on}$U-ureaN did not exceed the size of the symbol. The number of persons per decile ranged from 404 to 414.

FIGURE 3: Mean ± SE of eGFR plotted over median ± SE of $_{on}$U-ureaN per kg of ideal weight in $_{on}$U-ureaN decile (men and women combined). When non-indicated, the SE of $_{on}$U-ureaN did not exceed the size of the symbol. The number of persons per decile ranged from 404 to 414.

FIGURE 4: Mean ± SE of S-cr plotted over median ± SE of $_{on}$U-ureaN per kg of ideal weight in $_{on}$U-ureaN decile (men and women combined). When non-indicated, the SE of $_{on}$U-ureaN did not exceed the size of the symbol. The number of persons per decile ranged from 404 to 414.

at the same thresholds of $_{on}$U-ureaN (Figure 4). The trends towards sigmoid curves were identical in analyses with the use of $_{on}$U-ureaN quintiles (not shown).

On the basis of data in Figures 3 and 4, a multi-variable spline regression model was designed with knots for $_{on}$U-ureaN at thresholds of $_{on}$U-ureaN quintiles (mg/h: <5.19, 5.19–6.72, 6.73–8.15, 8.16–10.12 and >10.12). The list of covariates in the model included sex, age and all other covariates listed in MATERIALS AND METHODS—Statistics (other indices of dietary habits, comorbidities and factors possibly responsible for bias in evaluation of GFR indices). Figure 5 summarizes the results of this multi-variable model. The regression coefficient of eGFR over $_{on}$U-ureaN was not different from zero for $_{on}$U-ureaN <5.19 mg/h, similarly positive for $_{on}$U-ureaN in the range from 5.19 to 10.12 mg/h, and not different from zero for $_{on}$U-ureaN >10.12 mg/h. Mean eGFR differed by ≈8 mL/min

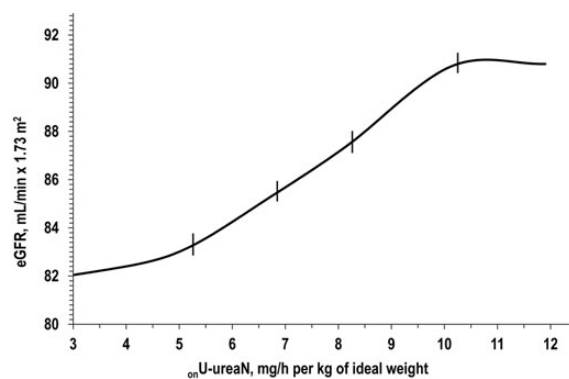× 1.73 m^2 between persons in the lowest $_{on}$U-ureaN quintile and persons in the highest $_{on}$U-ureaN quintile. Non-adjusted data of Figure 3 underscored the association of $_{on}$U-ureaN with eGFR for the confounding of age and hypertension which differed between quintiles 1 and 5 of $_{on}$U-ureaN (mean age = 49.1 and 53.5 years; hypertension prevalence = 33.8 and 40.4%). Findings with S-cr as dependent variable mirrored the results summarized in Figure 5. The regression coefficients of S-cr over $_{on}$U-ureaN were not different from zero for $_{on}$U-ureaN <5.19 mg/h (regression coefficient, 95% CI = −0.002, −0.009/+0.005, P = 0.540), similarly negative for $_{on}$U-ureaN in the range 5.19–6.72 mg/h (−0.016, −0.026/−0.006, P = 0.002), 6.73–8.15 mg/h (−0.015, −0.026/−0.004, P = 0.007), and 8.16–10.12 mg/h (−0.017, −0.024/−0.010, P < 0.001), and again not different from zero for $_{on}$U-ureaN >10.12 mg/h (−0.001, −0.002/+0.001, P = 0.447).

FIGURE 5: The curve summarizes the results of the multi-variable, four-knot, spline regression analysis of eGFR over $_{on}$U-ureaN per kg of ideal weight in men and women combined. The four knots of $_{on}$U-ureaN were at thresholds for definition of quintiles and are indicated by the small vertical lines on the curve. The table at the bottom reports the thresholds for definition of quintiles (knots), the multi-variable regression coefficients (slope) with 95% CI, and P-values of regression coefficients.

$_{on}$U-ureaN	<5.19	5.19–6.72	6.73–8.15	8.16–10.12	>10.12
slope (95%CI)	0.27 (-0.31/0.84)	1.35 (0.48/2.22)	1.49 (0.54/2.44)	1.65 (1.03/2.27)	0.05 (-0.06/0.16)
P	0.364	0.002	0.002	<0.001	0.394

DISCUSSION

The study reports the first data about the shape of the relationship between an objective marker of recent protein intake and eGFR taken as index of kidney function. The relationship of $_{on}$U-ureaN with eGFR was fitted by a sigmoid curve characterized by a trend towards flatness in the lowest 20% and the highest 20% of the $_{on}$U-ureaN distribution and by significant regression coefficients in the intermediate range of $_{on}$U-ureaN. Findings were consistent in both sexes, over a wide range of ages, and independent of several possible confounders.

Study results proved that $_{on}$U-ureaN reflected urea generation. The alternative possibility that high $_{on}$U-ureaN reflected high renal clearance of urea was excluded by the finding that high $_{on}$U-ureaN associated with high serum urea nitrogen in the morning assessment at completion of the overnight urine collection. If high $_{on}$U-ureaN were due to high renal urea excretion without high urea generation, the association between $_{on}$U-ureaN and serum urea nitrogen would have been necessarily inverse. Results from several previous studies [4–8] suggest that the association of $_{on}$U-ureaN with short-term up-regulation of kidney function reflects the functional stimulation of protein intake upon renal haemodynamics and glomerular filtration rate. Study results were in accordance with this interpretation because a direct association of recent protein intake with renal creatinine excretion was the sole mechanism that could explain the association of higher $_{on}$U-ureaN with lower S-cr after control for creatinine generation also. Renal creatinine excretion occurs mostly via glomerular filtration but also via tubular secretion [18]. Present results pointed to a key role for glomerular filtration because the analyses were also controlled for conditions associated with tubular hyper-secretion of

creatinine (obesity) and for drug-inhibited tubular creatinine secretion. However, an involvement of renal tubule creatinine secretion could not be excluded. A cross-sectional association between a marker of protein intake and eGFR could reflect the influence of protein intake on kidney function and/or changes in protein intake secondary to pre-existing eGFR alterations. The association of $_{on}$U-ureaN with eGFR indices was consistent also in apparently healthy persons, that is, in persons without history or evidence of several disorders with inclusion of kidney diseases, hypertension, metabolic syndrome, and diabetes. Therefore, with the exception of the few persons on low-protein diet secondary to kidney disorders, a stimulatory effect of protein intake on glomerular filtration appeared as the prevailing mechanism to explain the association of higher $_{on}$U-ureaN with higher eGFR in the general population. Given that, in individuals on unrestricted diet, protein intake is characterized by day-to-day variability and tracking over time [15, 25], study results could reflect short-term effects of protein intake occasionally high in the meal prior to blood sample, or long-term effects secondary to protein intake habitually high, or a combination thereof. In all analyses, the association was non-linear and characterized by a trend towards flatness in the lowest 20% and the highest 20% of the $_{on}$U-ureaN distribution. This finding is well in keeping with the general view that a sigmoid dose–response curve is frequent for physiologic and pathologic phenomena affected by dietary components [25]. The extrapolation of $_{on}$U-ureaN to an estimate of 24-h protein intake by the 0.150 conversion factor indicated that the protein-dependent up-regulation of eGFR appeared only for $_{on}$U-ureaN corresponding to an estimated protein intake close to the recommended daily allowance of 0.8 g of total protein/day per kg of ideal weight [25, 26].

Possible limitations of the present study are the observational design, the lack of measurements of true glomerular filtration rate, the lack of information about types of dietary protein and other nutrients, the lack of data in various ethnic groups, the use of overnight urine collection instead of 24-h urine collection and the use of urinary urea nitrogen instead of total urinary nitrogen. With regard to the observational design, the lack of dose–response data from interventional studies reflects the unfeasibility of experiments with analyses of kidney function after the administration of meals with a wide range of protein contents. The lack of measurements of true glomerular filtration rate measurements is a limitation that applies to all population-based studies which necessarily focus on indirect indices of glomerular filtration rate derived from endogenous markers. Moreover, at variance with other population-based studies, the present study was controlled also for creatinine generation which is an important cause of inaccuracies in the use of eGFR and S-cr as indices of glomerular filtration rate [22, 23]. For the lack of information about types of dietary protein and other nutrients, the study results cannot exclude that only a specific group of dietary protein accounted for the up-regulation of eGFR, although data in support of this possibility are inconsistent [4–8]. If this were the case, however, the results should represent an underestimate of the true relationship because of a regression dilution bias. Study results cannot exclude also that non-investigated nutrients as fats and carbohydrates could have

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played a confounding role, although available data unanimously indicate that protein is much more important than other nutrients in the regulation of kidney function [4–8]. The lack of data about 24-h urinary excretion certainly implied some misclassification in the estimate of daily protein intake. However, it is likely that the overnight collection is actually more reliable than the 24-h collection for investigations about the relationship of protein intake in the meal preceding the blood withdrawal with eGFR, given that the protein-induced up-regulation of kidney function is a transient phenomenon which lasts for a limited number of hours [4–8]. In fact, the use of a 24-h urine collection would have necessarily implied the confounding of cases with high protein intake only in the beginning of the 24-h collection, that is, too many hours before the blood sampling for assessment of S-cr and eGFR. Finally, the use of urinary urea nitrogen instead of total urinary nitrogen certainly implied an underestimate of estimated protein intake. However, this underestimate was certainly minor, given that urinary urea nitrogen accounts for the most of urinary total nitrogen in the clinical setting and in population-based data [15, 30].

The practical implications of the study are relevant to the assessment of S-cr and eGFR as indices of kidney function. The study shows that the variability in the protein intake in the hours preceding the assessment of kidney function plays a non-negligible confounding on eGFR, given that, in multivariable analyses, eGFR differed by at least $8 \text{ mL/min} \times 1.73 \text{ m}^2$ between persons with protein intake in the lowest 20% and the highest 20% of the distribution. Thus, study results prove that protein intake in the meal preceding the blood withdrawal may play a confounding in the assessment of kidney function and suggest that this confounding could be reduced by standardization of protein intake or measurement of the protein intake in the hours prior to the assessment of kidney function.

In conclusion, the study showed a sigmoid independent relationship between an objective marker of protein intake in the meal preceding the blood withdrawal and a widely used index of kidney function in a sample of the general population. It can be speculated that this relationship could be important in epidemiological studies about the role of kidney function as a risk factor as well as in medical practice for accurate assessment of kidney function independently of the confounding of dietary factors.

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Chronic kidney disease and the risk of stroke: a systematic review and meta-analysis

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ABSTRACT

Background. People with chronic kidney disease (CKD) have an increased risk of stroke but the magnitude of increased risk and the independent effects of glomerular filtration rate (GFR) and albuminuria are unclear. We aimed to quantify the association between the independent and combined effects of GFR and albuminuria on stroke risk.

Methods. We searched MEDLINE and EMBASE (February 2014) for cohort studies or randomized controlled trials (RCTs) which reported stroke incidence in adults with a baseline measurement of GFR and/or albuminuria. We extracted study and participant characteristics, risk of bias and relative risks (RR, with confidence interval; CI) of stroke associated with GFR and/or quantity of albuminuria, synthesized data using random effects meta-analysis and explored heterogeneity using meta-regression.

Results. We identified 83 studies; 63 cohort studies (2 085 225 participants) and 20 RCTs (168 516 participants) reporting 30 392 strokes. There was an inverse linear relationship between GFR and risk of stroke, with risk of stroke increasing 7% (RR: 1.07, CI: 1.04–1.09) for every 10 mL/min/1.73 m^2 decrease in GFR. A 25 mg/mmol increase in albumin–creatinine ratio was associated with a 10% increased risk of stroke (RR: 1.10, 95% CI: 1.01–1.20). The effect of albuminuria was independent of GFR. Results were not different across subtypes of stroke, sex and varying prevalence of cardiovascular risk factors.

Conclusions. Stroke risk increases linearly and additively with declining GFR and increasing albuminuria. CKD staging may also be a useful clinical tool for identifying people who may benefit most from interventions to reduce cardiovascular risk.

Keywords: albuminuria, chronic kidney disease, glomerular filtration rate, stroke, systematic review