

# Welkom bij sessie 23

Wat opgevangen dialysaat  
zegt over eiwitname en  
spierstatus

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**NIERCONGRES**  
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Dé dag voor professionals  
in de **nierzorg**

## Disclosure belangen

### Voor bijeenkomst mogelijk relevante relaties

- Sponsoring of onderzoeksgeld

### Bedrijfsnamen:

Asqa Subsidies, Vivaltes, Lodeholding, Paramedir B.V., Precision Cognition, Behapp, Osasense

# Problemen in Voedingsonderzoek

- Tekortkoming van vragenlijsten en anamnese
  - Sociaal wenselijke antwoorden
    - Selectieve onder- en overrapportage
  - Heel slechte schatting van energie intake
  - Geen valide schatting van belangrijke factoren zoals zout intake
  - Heel hoge correlatie tussen actieve substanties, bijv. vezels en thiamine
  - Inadequate inschatting van belangrijke potentiële confunders, zoals alcohol en roken

# Problemen in Voedingsonderzoek

- Tekortkomingen bij Phenotypering
  - Variabelen laten niet zien wat ze verondersteld worden te weerspiegelen
    - Voorbeelden:
      - BMI (bedoeld om vetmassa te weerspiegelen, maar geeft daadwerkelijk vetmassa + spiermassa + botmassa + ... weer)
      - DEXA / CT (bedoeld om vetmassa en spiermassa apart te weerspiegelen, maar in feite wordt vetmassa onderschat en spiermassa overschat, vooral bij hogere vetmassa)

# Functies van de nier in relatie tot voeding: Glomerulaire Filtratie

- Glomerulaire filtratie van wateroplosbare klein moleculaire en middel moleculaire stoffen, bijv.
    - Water
    - Ureum (afbraakproduct van eiwit)
    - Natrium
    - Kalium
    - Fosfaat
    - Sulfaat (afbraakproduct uit zwavelhoudende aminozuren, noodzaak tot uitscheiding zuur / ammonia via de nier)
  
  - Glucose
  - Aminozuren
  - Wateroplosbare vitamines
  - Vitamine B12
  - Eiwit / albumine
- 
- Tubulaire secretie van (slechter) wateroplosbare klein moleculaire stoffen
  - Terugwinnen uit het ultrafiltraat van belangrijke glomerulair gefiltreerde klein moleculaire en middel moleculaire stoffen
  - Bewaren van homeostase / evenwicht

# Functies van de nier in relatie tot voeding:

## Tubulaire secretie

- Glomerulaire filtratie van wateroplosbare klein moleculaire en middel moleculaire stoffen, bijv.
- Tubulaire secretie van klein moleculaire stoffen, bijv.
  - Creatinine
  - Kalium
  - Geneesmiddelen / toxines
  - $H^+$
  - $NH_4^+$
- Terugwinnen uit het ultrafiltraat van belangrijke glomerulair gefiltreerde klein moleculaire en middel moleculaire stoffen
- Bewaren van homeostase / evenwicht

# Functies van de nier in relatie tot voeding:

## Tubulaire terugresorptie

- Glomerulaire filtratie van wateroplosbare klein moleculaire en middel moleculaire stoffen, bijv.
- Tubulaire secretie van klein moleculaire stoffen
- Terugwinnen uit het ultrafiltraat van belangrijke glomerulair gefiltreerde klein moleculaire en middel moleculaire stoffen, bijv.
  - Glucose
  - Amino-zuren
  - Wateroplosbare vitamines
  - Vitamine B12
  - Eiwit / albumine
- Bewaren van homeostase / evenwicht

# Functies van de nier in relatie tot voeding: Homeostase

- Glomerulaire filtratie van wateroplosbare klein moleculaire en middel moleculaire stoffen, bijv.
- Tubulaire secretie van klein moleculaire stoffen
- Terugwinnen uit het ultrafiltraat van belangrijke glomerulair gefiltreerde klein moleculaire en middel moleculaire stoffen
- Bewaren van homeostase / evenwicht, bijv.
  - Water
  - Natrium (hypertensie, volume overbelasting, hartfalen)
  - Kalium (hyperkaliaemie, hartritme stoornissen, hartstilstand)
  - Zuur-base (metabole acidose, botontkalking, sarcopenie)
  - Fosfaat (vaatverkalking, botontkalking)

# Voedingsfocus bij Chronic Kidney Disease (voorafgaand aan dialyse)

- Laag eiwit
  - Minder glomerulaire hyperfiltratie
  - Minder uremische toxines
- Plantaardig
  - Minder fosfaat load
  - Minder zuur load
  - Meer vezels
  - Minder natrium
- Nadelen
  - Verhoogd risico op ondervoeding, sarcopenie, meer ziekenhuisopnames en voortijdige sterfte

# Belangrijke componenten die voeding bij dialyse complexer maken

- Dialyse
  - Geen terugwinning belangrijke stoffen uit het ultrafiltraat
  - Verlies van aminozuren, micro-nutrienten en eiwit naar het dialysaat
    - Verhoogde neiging verlies van spiermassa
    - Verhoogde kans op deficiënties

# Bovendien ligt het focus/prioriteit van het met voeding te bereiken doelen (wellicht) anders

- Focus bij Chronic Kidney Disease
  - Voorkomen progressie nierschade
  - Voorkomen cardio-metabole complicaties
- Focus bij Dialyse
  - Voorkomen voortijdig overlijden
  - Optimalisering kwaliteit van leven
  - Voorkomen van ziekenhuisopnames
  - Voorkomen van cardio-metabole complicaties

# Verschuiving naar “Plant-Based” Voeding

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## Food in the Anthropocene: the EAT–Lancet Commission on healthy diets from sustainable food systems



*Walter Willett, Johan Rockström, Brent Loken, Marco Springmann, Tim Lang, Sonja Vermeulen, Tara Garnett, David Tilman, Fabrice DeClerck, Amanda Wood, Malin Jonell, Michael Clark, Line J Gordon, Jessica Fanzo, Corinna Hawkes, Rami Zurayk, Juan A Rivera, Wim De Vries, Lindiwe Majele Sibanda, Ashkan Afshin, Abhishek Chaudhary, Mario Herrero, Rina Agustina, Francesco Branca, Anna Lartey, Shenggen Fan, Beatrice Crona, Elizabeth Fox, Victoria Bignet, Max Troell, Therese Lindahl, Sudhvir Singh, Sarah E Cornell, K Srinath Reddy, Sunita Narain, Sania Nishtar, Christopher J L Murray*

*The NEW ENGLAND JOURNAL of MEDICINE*

REVIEW ARTICLE

*Julie R. Ingelfinger, M.D., Editor*

## Nutritional Management of Chronic Kidney Disease

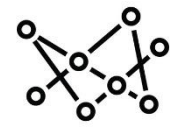
*Kamyar Kalantar-Zadeh, M.D., M.P.H., Ph.D., and Denis Fouque, M.D., Ph.D.*

Willett W et al. *Lancet* 2019; 393: 447-492 & Kalantar-Zadeh K et al. *New Engl J Med* 2017; 377: 1765-1776

# KDOQI 2020: Voedingrichtlijn bij CKD



Adequate energy intake: 25 à 30 kcal/kg



Proteins: 0,6- 0,8 g/kg ( LPD) / 0,3 à 0,6 g/kg (sVLPD) + ketoanalogues supplementation



Fibers : 25 à 30 g/day  
> 50 à 70 % food of plant origin



Potassium : < 4 g/day only if hyperkalemia



Phosphore : < 800-1000 mg



Salt : < 4 g/day



**KDOQI CLINICAL PRACTICE GUIDELINE FOR NUTRITION IN  
CKD: 2020 UPDATE**

# Belangrijke vragen bij Dialyse

- Is het – gegeven de verschillen met Chronic Kidney Disease – wel verstandig de focuspunten van de dieetbegeleiding bij Chronic Kidney Disease 1 op 1 over te nemen?
- Is het – gegeven het nog grotere belang van goede dieetbegeleiding bij dialysepatiënten dan bij patiënten met CKD – wel verstandig om hierbij grotendeels te varen op subjectieve informatie verkregen uit de anamnese?

# Example: Protein Consensuses

CKD	Dialysis	Transplantation
RDA = 0.8 g/kg/day	Dialysis induced protein catabolism and losses	No RDA, similar to CKD?
Prevention of Progression	RDA $\geq$ 1.1 g/kg/day	Chronic immunosuppres sion
Prevention of Uremic symptoms		Catabolism induced by glucocorticoids

# Onderzoek naar gezondheid bij dialyse (1)

- Hoe definieer je gezondheid?
  - Niet ziek worden?
  - Lang leven?
  - Hoge kwaliteit van leven?

# Onderzoek naar gezondheid bij dialyse (2)

- Wat zouden oorzaken van “ongezondheid” bij dialyse?
  - Slechte voeding?
  - Weinig beweging?
  - Te dik?
  - Weinig slaap?
  - Bijwerkingen medicijnen?
  - Bijkomende aandoeningen?

# Onderzoek naar gezondheid bij dialyse (3)

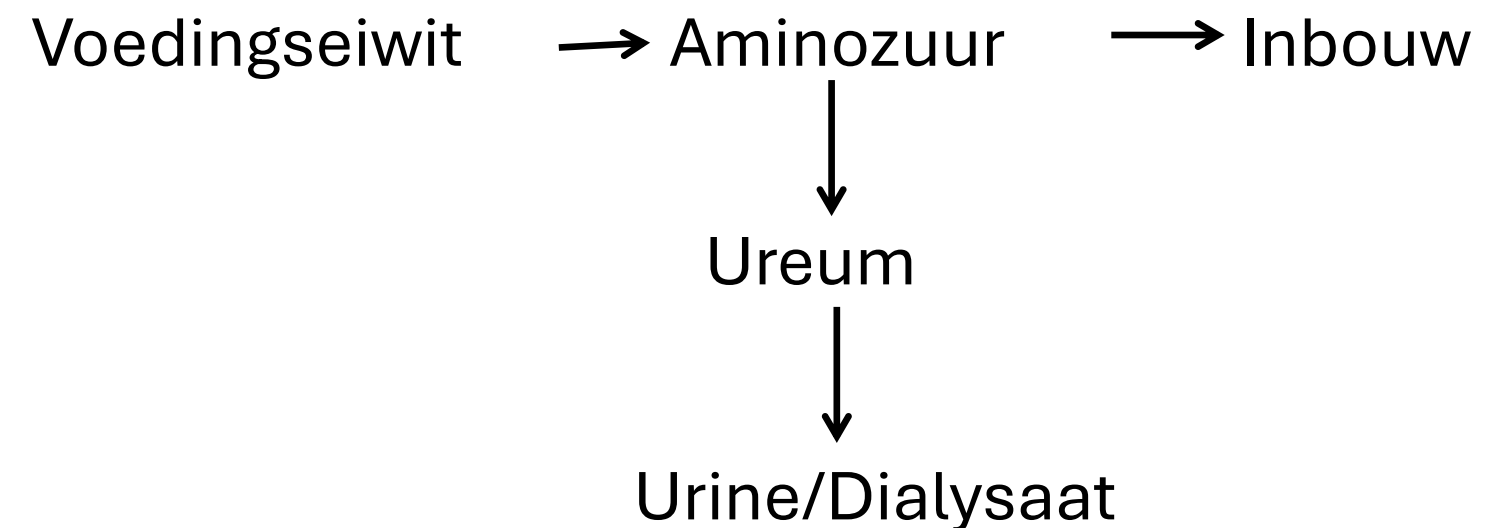
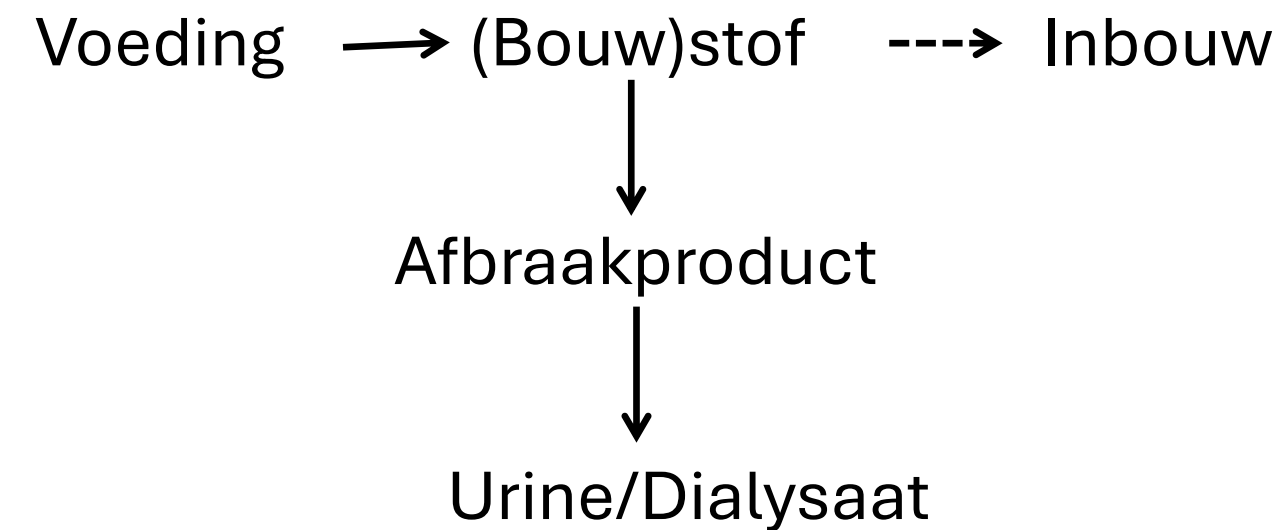
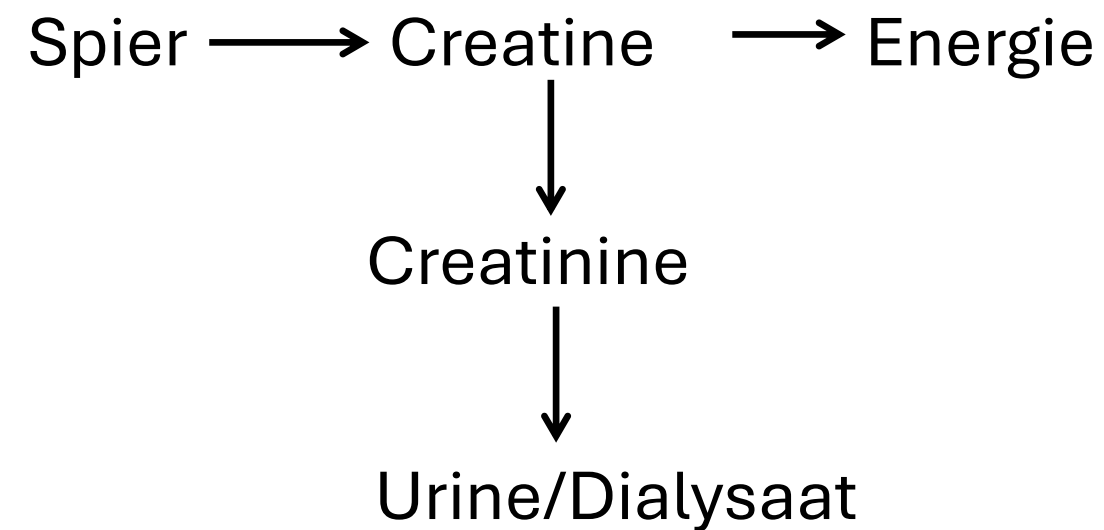
- Wat zouden uitkomstmaten van “ongezondheid” bij dialyse kunnen zijn?
  - Matige kwaliteit van leven?
  - Veel ziekenhuisopname?
  - Noodzaak tot operaties?
  - Gebruik antibiotica?
  - Hart- en vaatziekten?
  - Diabetes?
  - Functieverlies van het getransplanteerde orgaan?
  - Sterfte?

# Hoe kun je onderzoek naar gezondheid bij dialyse doen?

- Dwarsdoorsnede onderzoek
  - Metingen
  - Onderlinge verbanden
- Cohortonderzoek
  - Metingen
  - Nagaan of de metingen die je gedaan hebt “voorspellen” wat er in de toekomst gaat gebeuren
- Interventie onderzoek
  - iets veranderen
  - Nagaan of er iets gebeurt

# Wij hebben gekozen voor cohortonderzoek bij dialyse

- Onze truc in cohortonderzoek: 24 uurs urine



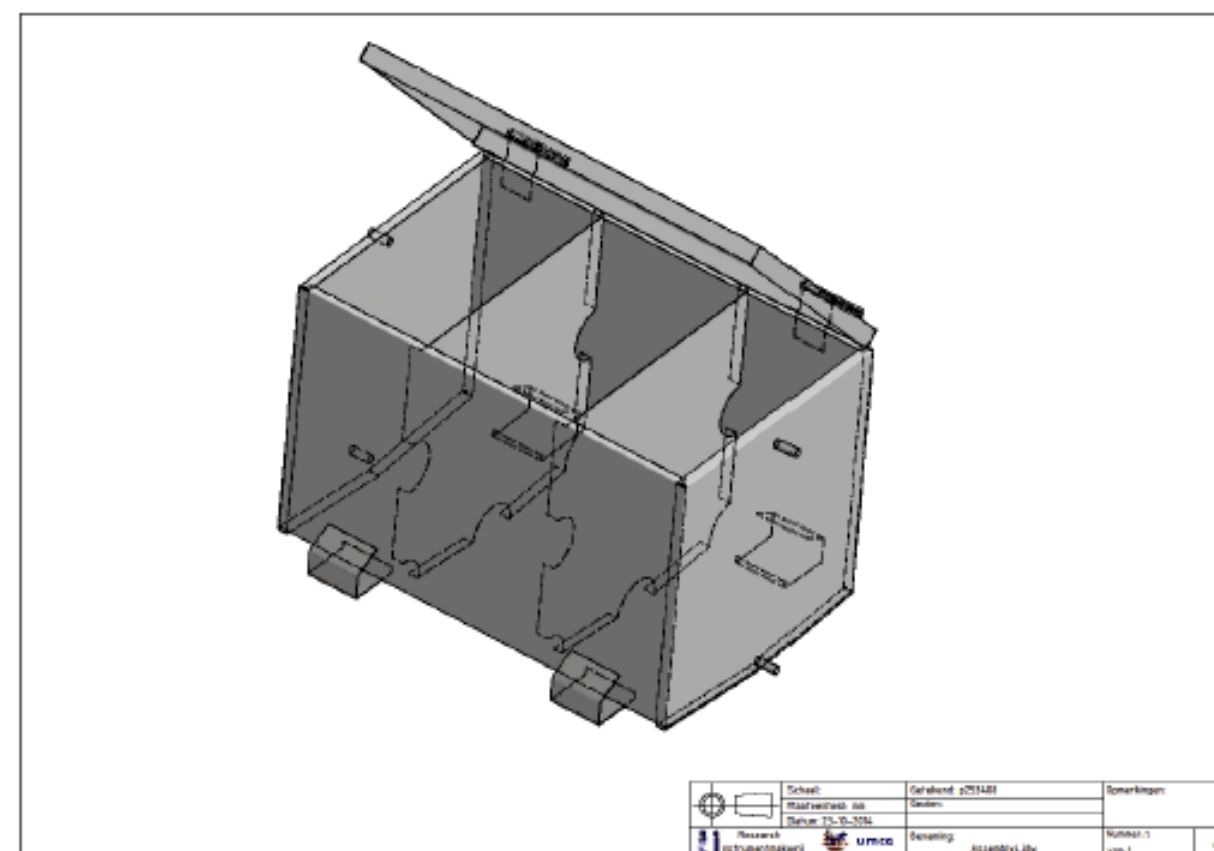
# Afgeleid van 24 uren urine: “unbiased”

- Intake ~ Excretie
  - Natrium (gouden standaard voor zout intake)
  - Ureum (gouden standaard voor eiwit intake)
  - Jodium (gouden standaard voor jodium intake)
  
- Opname ~ Excretie
  - Kalium
  - Magnesium
  - Cotinine

# Dialyse

- Verlies van klein moleculaire, water-oplosbare toxische metabolieten en toxines (bijv. ureum, creatinine)
- Verlies van waardevolle klein-moleculaire, water-oplosbare metabolieten en moleculen
  - Aminozuren (bijv. arginine, tryptofaan, serine, etc.)
  - Secondaire metabolieten van aminozuren (bijv. guanidinoacetate, serotonine, agmatine, polyaminen)
  - Vitamins (vitamine C, foliumzuur, vitamine B6, etc.)
  - Jodium, selenium, etc.
- Bijna geen data beschikbaar over daadwerkelijke verliezen tijdens dialyse
  - Beschouwd als te moeilijk en niet mogelijk

# Dialysaat Verzamel Bak (Eenvoudige Versie)



# Dialysaat Verzamel Bak (Uitgebreide Versie)



# Parameters voor en na dialyse

Table 2. Clinical and laboratory parameters before and after dialysis.

Variable	Before Dialysis	After Dialysis	<i>p</i> -Value
Clinical			
Systolic blood pressure (mmHg)	147 ± 21	138 ± 27	0.012
Diastolic blood pressure, (mmHg)	69 ± 12	67 ± 11	0.163
Pulse, min <sup>-1</sup>	74 ± 14	73 ± 12	0.631
Body weight, kg	80.0 ± 16.0	78.7 ± 16.0	< 0.001
Laboratory			
Hemoglobin (mmol/L)	6.9 ± 0.7	7.4 ± 1.0	0.001
Hematocrit	0.34 ± 0.04	0.36 ± 0.04	0.012
Sodium (mmol/L)	138 ± 3	139 ± 2	0.023
Potassium (mmol/L)	4.9 ± 0.5	3.5 ± 0.4	< 0.001
Phosphate (mmol/L)	1.6 ± 0.6	0.8 ± 0.2	< 0.001
Albumin (g/L)	40 ± 5	43 ± 4	< 0.001
Urea (mmol/L)	20 ± 5	6 ± 2	< 0.001
Creatinine (μmol/L)	707 ± 196	265 ± 94	< 0.001

Post A et al. Nutrients 2018; 10: 1827

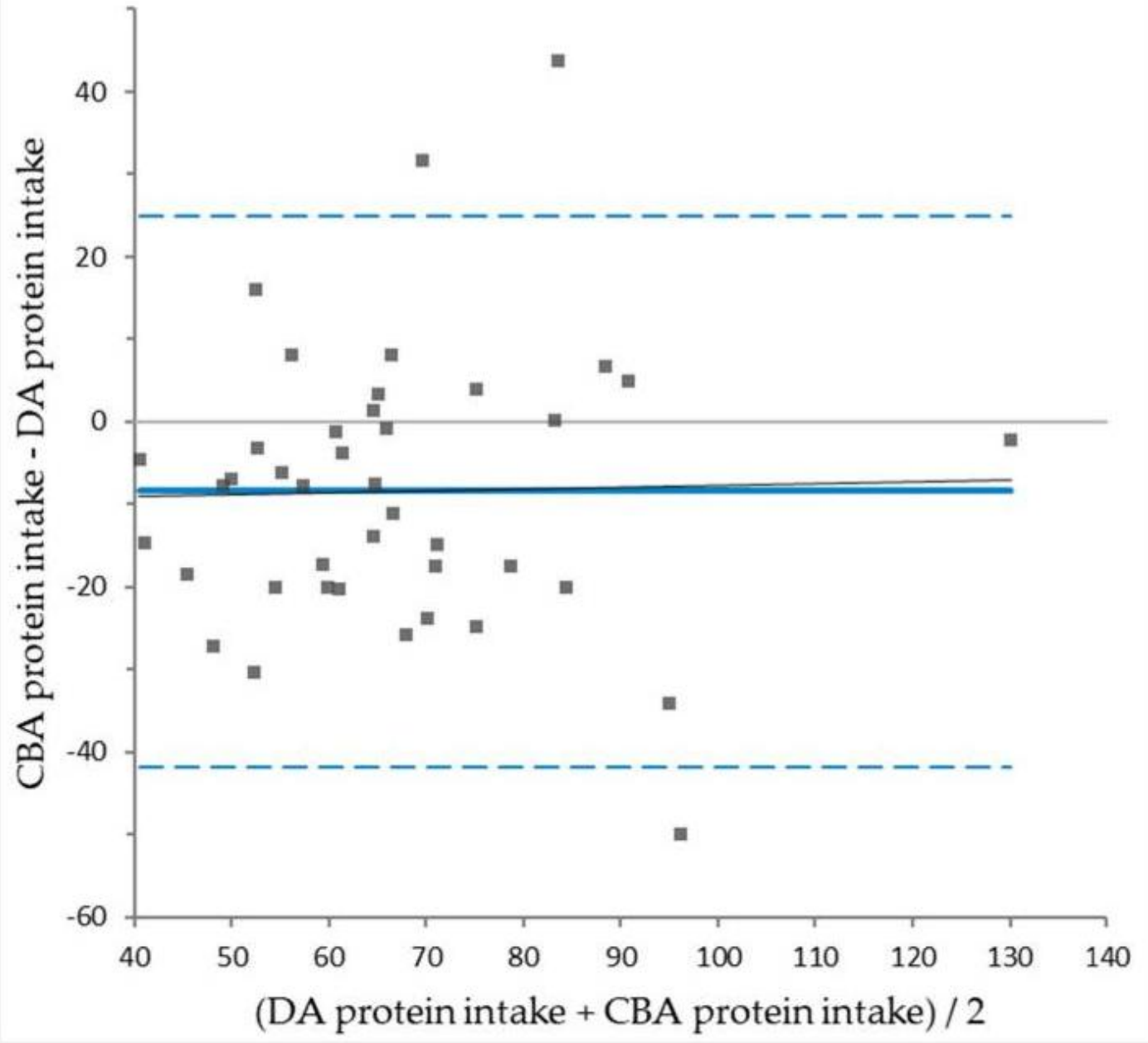
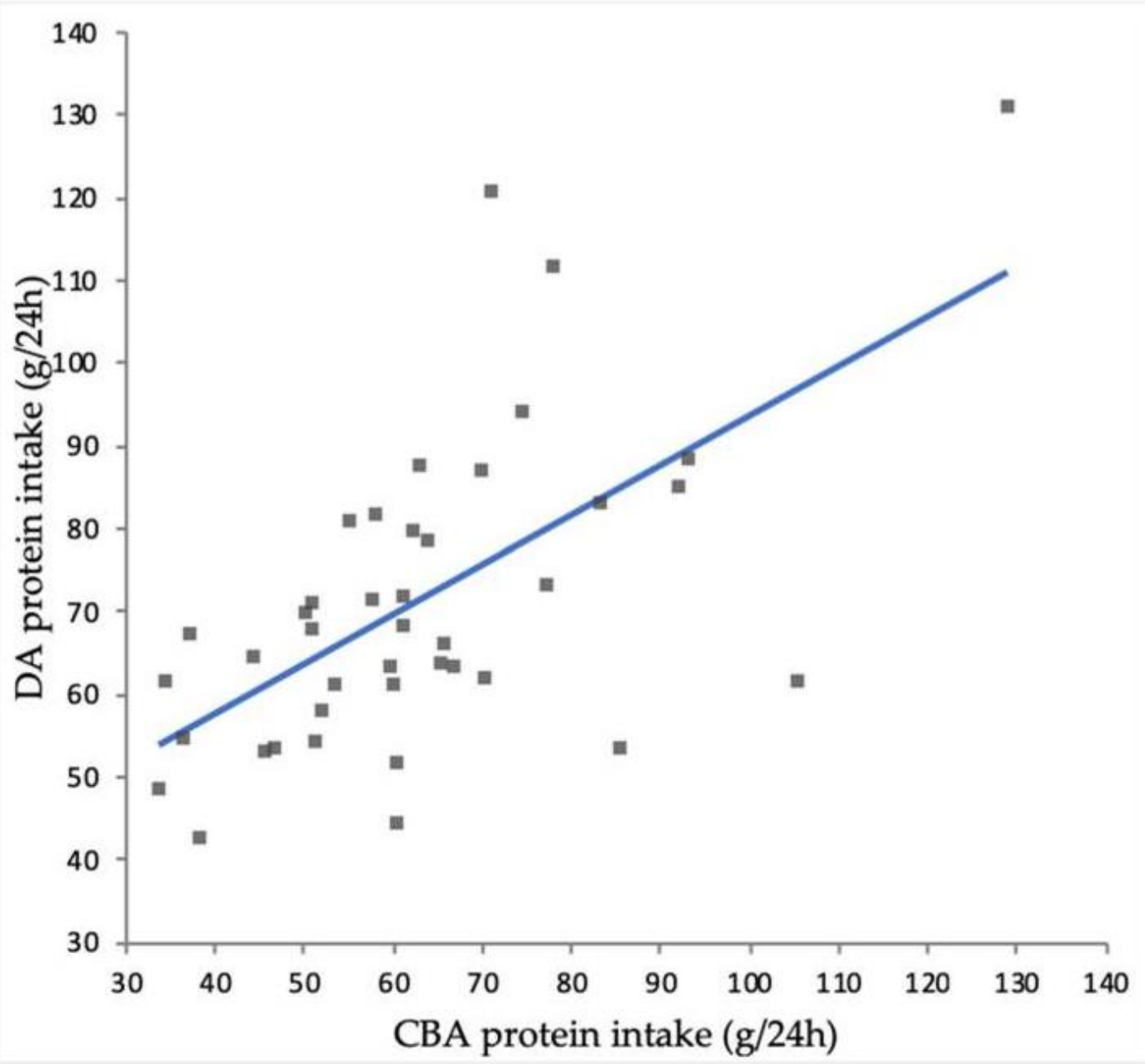
# Verskil tussen aan de hand van biomarkers bepaalde intake en door anamnese bepaalde intake

**Table 3.** Mean values of complementary biomarker assessed (CBA) intakes and dietary assessed (DA) intakes of protein, sodium, potassium and phosphate.

Variable	CBA Intake *	DA Intake	<i>p</i> -Value
Protein (g/24 h)	63 ± 19	71 ± 19	0.003
Sodium (mg/24 h)	4035 ± 2316	2123 ± 616	< 0.001
Potassium (mg/24 h)	2041 ± 907	2445 ± 568	0.008
Phosphate (mg/24 h)	1427 ± 637	1221 ± 276	0.029

\* = uptake in the case of phosphate.

# Eiwit intake (Anamnese vs biomarker)



Post A et al. Nutrients 2018; 10: 1827

# Sodium Intake

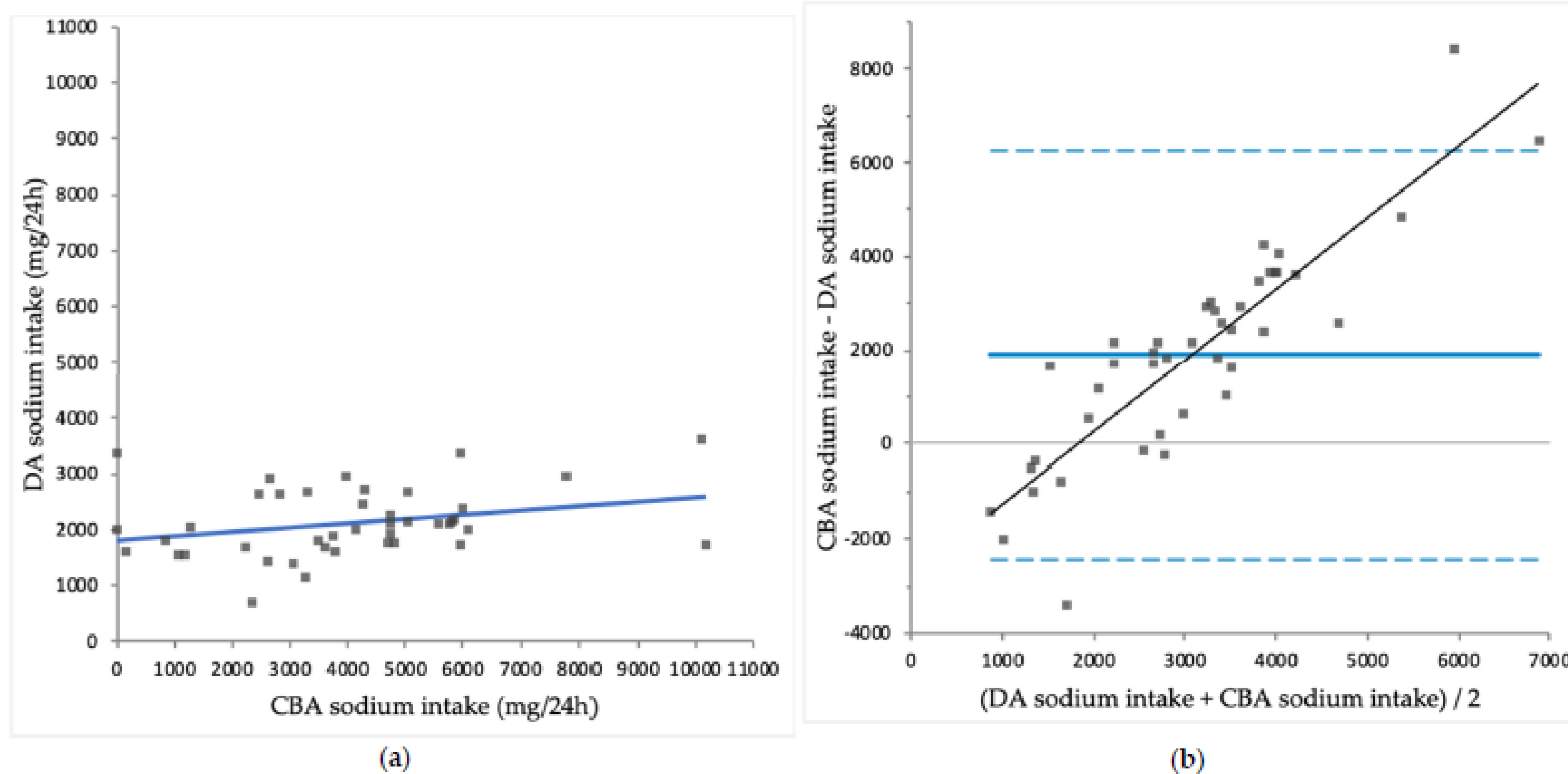
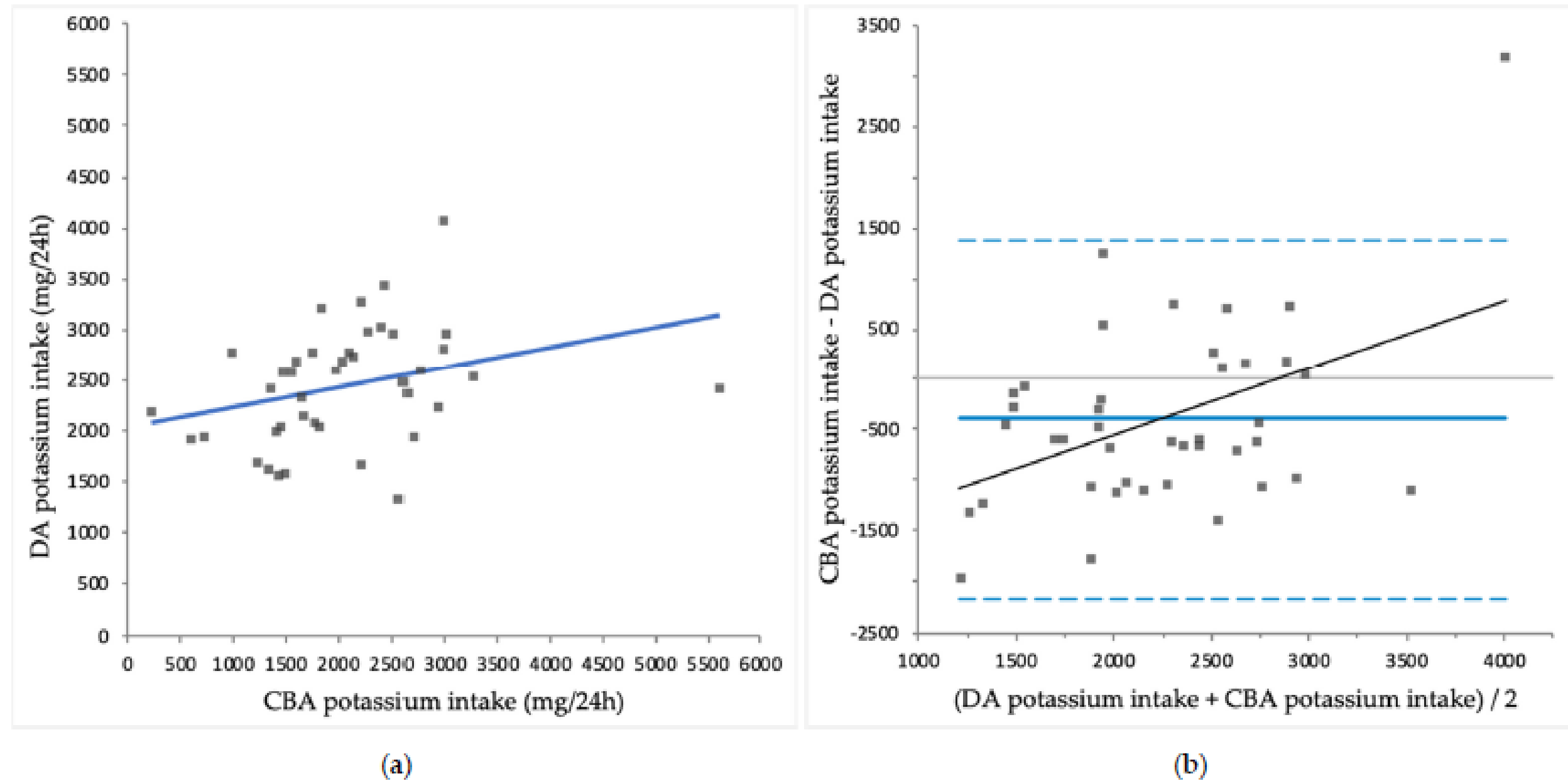


Figure 2. (a) Comparison of complementary biomarker assessed (CBA) sodium intake and diary assessed (DA) sodium intake ( $r = 0.297$ ;  $p = 0.056$ ); (b) Bland-Altman plot for CBA sodium intake and DA sodium intake, with significant proportional bias ( $r = 0.887$ ;  $p < 0.001$ ).

Post A et al. Nutrients 2018; 10: 1827

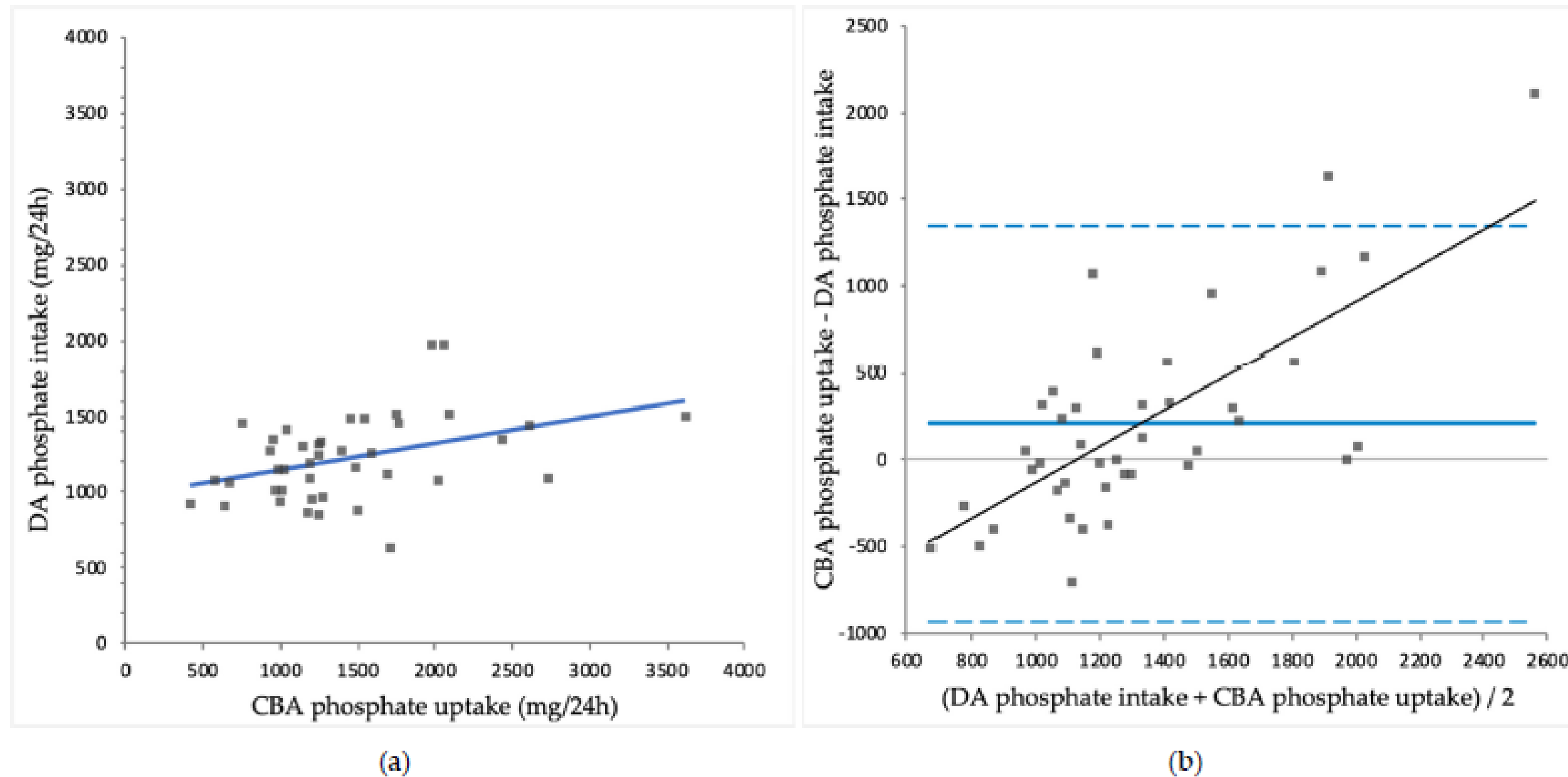
# Kalium Intake



**Figure 3.** (a) Comparison of complementary biomarker assessed (CBA) potassium intake and diary assessed (DA) potassium intake ( $r=0.312$ ;  $p = 0.047$ ); (b) Bland-Altman plot for CBA potassium intake and DA potassium intake, with significant proportional bias ( $r = 0.446$ ;  $p = 0.003$ ).

Post A et al. Nutrients 2018; 10: 1827

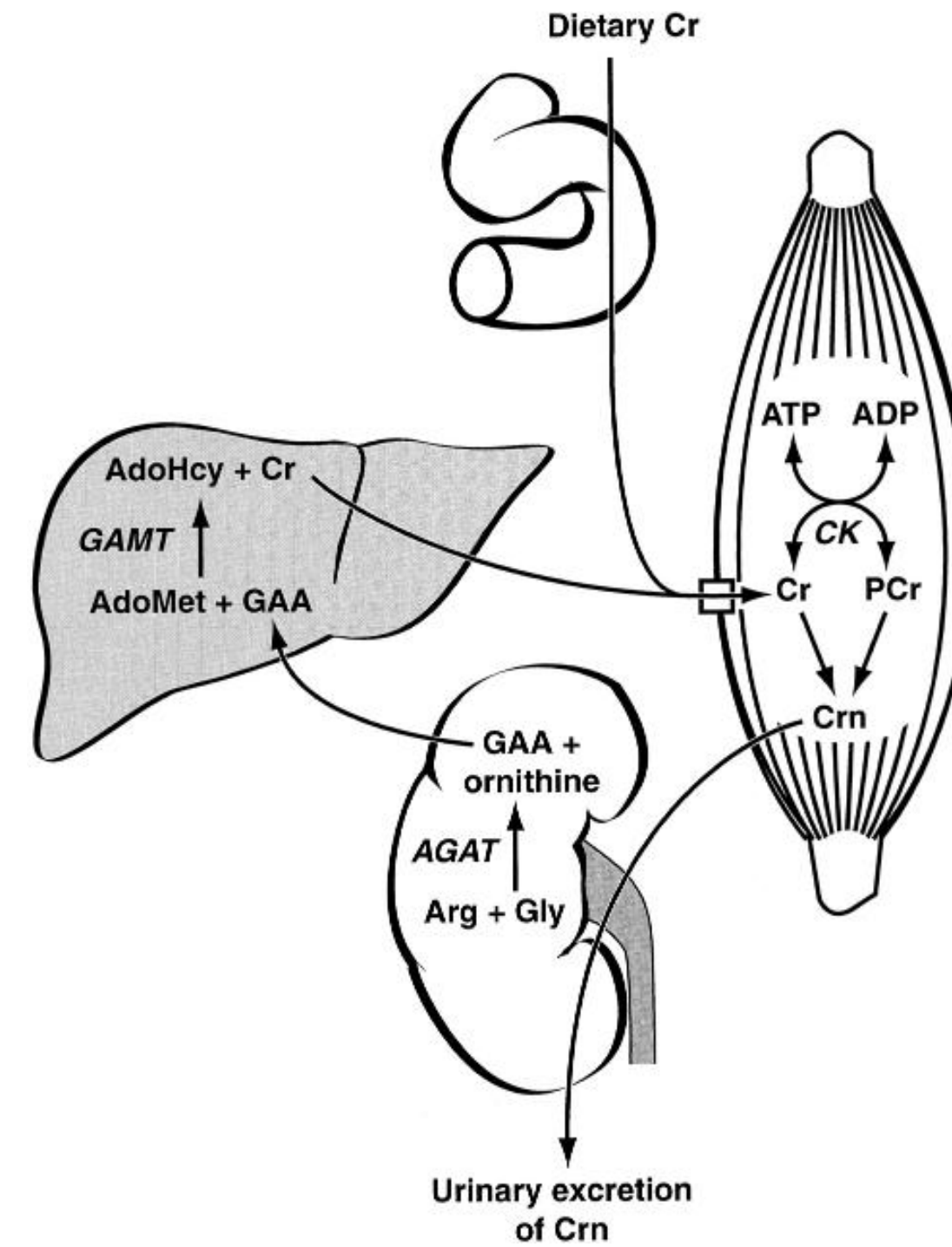
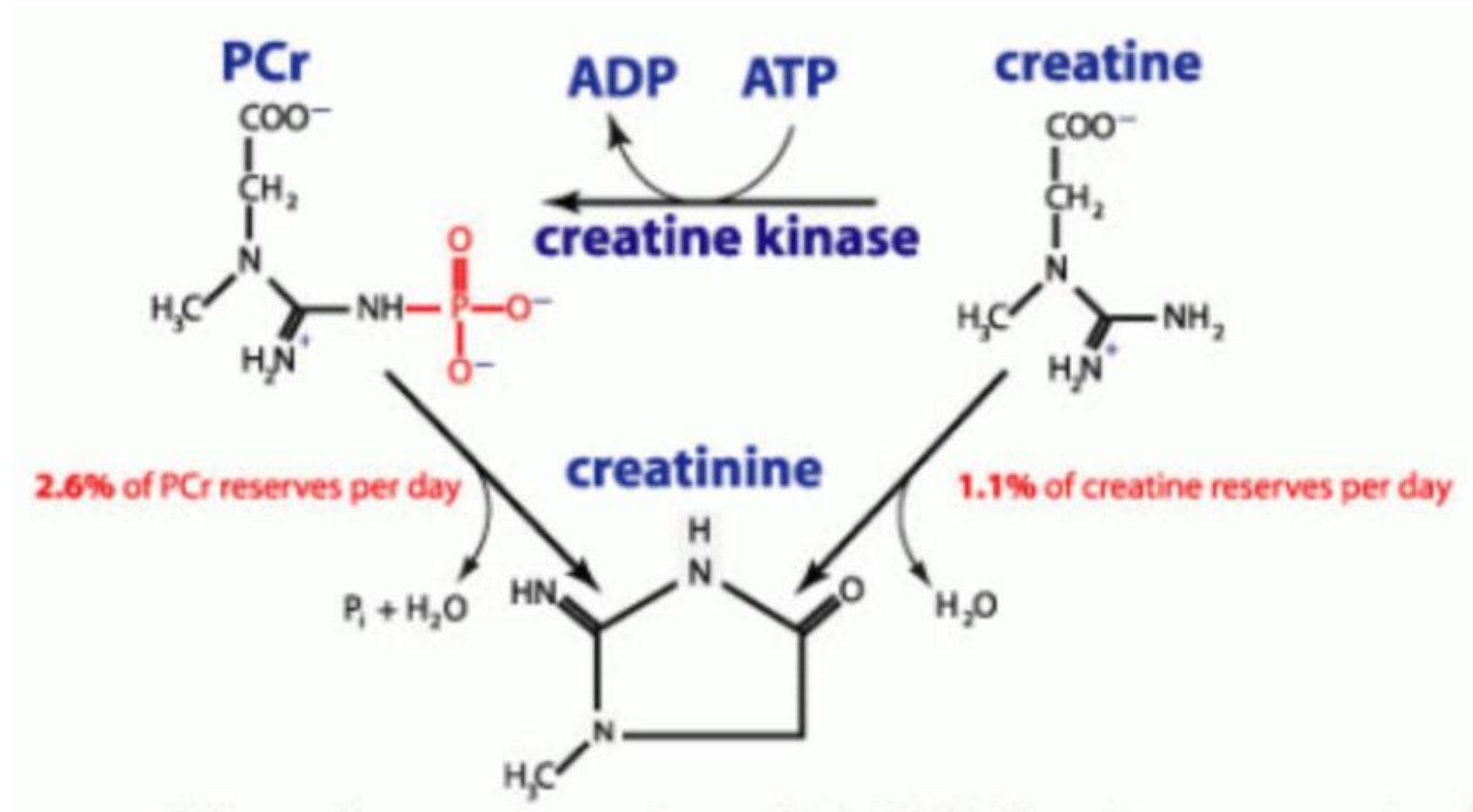
# Fosfaat intake



**Figure 4.** (a) Comparison of complementary biomarker assessed (UBA) phosphate uptake and diary assessed (DA) phosphate intake ( $r = 0.409$ ;  $p = 0.008$ ); (b) Bland-Altman plot for CBA phosphate uptake and DA phosphate intake, with significant proportional bias ( $r = 0.710$ ;  $p < 0.001$ ).

Post A et al. Nutrients 2018; 10: 1827

# Creatine – Creatinine – Spieren

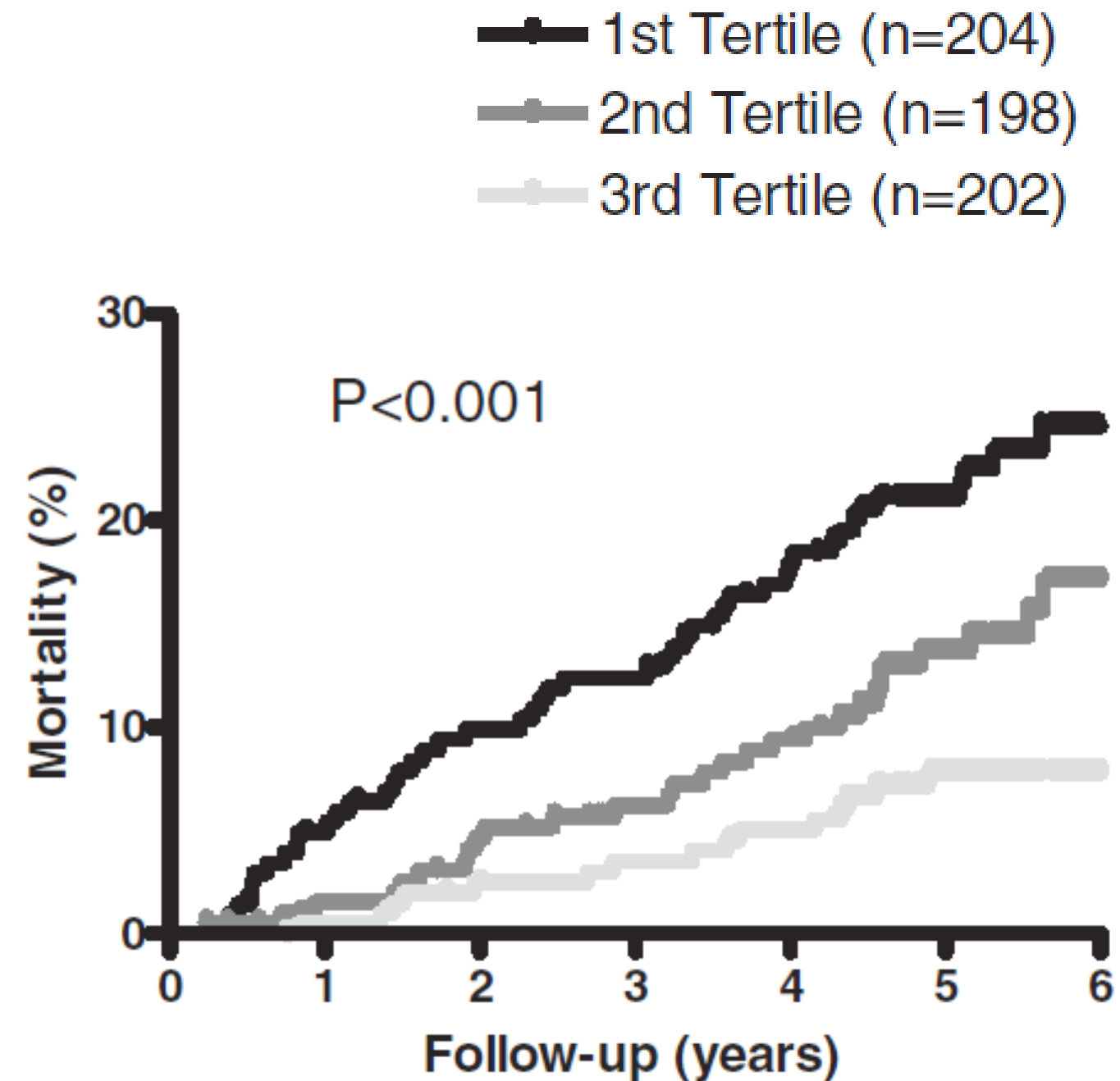


24 uurs Creatinine Excretie is de Gouden Standaard voor bepaling functionele spiermassa

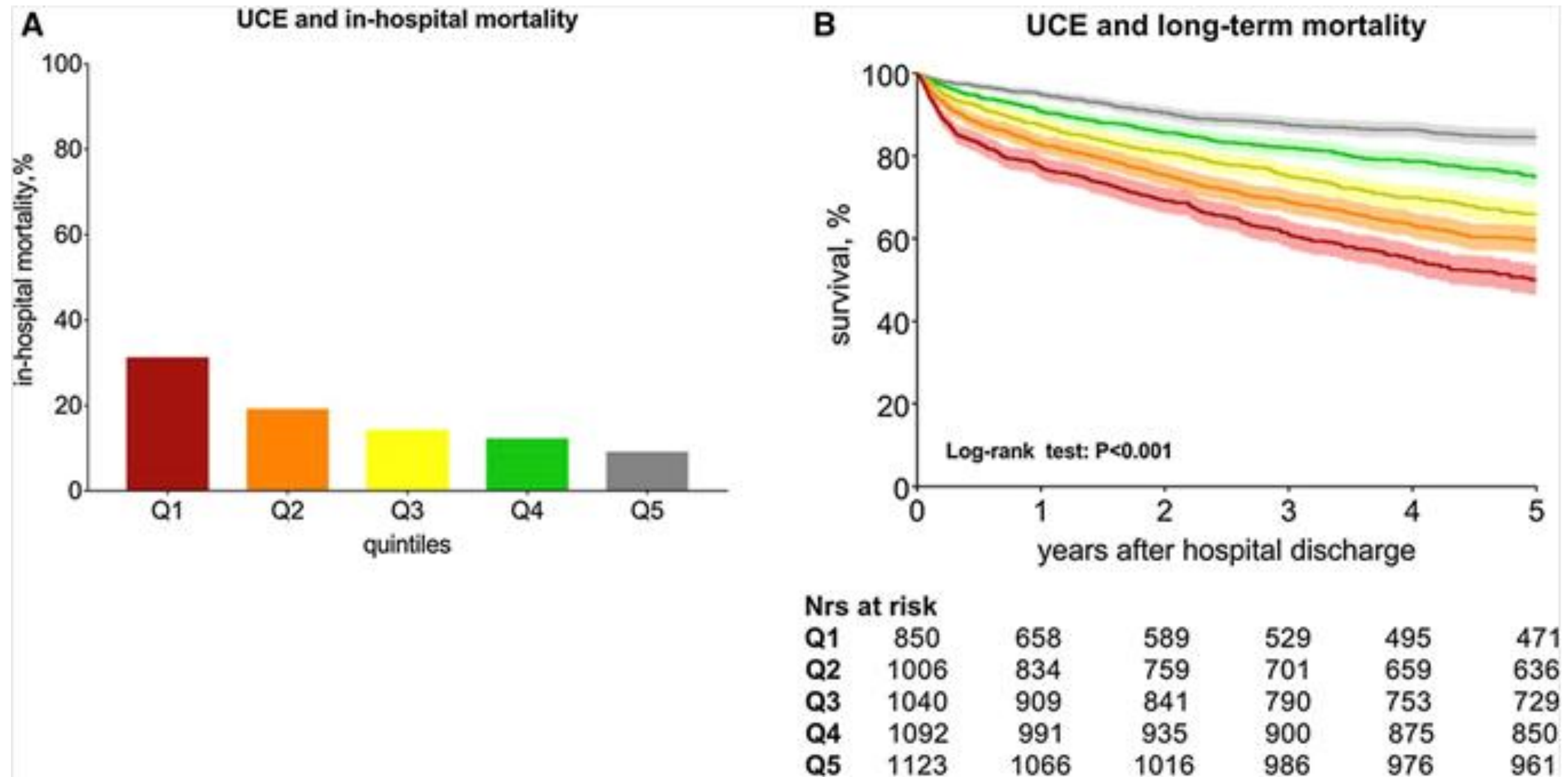
Beter dan CT, MRI, DEXA en BIA, omdat er geen interferentie is van lichaamswater, inter- en intramusculair vet, bindweefsel, zenuwweefsel en bloedvaten

# 24 uurs Urine Creatinine Excretie is een Uitstekende Gezondheidsmaat

- Kidney Transplant Recipients (Oterdoom LH et al. Transplantation 2008)
- General Population (Oterdoom LH et al. Atherosclerosis 2009)
- Diabetes (Sinkeler SJ et al. Diabetes Care 2013)
- Heart Failure (ter Maaten JM et al. Clin Res Cardiol 2014)

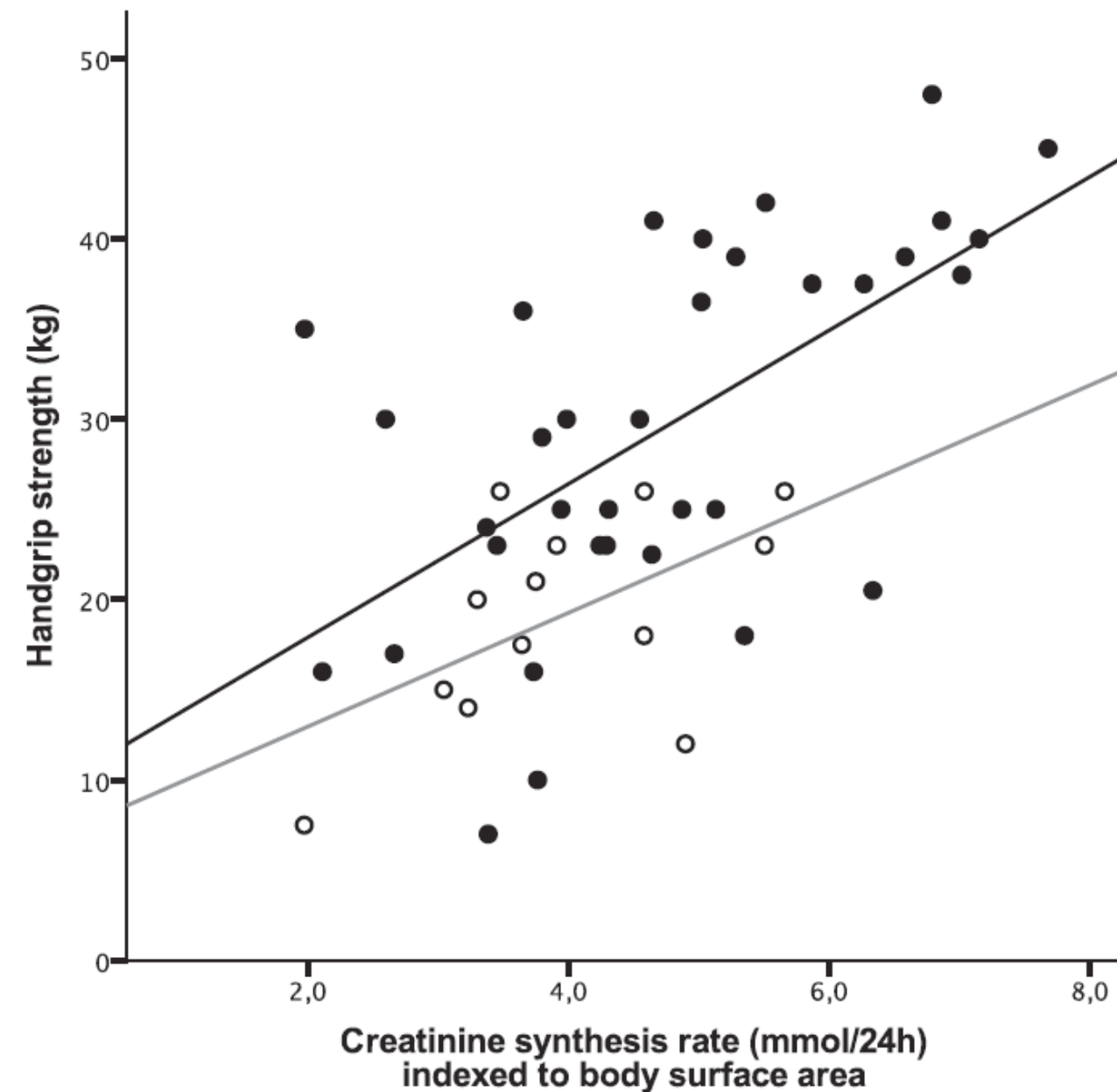


# 24 uurs Urine Creatinine Excretie en Sterfte bij ICU patiënten



Hessels L et al. Intensive Care Med 2018; 44: 1699-1708

# Dialysaat Creatinine Excretie als maat voor spiermassa



**Fig. 1.** Scatter plot of the correlation between Creatinine Synthesis Rate, indexed to BSA, and handgrip strength. Legend Fig. 1: Scatter plot of the correlation between creatinine synthesis rate, indexed to body surface area, and handgrip strength. For the total cohort the correlation coefficient was 0.63 ( $P < 0.001$ ); The correlation coefficient was 0.61 in men (solid circles,  $P < 0.001$ ), and 0.56 (open circles,  $P = 0.045$ ) in women.

Poppe ESJM et al. Clin Nutr 2019

# Creatine, Creatinine en Guanidinoacetate concentraties in dialyse patienten

	Overall	Males	Females	
Creatine				
Predialysis concentration, $\mu\text{mol/L}$	26 [16–41] ***	19 [15–33] *	33 [24–56] ***	0.01
Postdialysis concentration, $\mu\text{mol/L}$	21 [15–30] ***	20 [15–25] *	24 [15–37] ***	0.01
Absolute decrease, $\mu\text{mol/L}$	5 [1–14] ***	3 [0–8] *	10 [3–18] ***	0.02
Proportional decrease, %	13 $\pm$ 39*	5 $\pm$ 43	27 $\pm$ 26***	0.02
Creatinine				
Predialysis concentration, $\mu\text{mol/L}$	689 $\pm$ 207***	706 $\pm$ 224***	660 $\pm$ 175***	0.4
Postdialysis concentration, $\mu\text{mol/L}$	257 $\pm$ 92***	274 $\pm$ 97***	228 $\pm$ 78***	0.07
Absolute decrease, $\mu\text{mol/L}$	432 $\pm$ 146***	432 $\pm$ 156***	432 $\pm$ 130***	0.9
Proportional decrease, %	63 $\pm$ 8***	61 $\pm$ 9***	65 $\pm$ 7***	0.05

Differences between males and females are tested using an independent sample t-test. Differences between predialysis and postdialysis plasma concentrations are tested using paired sample t-test or the paired samples Wilcoxon test. Absolute decrease and proportional decrease are test against no decrease by t-test or Wilcoxon test. Statistical significance is indicated with asterixis (\* P < 0.05; \*\* P < 0.01; \*\*\* P < 0.001)

reported variation in fasting plasma creatine concentrations is high [62, 63], the median fasting plasma concentration of 26  $\mu\text{mol/L}$  observed in the hemodialysis patients in the current report is appreciably lower than reported mean values of 40.5  $\mu\text{mol/L}$  in 6 healthy subjects in a creatine supplementation study and 36.7  $\mu\text{mol/L}$  in 4,735 subjects of the general population [62, 63]. Inter-

Post A et al. J Transl Med 2021; 19: 115

# Ongewild creatine verlies gedurende dialyse

	Overall	Males	Females	
Creatine				
Total loss, $\mu\text{mol}$	719 [399–1070]	655 [397–1015]	867 [464–1363]	0.2
Estimated extracellular loss, $\mu\text{mol}$	79 [19–196] ***	58 [5–144] ***	147 [42–231] ***	0.04
Estimated intracellular loss, $\mu\text{mol}$	612 [365–902] ***	545 [365–871] ***	697 [413–1052] ***	0.4
Creatinine				
Total loss, mmol	15.5 $\pm$ 8.4	17.5 $\pm$ 9.6	12.0 $\pm$ 3.9	0.003
Estimated extracellular loss, mmol	6.8 $\pm$ 2.5*	7.2 $\pm$ 2.7*	6.2 $\pm$ 1.9	0.2
Estimated intracellular loss, mmol	8.7 $\pm$ 7.1*	10.4 $\pm$ 8.4*	5.8 $\pm$ 2.2	0.003

ECV is calculated according to the formula by Abraham et al. [27]

Differences between males and females are tested using an independent sample t-test or Mann–Whitney U test. Differences between extracellular and intracellular removal are tested using paired sample t-test or the paired samples Wilcoxon test, and statistical significance is indicated with asterix (\* P < 0.05; \*\* P < 0.01; \*\*\* P < 0.001)

Post A et al. J Transl Med 2021; 19: 115

# 24uurs Creatinine Productie en Sterfte bij Dialysis Patiënten

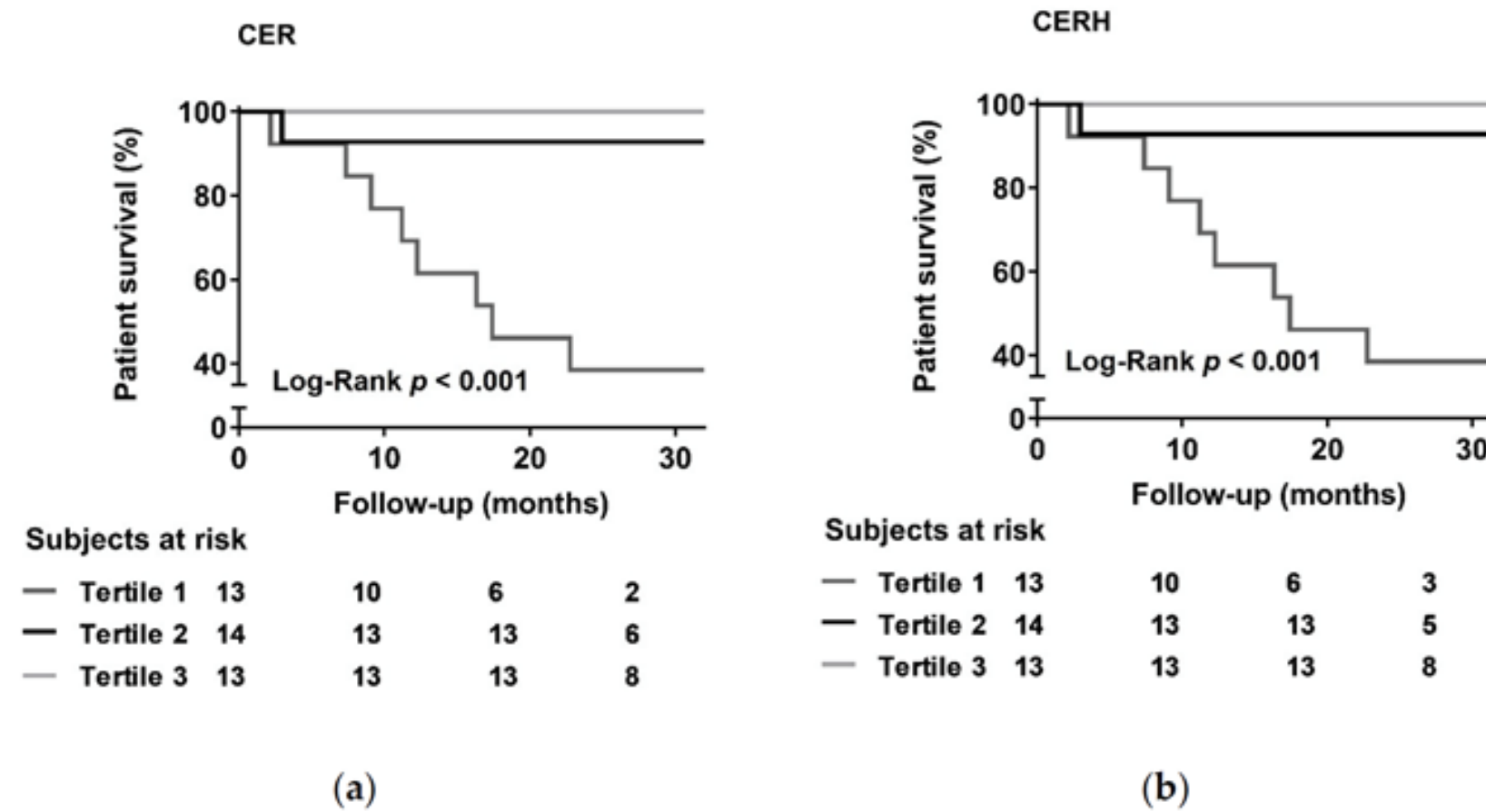


Figure 5. (a) Kaplan-Meier curves for sex-stratified tertiles of creatinine excretion rate (CER) and (b) creatinine excretion rate, indexed to height<sup>2</sup> (CERH).

Table 4. Cox regression analyses for prediction of patient mortality based on excretion of creatinine excretion rate (CER) and creatinine excretion indexed to height<sup>2</sup> (CERH).

Model	CER		CERH	
	HR (95% CI)	p-Value	HR (95% CI)	p-Value
1	0.59 (0.42–0.84)	0.003	0.13 (0.04–0.45)	0.001
2	0.50 (0.29–0.83)	0.007	0.14 (0.03–0.61)	0.009
3	0.47 (0.28–0.79)	0.005	0.12 (0.03–0.56)	0.007
4	0.49 (0.29–0.82)	0.007	0.14 (0.03–0.62)	0.010
5	0.50 (0.30–0.82)	0.007	0.14 (0.03–0.61)	0.009

Model 1, crude model; model 2, adjusted for age and sex; model 3, as model 2, additionally adjusted BMI; model 4, as model 2, additionally adjusted for BSA; model 5, as model 2, additionally adjusted for systolic blood pressure.

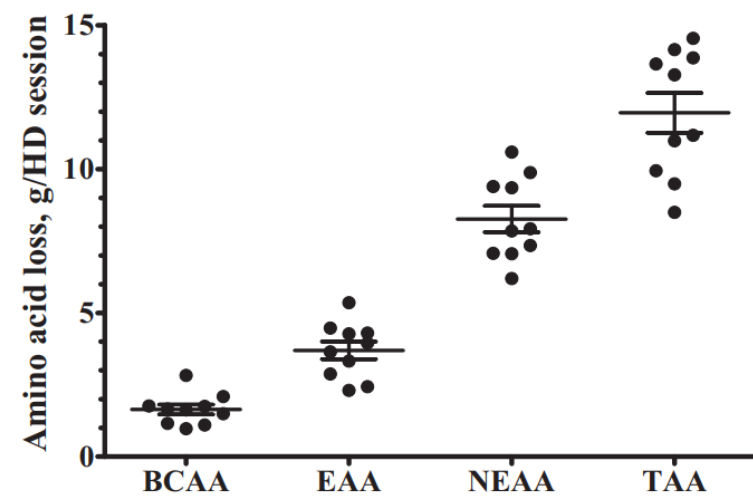
Post A et al. Nutrients 2018; 10: 1827

# Verlies van aminozuren tijdens dialyse

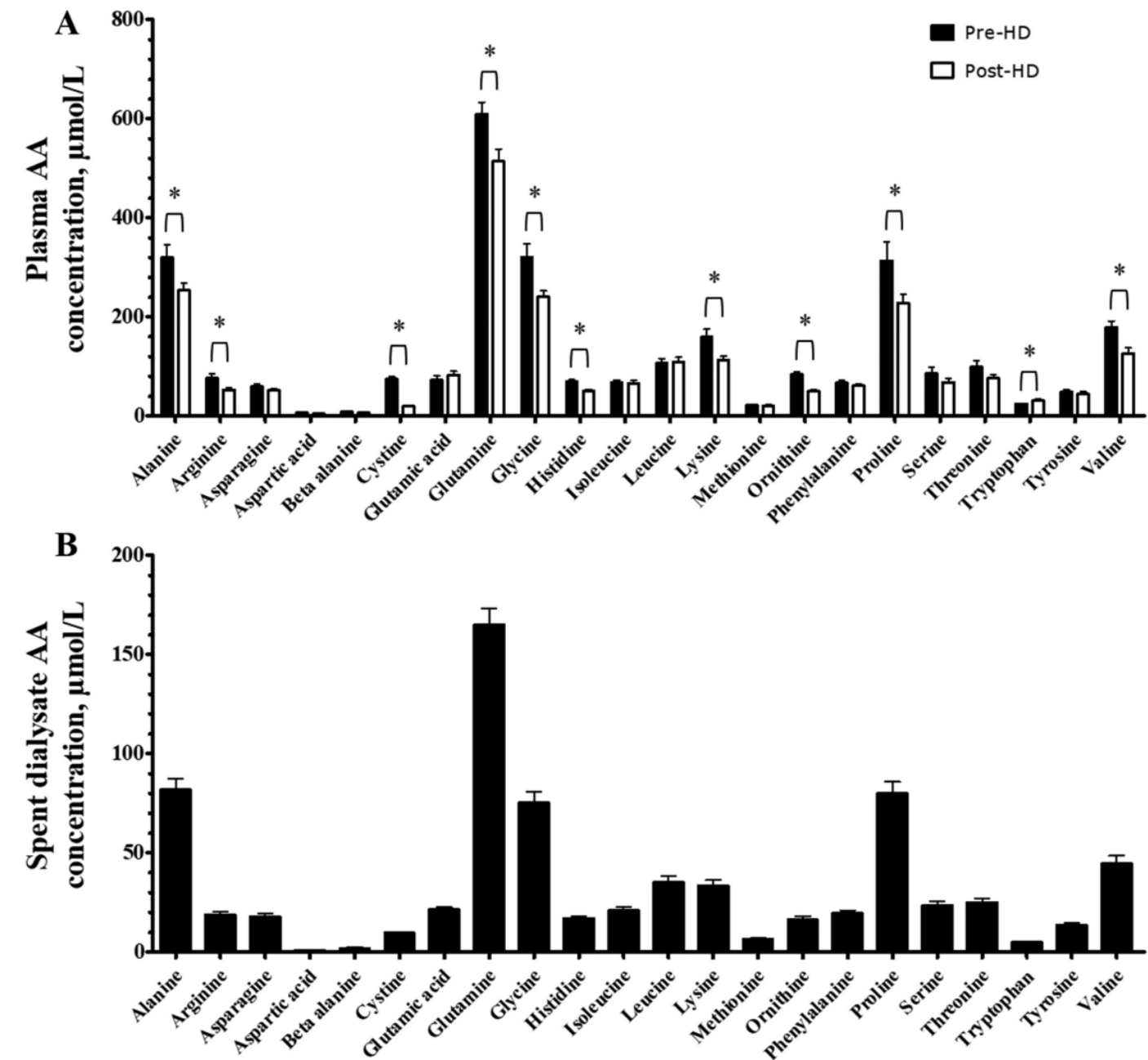
**TABLE 1** Characteristics of included CHD patients<sup>1</sup>

	Patients
Age, y	67.9 ± 19.3
Gender, <i>n</i>	
Male	7
Female	3
Cause of ESRD, <i>n</i>	
Hypertension	4
Diabetes mellitus	2
Autoimmune	2
Other	2
Dialysis vintage, mo	46.8 ± 28.4
Height, cm	166 ± 9
Weight, kg	64.4 ± 15.9
BMI, kg/m <sup>2</sup>	23.2 ± 3.5
Lean tissue index, kg/m <sup>2</sup>	11.7 ± 1.7
Handgrip strength, kg	24.5 ± 11.7
Serum albumin, g/L	33.5 ± 2.6

<sup>1</sup>All values are expressed as mean ± SD, *n* = 10. CHD, chronic hemodialysis; ESRD, end-stage renal disease.



**FIGURE 2** AA loss during a single HD session in CHD patients. Filled circles represent individual data points and bars represent group means ± SEMs, *n* = 10. AA, amino acid; BCAA, branched-chain amino acid; CHD, chronic hemodialysis; EAA, essential amino acid; HD, hemodialysis; NEAA, nonessential amino acid; TAA, total amino acid.



**FIGURE 1** AA concentrations in (A) pre- and post-HD plasma and (B) spent dialysate of CHD patients. Plasma concentrations of 22 AAs are expressed as µmol/L. Values represent means ± SEMs, *n* = 10. \*Post-HD plasma AA concentrations are significantly different from pre-HD plasma AA concentrations, *P* < 0.05. AA, amino acid; CHD, chronic hemodialysis; HD, hemodialysis.

# Het belang van het hebben van genoeg spiermassa bij dialyse

Table 1. Baseline patient characteristics by body mass index (BMI) groups ( $N = 70,028$ )<sup>a</sup>

Characteristic	Normal BMI ( $n = 34,046$ )	High BMI ( $n = 35,982$ )
Age, mean $\pm$ SD (yr)	66 $\pm$ 15.0	64 $\pm$ 13.3
Male gender, $n$ (%)	18,106 (53)	15,582 (43)
Race, $n$ (%)		
white	23,231 (68)	23,431 (65)
African American	7891 (23)	10,033 (28)
other	2924 (9)	2518 (7)
Medicare insurance, $n$ (%)	22,043 (65)	21,179 (59)
Comorbid condition, $n$ (%)		
diabetes as cause of renal failure	13,057 (38)	18,795 (52)
coronary artery disease	11,727 (34)	11,630 (32)
cerebrovascular accident	4123 (12)	3677 (10)
peripheral vascular disease	6783 (20)	6385 (18)
heart failure <sup>b</sup>	13,962 (41)	14,976 (42)
lung disease	3412 (10)	2713 (8)
cancer	2084 (6)	1713 (5)
current smoker	2334 (7)	1691 (5)
Functional status, $n$ (%)		
requires assistance to transfer <sup>b</sup>	626 (2)	610 (2)
requires assistance to ambulate <sup>b</sup>	1819 (5)	1850 (5)
Nutritional parameters		
BMI, mean $\pm$ SD ( $\text{kg}/\text{m}^2$ )	22.0 $\pm$ 1.8	30.5 $\pm$ 4.9
weight (kg)	62.2 $\pm$ 9.2	82.9 $\pm$ 14.6
24-h urine creatinine (g/dl)	0.76 $\pm$ 0.35	0.86 $\pm$ 0.39
Serum albumin, mean $\pm$ SD (g/dl)	3.1 $\pm$ 0.7	3.2 $\pm$ 0.6
Outcome		
all-cause death	16,285 (48)	13,677 (38)
cardiovascular death	8388 (25)	7413 (21)

<sup>a</sup> Normal BMI,  $18.5 \leq \text{BMI} \leq 24.9 \text{ kg}/\text{m}^2$ ; high BMI,  $\geq 25.0 \text{ kg}/\text{m}^2$ .

<sup>b</sup> Differences between groups were not significant ( $P \geq 0.05$ ). For all other comparisons,  $P < 0.05$ .

Table 4. Multivariable Cox regression models of all-cause death and cardiovascular death with body-mass index (BMI) and urinary creatinine (UCr) as continuous variables in the entire cohort and in BMI subgroups<sup>a</sup>

Model	All-Cause Death		Cardiovascular Death	
	Hazard Ratio (95% CI)	$P$ value	Hazard Ratio (95% CI)	$P$ value
All patients ( $n = 70,028$ )				
each 5 $\text{kg}/\text{m}^2$ increase in BMI	0.95 (0.93 to 0.96)	<0.001	0.95 (0.94 to 0.97)	<0.001
each g/d increase in UCr	0.68 (0.65 to 0.70)	<0.001	0.67 (0.64 to 0.71)	<0.001
18.5 $\leq$ BMI < 25 ( $n = 34,046$ )				
each 5 $\text{kg}/\text{m}^2$ increase in BMI	0.87 (0.83 to 0.91)	<0.001	0.91 (0.85 to 0.96)	0.001
each g/d increase in UCr	0.70 (0.66 to 0.74)	<0.001	0.68 (0.63 to 0.73)	<0.001
25 $\leq$ BMI < 30 ( $n = 20,598$ )				
each 5 $\text{kg}/\text{m}^2$ increase in BMI	0.94 (0.87 to 1.01)	0.097	0.90 (0.81 to 1.00)	0.055
each g/d increase in UCr	0.68 (0.63 to 0.73)	<0.001	0.67 (0.61 to 0.74)	<0.001
BMI $\geq$ 30 ( $n = 15,384$ )				
each 5 $\text{kg}/\text{m}^2$ increase in BMI	1.04 (1.01 to 1.07)	0.021	1.02 (0.98 to 1.07)	0.317
each g/d increase in UCr	0.67 (0.62 to 0.73)	<0.001	0.69 (0.62 to 0.78)	<0.001

<sup>a</sup> Each model adjusted for age, gender, race, Medicare insurance, comorbid condition, functional status, and serum albumin levels.

# Huidige Dieet Richtlijnen bij Chronic Kidney Disease

- Gebaseerd op problemen met
  - Excretie van ureum (= Afbraakproduct van eiwit)
  - Excretie van zuur (= Afbraakproduct van zwavelhoudende aminozuren, vooral in dierlijk eiwit)
  - Excretie van fosfaat (= hoge hoeveelheid in dierlijk eiwit en natuurlijk in ultra-processed foods)
- Laag eiwit dieet
  - Als eiwit wordt gegeten, is het bij voorkeur uit plantaardig materiaal

# Dieet bij CKD

**Table 2. Recommended Dietary and Nutrient Intake in Adults, According to the CKD Stage.\***

Dietary Constituent	Normal Kidney Function with Increased CKD Risk	Mild-to-Moderate CKD†	Advanced CKD†	Transition to Dialysis‡	Ongoing Dialysis or Any Stage with Existing or Imminent PEW
Protein (g/kg/day)	<1.0; increase proportion of plant-based proteins	<1.0 (consider 0.6–0.8 if eGFR <45 ml/min/1.73 m <sup>2</sup> or rapid progression)	0.6–0.8, including 50% HBV protein, or <0.6 with addition of EAA or KA	0.6–0.8 on nondialysis days and >1.0 on dialysis days	1.2–1.4; may require >1.5 if hypercatabolic state develops
Sodium (g/day)‡	<4 (<3 in patients with hypertension)§	<4; avoid intake of <1.5 if hyponatremia likely	<3; avoid intake of <1.5 if hyponatremia likely	<3	<3
Potassium (g/day)¶	4.7 (same as recommended for general population)	4.7 unless frequent or severe hyperkalemia excursions likely	<3 if hyperkalemia occurs frequently during high-fiber intake	<3 if hyperkalemia occurs frequently during high-fiber intake	<3; target high-fiber intake
Phosphorus (mg/day)‖	<1000; minimize added inorganic phosphorus in preservatives and processed foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus and encourage consumption of more plant-based foods	<800; minimize added inorganic phosphorus; consider phosphorus binder	<800; minimize added inorganic phosphorus; add phosphorus binder as needed
Calcium (mg/day)	1000–1300 (adjusted for age)	800–1000	800–1000	800–1000 or less	<800
Fibers, alkali, and plant-based foods (g/day)	25–30; target higher proportion (>50%) of plant-based foods (e.g., DASH diet)	25–30 or more; higher proportion (>50%) of plant-based foods	25–30 or more; consider >70% plant-based foods	25–30 or more	25–30 or more; suggest avoiding strict vegan diet
Energy (kcal/kg/day)**	30–35; adjust to target weight reduction if BMI >30††	30–35; increase proportion with LPD	30–35; increase proportion with LPD	30–35	30–35; target higher intake if PEW present or imminent
Fats	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids; increase proportion with low-protein intake	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids	Mostly monounsaturated and polyunsaturated lipids, including n–3 fatty acids

Kalantar-Zadeh K et al. New Engl J Med 2017; 377: 1765-1776

# K/DOQI Richtlijn over voeding bij dialyse

S40

K/DOQI NUTRITION IN CHRONIC RENAL FAILURE

## 3. Management of Protein and Energy Intake

<b>G U I D E L I N E</b>	<b>Dietary Protein Intake (DPI) in Maintenance Hemodialysis (MHD)</b>
	The recommended DPI for clinically stable MHD patients is 1.2 g/kg body weight/d. ( <i>Evidence and Opinion</i> )
	<ul style="list-style-type: none"><li>• At least 50% of the dietary protein should be of high biological value.</li></ul>

RATIONALE

DPI is often reported to be low in MHD

ADULT GUIDELINES

S41

gested should be of high biological value. Protein of high biological value has an amino acid composition that is similar to human protein, is likely to be an animal protein, and tends to be utilized more efficiently by humans to conserve body proteins. The increased efficiency of utilization of high biological value protein is particularly likely to be observed in individuals with low protein intakes.

therefore recommended that a safe DPI that will maintain protein balance in almost all clinically stable MHD patients is 1.2 g protein/kg BW/d; at least 50% of the protein should be of high biological value.

It is difficult for some MHD patients to maintain this level of daily protein intake. Techniques must be developed to ensure this level of intake for all patients. Education and dietary counseling

## NUTRITION AND DIALYSIS

# National Kidney Foundation K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure

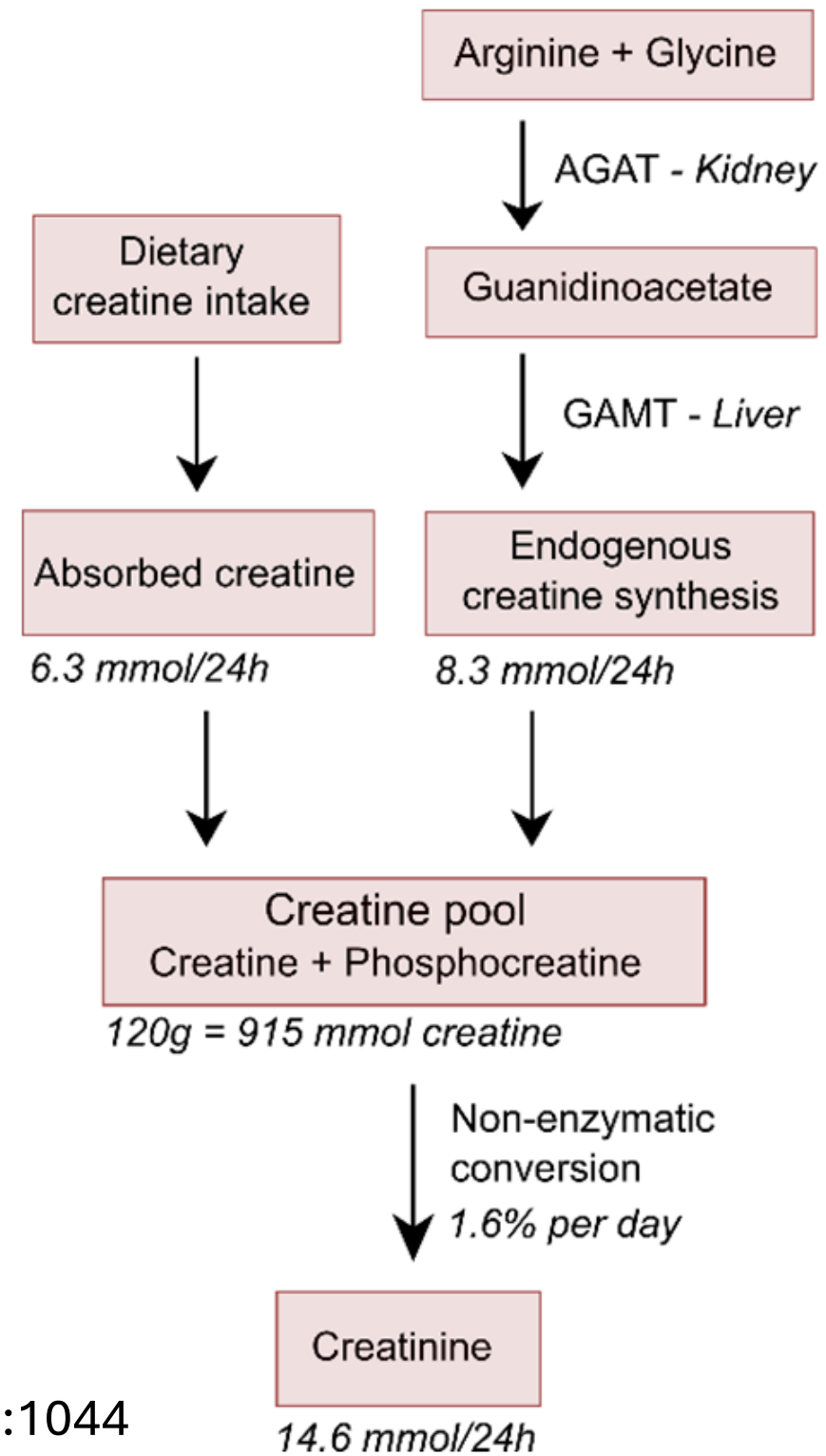
Joel D. Kopple, MD

● The National Kidney Foundation Kidney Disease Outcomes Quality Initiative Clinical Practice Guidelines for Nutrition in Chronic Renal Failure was recently published in the *American Journal of Kidney Diseases*. This publication provides 27 clinical practice guidelines for adults and 10 clinical practice guidelines for children. The adult guidelines focus primarily on patients undergoing maintenance dialysis therapy, although there are several clinical practice guidelines on nutritional issues for patients with advanced chronic renal failure (CRF) not undergoing dialysis therapy. The pediatric guidelines focus entirely on children undergoing maintenance dialysis treatment. The present article discusses a number of the more prominent clinical practice guidelines for the adults. Among these is the recommendation that the protein-energy nutritional status in these patients should be assessed by a panel of measures rather than by any single measure. Also, non-dialyzed patients with advanced CRF (ie, glomerular filtration rate <25 mL/min) and those undergoing maintenance hemodialysis or chronic peritoneal dialysis should be prescribed a dietary energy intake of 35 kcal/kg/day for patients who are <60 years of age and 30 kcal/kg for patients ≥60 years of age. Maintenance hemodialysis patients should be prescribed 1.2 g protein/kg/d; chronic peritoneal dialysis patients should be prescribed 1.2 to 1.3 g protein/kg/d. For non-dialyzed patients with CRF (glomerular filtration rate <25 mL/min), 0.60 g protein/kg/d should be prescribed. For patients who will not accept such a diet or are unable to maintain an adequate energy intake on that diet, a protein intake of up to 0.75 g protein/kg/d may be prescribed. At least 50% of the protein intake for all of these patients should be of high biologic value. A guideline concerning indications for inaugurating maintenance dialysis treatment or renal transplantation on the basis of deteriorating nutritional status is also given.

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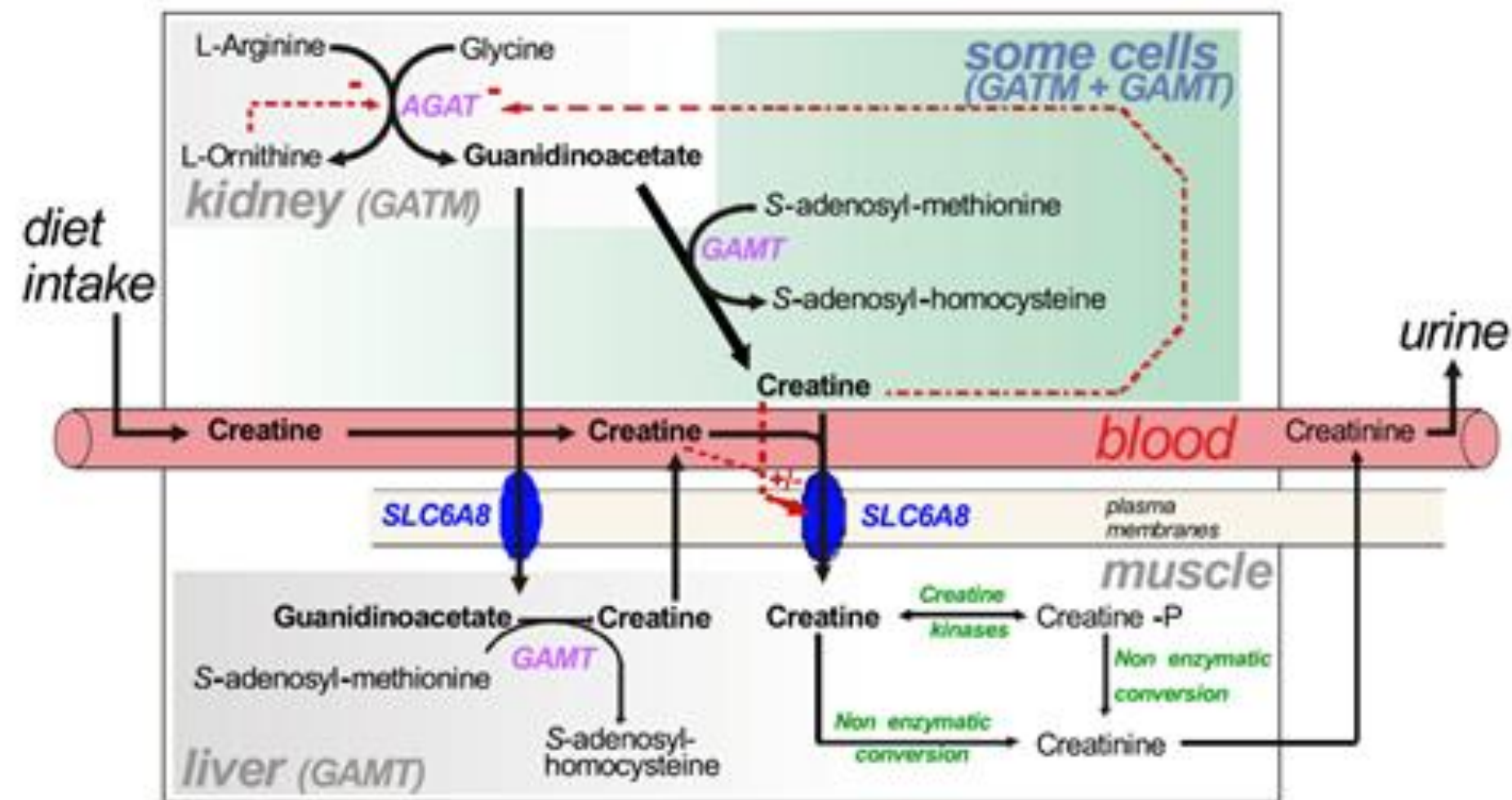
Kopple JD. Am J Kidney Dis 2001; 37 Suppl 2: S66-S70

# Creatine Homeostase bij 70-kg zware man



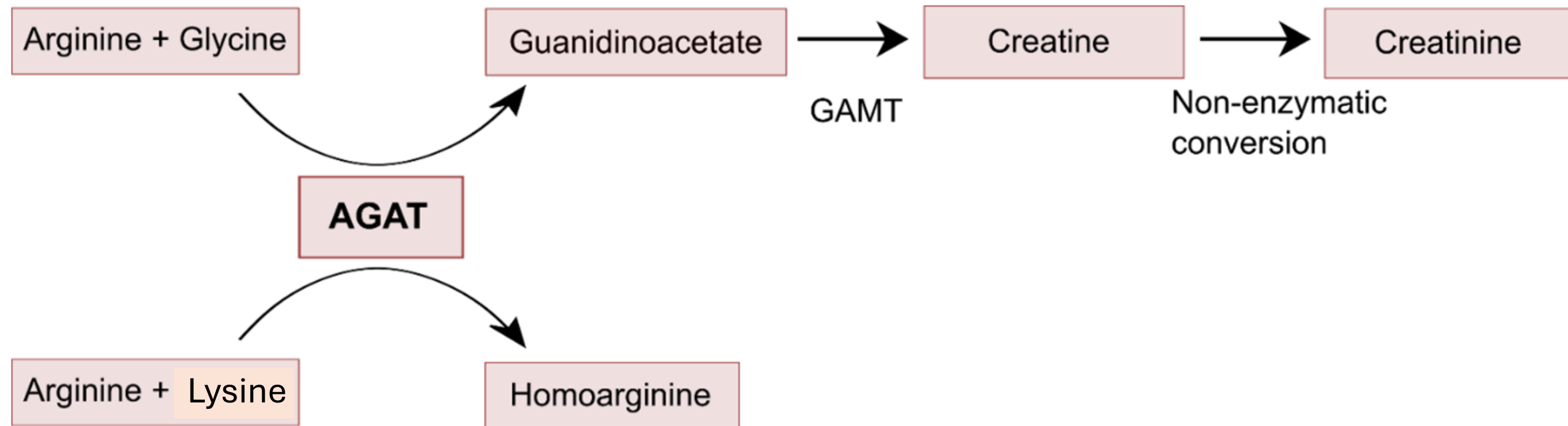
Post A et al. Nutrients 2019; 10;11(5):1044

# Essentiële Rol van de Nier in Endogene Creatine Biosynthese



**Fig. 2.** Creatine metabolism: biosynthesis, transport and intra-regulatory interactions. Kidney is the major site for the expression of AGAT which converts arginine and glycine to guanidinoacetate (and L-ornithine). For pursuing creatine biosynthesis, guanidinoacetate is methylated essentially in liver by GAMT using S-adenosylmethionine as a methyl donor. Creatine from *de novo* biosynthesis or from diet source transits by blood and is up-taken by tissues or cells expressing Na<sup>+</sup>-dependent SLC6A8, a plasmic membrane transporter responsible for intracellular incorporation of creatine. Cellular creatine may be phosphorylated to creatine phosphate by creatine kinase(s) in muscle and many other cell types including CNS cells. Creatinine, the formation of which is correlated with muscle mass, is an end-product of metabolism which is removed in the urine, stagnation in blood being observed when renal function is altered. Dashed red lines/arrows/symbols emphasize the major regulations taking place in creatine metabolism. Abbreviations are: AGAT, L-arginine:glycine amidinotransferase; GAMT, N-guanidinoacetate methyltransferase; SLC6A8, creatine transporter.

# Endogene creatine synthese and afbraak



**Figure 2.** Enzymatic functions of AGAT, showing that guanidinoacetate is further metabolized to creatine and eventually creatinine, while homoarginine is not further metabolized.

# Verminderde homoarginine en guanidinoacetate productie na nierdonatie

**Table 1.** Effect of unilateral nephrectomy on biochemical parameters in 127 healthy kidney donors. Study design and methods are described previously [51,52].

Variable	N	Before Donation	After Donation	Absolute Difference	Change in Mean (%)	p-Value
Urinary <u>homoarginine</u> excretion ( $\mu\text{mol}/24\text{h}$ )	127	4.0 $\pm$ 4.4	3.0 $\pm$ 2.3	1.1 $\pm$ 3.4	-25	0.001
Urinary urea excretion ( $\text{mmol}/24\text{h}$ )	125	420 $\pm$ 127	394 $\pm$ 111	26 $\pm$ 140	-6	0.04
Urinary sodium excretion ( $\text{mmol}/24\text{h}$ )	125	203 $\pm$ 72	176 $\pm$ 65	27 $\pm$ 82	-13	<0.001
Plasma <u>homoarginine</u> ( $\mu\text{mol}/\text{L}$ )	125	1.7 $\pm$ 0.6	1.5 $\pm$ 0.5	0.2 $\pm$ 0.4	-12	<0.001
Plasma <u>guanidinoacetate</u> ( $\mu\text{mol}/\text{L}$ )	127	2.9 $\pm$ 1.1	2.3 $\pm$ 0.5	0.6 $\pm$ 1.0	-23	<0.001
Serum creatinine ( $\mu\text{mol}/\text{L}$ )	127	73 $\pm$ 12	107 $\pm$ 21	-35 $\pm$ 11	+47	<0.001
<u>mGFR</u> ( $\text{mL}/\text{min}$ )	127	118 $\pm$ 24	74 $\pm$ 14	43 $\pm$ 14	-37	<0.001
<u>eGFR</u> ( $\text{mL}/\text{min}/1.73 \text{ m}^2$ )	127	95 $\pm$ 16	60 $\pm$ 12	34 $\pm$ 10	-37	<0.001

Abbreviations: eGFR: estimated glomerular filtration rate. mGFR: measured glomerular filtration rate.

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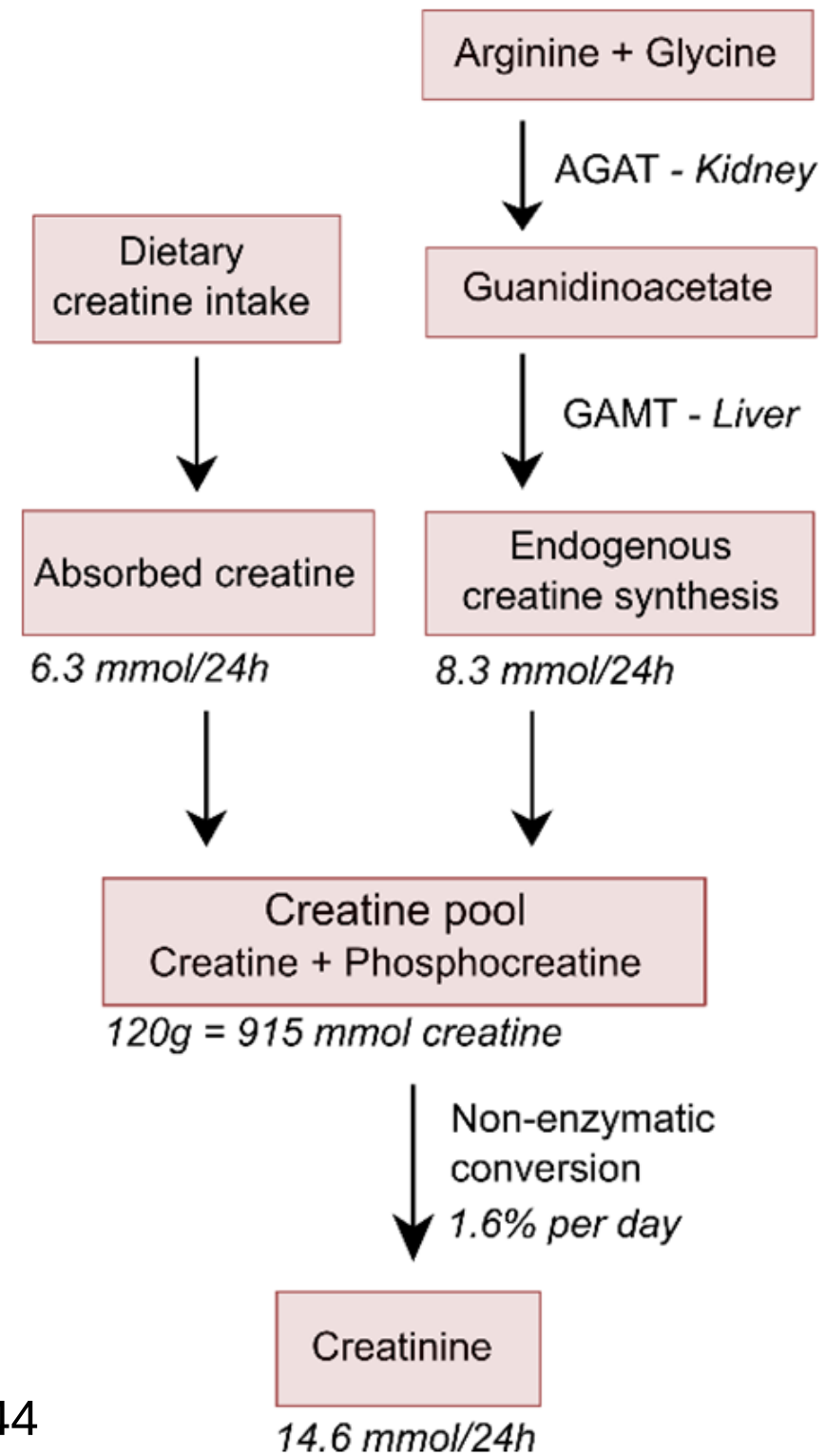
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# Creatine Homeostase bij een 70 kg wegende man



Post A et al. Nutrients 2019; 11: E1044

# Genetische AGAT deficiëntie

Molecular Genetics and Metabolism 116 (2015) 252–259



Contents lists available at ScienceDirect

Molecular Genetics and Metabolism

journal homepage: [www.elsevier.com/locate/ymgme](http://www.elsevier.com/locate/ymgme)



## Arginine:glycine amidinotransferase (AGAT) deficiency: Clinical features and long term outcomes in 16 patients diagnosed worldwide



Sylvia Stockler-Ipsiroglu<sup>a,b,\*</sup>, Delia Apatean<sup>a</sup>, Roberta Battini<sup>c</sup>, Suzanne DeBrosse<sup>d</sup>, Kimberley Dessoify<sup>d</sup>, Simon Edvardson<sup>e</sup>, Florian Eichler<sup>f</sup>, Katherine Johnston<sup>g</sup>, David M. Koeller<sup>h</sup>, Sonia Nouioua<sup>i</sup>, Meriem Tazir<sup>i</sup>, Ashok Verma<sup>j</sup>, Monica D. Dowling<sup>k</sup>, Klaas J. Wierenga<sup>l</sup>, Andrea M. Wierenga<sup>l</sup>, Victor Zhang<sup>m</sup>, Lee-Jun C. Wong<sup>m</sup>

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### ABSTRACT

**Background:** Arginine:glycine aminotransferase (AGAT) (*GATM*) deficiency is an autosomal recessive inborn error of creative synthesis.

**Objective:** We performed an international survey among physicians known to treat patients with AGAT deficiency, to assess clinical characteristics and long-term outcomes of this ultra-rare condition.

**Results:** 16 patients from 8 families of 8 different ethnic backgrounds were included. 1 patient was asymptomatic when diagnosed at age 3 weeks. 15 patients diagnosed between 16 months and 25 years of life had intellectual disability/developmental delay (IDD). 8 patients also had myopathy/proximal muscle weakness. Common biochemical denominators were low/undetectable guanidinoacetate (GAA) concentrations in urine and plasma, and low/undetectable cerebral creatine levels. 3 families had protein truncation/null mutations. The rest had missense and splice mutations.

Treatment with creatine monohydrate (100–800 mg/kg/day) resulted in almost complete restoration of brain creatine levels and significant improvement of myopathy. The 2 patients treated since age 4 and 16 months had normal cognitive and behavioral development at age 10 and 11 years. Late treated patients had limited improvement of cognitive functions.

**Conclusion:** AGAT deficiency is a treatable intellectual disability. Early diagnosis may prevent IDD and myopathy. Patients with unexplained IDD with and without myopathy should be assessed for AGAT deficiency by determination of urine/plasma GAA and cerebral creatine levels (via brain MRS), and by *GATM* gene sequencing.

# Creatine als een conditioneel essentiële nutriënt

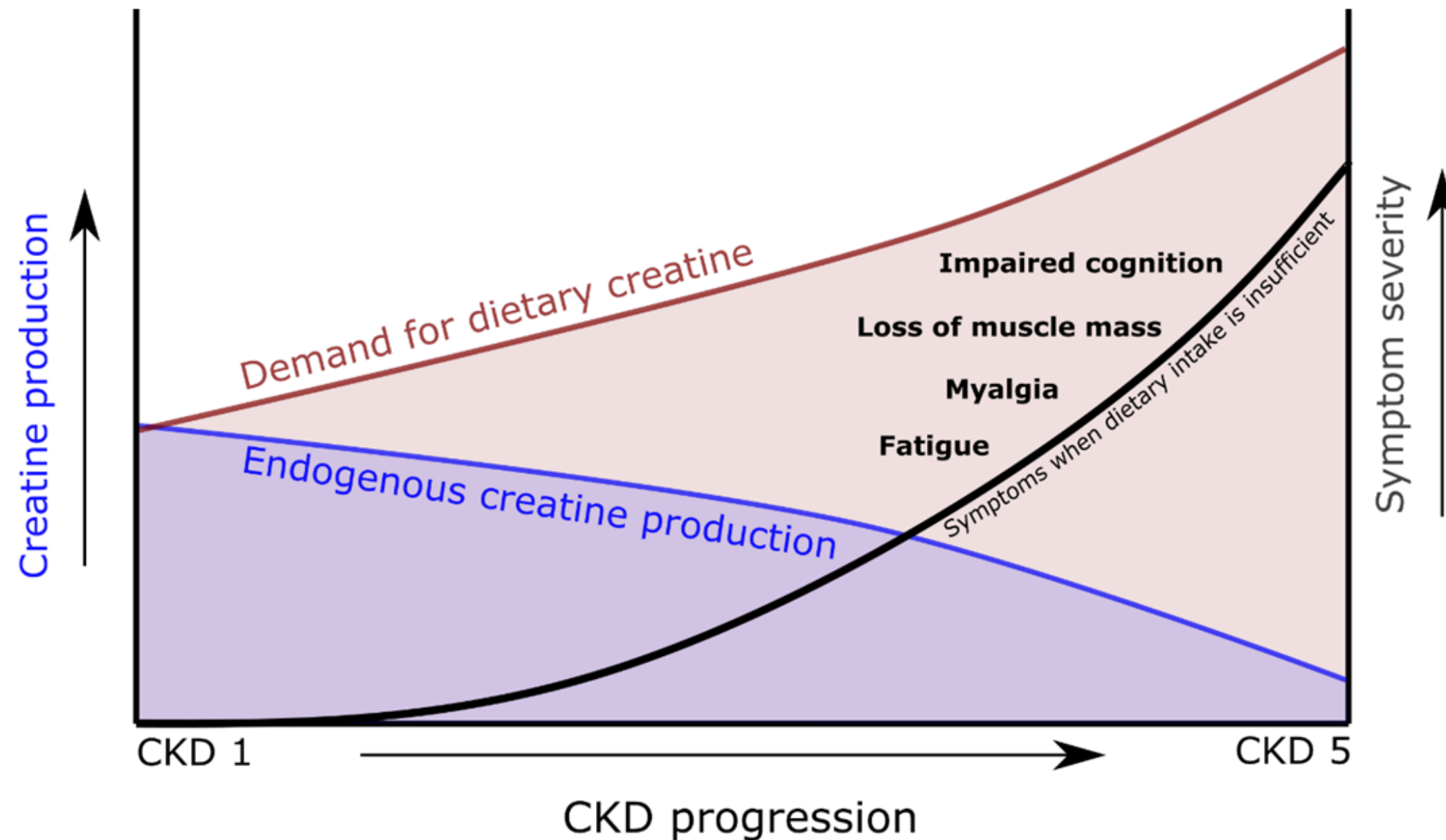


Figure 3. Schematic overview indicating the increasing demand for dietary creatine as endogenous creatine production falls during chronic kidney disease (CKD) progression.

Post A et al. Nutrients 2019; 11: E1044

# Algemene symptomen bij dialyse patienten die deels gerelateerd zouden kunnen zijn aan creatine deficiëntie

- Spierzwakte
- Spierkrampen
- Vermoeidheid
- Verminderd cognitief functioneren
- Depressie
- Hartfalen

# Veelvoorkomende Fenomenen bij Dialyse Patiënten die gerelateerd zouden kunnen zijn aan creatine deficientie

- Progressief verlies van spiermassa
- Volume overload
- Onverklaarde hyperphosphatemie
- Onverklaarde hyperkaliemie
- Gevoeligheid voor infecties

# En is het bij plantaardige voeding niet gewoon zo dat we makkelijker en meer wegblijven van ultraprocessed foods?

## Ultra-processed Foods Characteristics and Examples

### Ultra-processed foods typically contain:

- Artificial additives
- Preservatives
- Flavor enhancers



### Types of ultra-processed foods

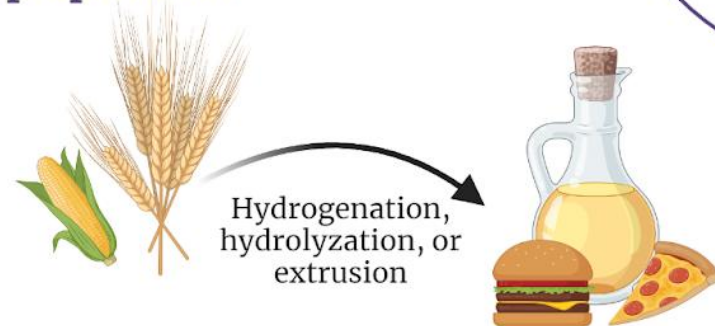
- Instant noodles
- Artificially sweetened foods
- Sugary cereals
- Microwaveable meals
- Reconstituted meat products
- Sweet and savory packaged snacks
- Pre-prepared frozen dishes
- Soft drinks



### Ultra-processed foods

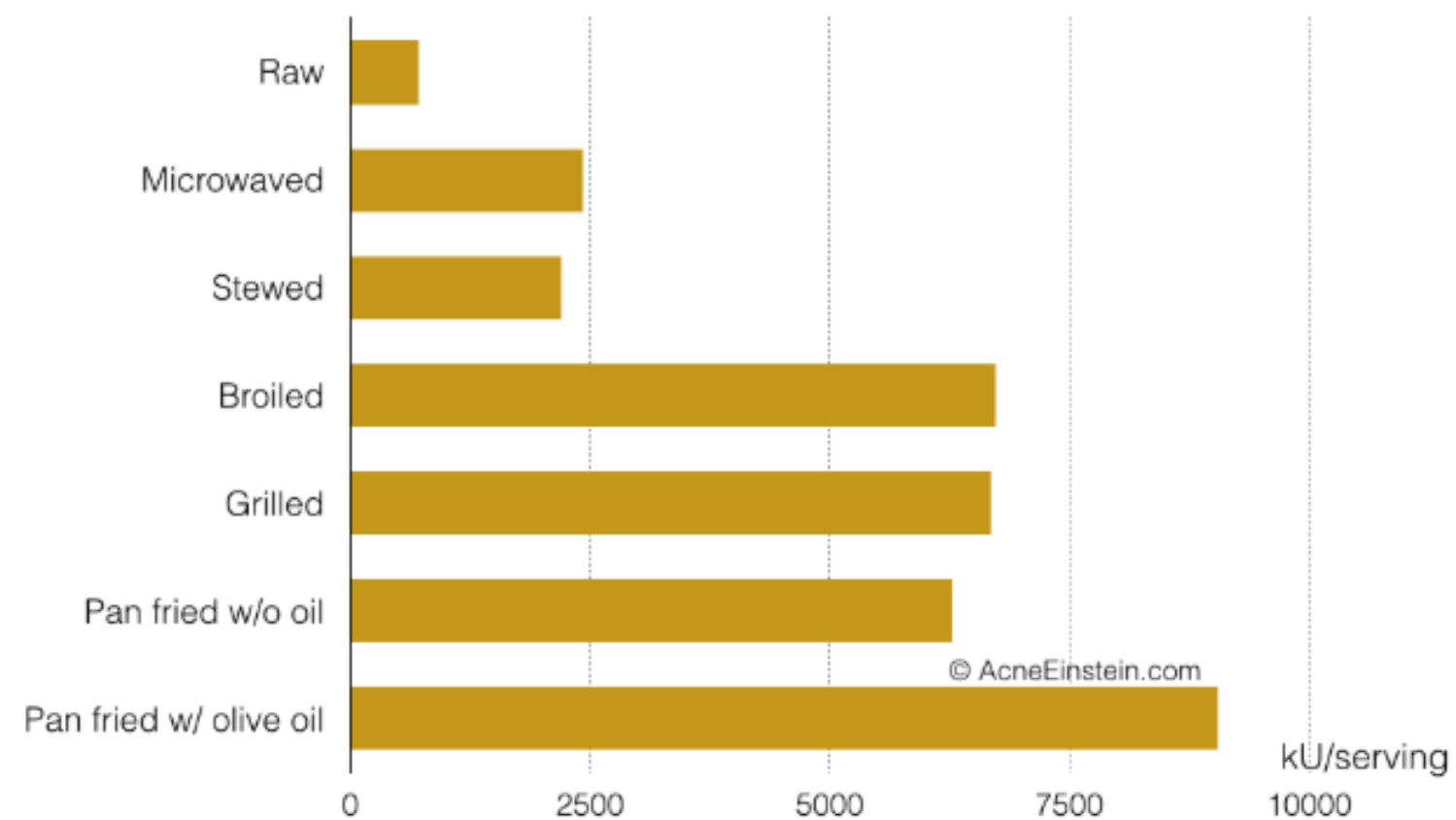


### Ultra-processed food preparation



# Effect van bereiding methode op de vorming van Advanced Glycation End products in rundvlees

Effect of cooking on AGE content in beef



The cooking methods that use dry heat and high temperatures create the most AGEs, whereas cooking techniques that use water or low to medium temperatures cause much less damage. The safest cooking methods include:

Boiling

Steaming

Microwave cooking

Pan frying in low to medium heat

Stewing

Poaching

Slow cookers

# Vragenlijst naar intake van fruit en sterfte bij niertransplantatiepatiënten

**Table 3. Association of fruit consumption with risk of cardiovascular and all-cause mortality in 400 RTRs, adjusted for confounders<sup>a</sup>**

Outcomes, mortality	Categories of fruit consumption, servings/day								Fruit consumption, servings/day (N = 400)		
	0-1 (n = 207)		2 (n = 129)			≥3 (n = 64)			Events	HR (95% CI)	P-value
	Events	Reference	Events	HR (95% CI)	ARR (%)	Events	HR (95% CI)	ARR (%)			
Cardiovascular	25	-	17	-	1	7	-	-1	49	-	-
Model 1 <sup>b</sup>		1.00		0.74 (0.39-1.41)			0.59 (0.24-1.47)			0.82 (0.60-1.12)	0.21
Model 2 <sup>c</sup>		1.00		0.74 (0.38-1.44)			0.62 (0.25-1.55)			0.82 (0.60-1.14)	0.24
Model 3 <sup>d</sup>		1.00		0.84 (0.41-1.71)			0.82 (0.31-2.12)			0.90 (0.64-1.27)	0.55
Model 4 <sup>e</sup>		1.00		0.78 (0.38-1.57)			0.82 (0.32-2.12)			0.79 (0.57-1.10)	0.16
All-cause	45	-	36	-	6	12	-	-3	93	-	-
Model 1 <sup>b</sup>		1.00		0.77 (0.39-1.49)			0.52 (0.20-1.35)			0.86 (0.69-1.08)	0.19
Model 2 <sup>c</sup>		1.00		0.89 (0.56-1.41)			0.60 (0.31-1.17)			0.87 (0.69-1.09)	0.23
Model 3 <sup>d</sup>		1.00		0.90 (0.56-1.43)			0.63 (0.32-1.26)			0.91 (0.71-1.16)	0.45
Model 4 <sup>e</sup>		1.00		0.89 (0.55-1.46)			0.75 (0.37-1.50)			0.83 (0.65-1.05)	0.12

<sup>a</sup>Cox proportional hazards regression analysis was performed to assess the association of fruit consumption with outcomes.

<sup>b</sup>Adjusted for age, sex, income and education level.

<sup>c</sup>Model 1 plus adjustment for eGFR, proteinuria, time since transplantation and primary renal disease.

<sup>d</sup>Model 2 plus adjustment for physical activity, total cholesterol, systolic blood pressure, BMI, diabetes and smoking status.

<sup>e</sup>Model 2, plus adjustment for cardiovascular history, alcohol use and hs-CRP.

# Vragenlijst naar intake van groente en sterfte bij niertransplantatiepatiënten

**Table 4. Association of vegetable consumption with risk of cardiovascular and all-cause mortality in 400 RTRs, adjusted for confounders<sup>a</sup>**

Outcomes, mortality	Categories of vegetable consumption, tablespoons/day								Vegetable consumption, tablespoons/day (N = 400)		
	0-1 (n = 35)		2 (n = 175)			≥3 (n = 190)			Events	HR (95% CI)	P-value
	Events	Reference	Events	HR (95% CI)	ARR (%)	Events	HR (95% CI)	ARR (%)			
Cardiovascular	10	-	27	-	-14	12	-	-23	49	-	-
Model 1 <sup>b</sup>		1.00		0.44 (0.20-0.94)			0.19 (0.08-0.46)			0.52 (0.36-0.74)	<0.001
Model 2 <sup>c</sup>		1.00		0.42 (0.19-0.93)			0.18 (0.07-0.43)			0.49 (0.34-0.71)	<0.001
Model 3 <sup>d</sup>		1.00		0.44 (0.20-0.98)			0.18 (0.07-0.44)			0.50 (0.35-0.72)	<0.001
Model 4 <sup>e</sup>		1.00		0.40 (0.18-0.89)			0.17 (0.07-0.41)			0.48 (0.33-0.70)	<0.001
All-cause	12	-	46	-	-8	35	-	-16	93	-	-
Model 1 <sup>b</sup>		1.00		0.61 (0.31-1.20)			0.44 (0.22-0.89)			0.75 (0.58-0.99)	0.04
Model 2 <sup>c</sup>		1.00		0.60 (0.31-1.19)			0.41 (0.21-0.82)			0.73 (0.56-0.95)	0.02
Model 3 <sup>d</sup>		1.00		0.60 (0.31-1.19)			0.41 (0.21-0.83)			0.73 (0.56-0.95)	0.02
Model 4 <sup>e</sup>		1.00		0.60 (0.30-1.19)			0.41 (0.20-0.81)			0.72 (0.55-0.95)	0.02

<sup>a</sup>Cox proportional hazards regression analysis was performed to assess the association of fruit consumption with outcomes.

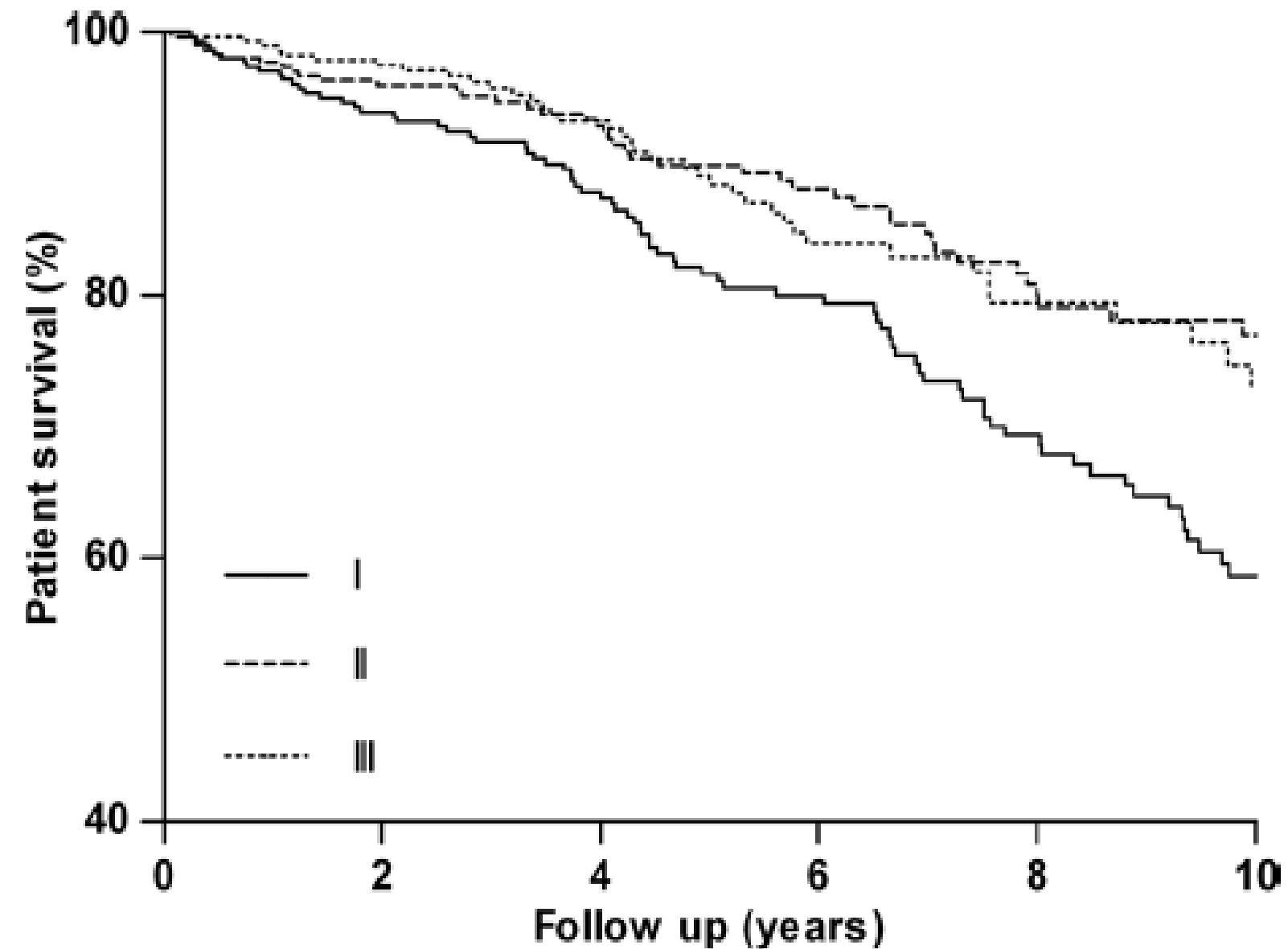
<sup>b</sup>Adjusted for age, sex, income and education level.

<sup>c</sup>Model 1 plus adjustment for eGFR, proteinuria, time since transplantation and primary renal disease.

<sup>d</sup>Model 2 plus adjustment for physical activity, total cholesterol, systolic blood pressure, BMI, diabetes and smoking status.

<sup>e</sup>Model 2, plus adjustment for cardiovascular history, alcohol use and hs-CRP.

# Eiwit Intake en Sterfte na Niertransplantatie



**FIGURE 2.** Kaplan-Meier curves for mortality according to tertiles of urinary urea excretion. Log-rank test for mortality ( $P = 0.001$ ). Range of urinary urea excretion (g/24 hr) in tertiles: I, 20.1 or less; II, 20.1–24.8; III, 24.8 or greater.

# Eiwit intake en sterfte bij niertransplantatiepatiënten, de rol van spiermassa

Table 4. Association of urea excretion with risk of mortality and graft failure, adjusted for confounders

Outcome	HR (95% CI) of continuous urea excretion (per 100 mmol/24-h)		Graft failure	
	Mortality	p		p
Mortality, n (%)	133 (22.0)		53 (8.8)	
Person-years	3860		3710	
Model 1	0.75 [0.63–0.89]	0.001	0.67 [0.52–0.87]	0.002
Model 2	0.75 [0.63–0.90]	0.001	0.73 [0.56–0.97]	0.03
Model 3	0.76 [0.63–0.90]	0.002	0.61 [0.45–0.84]	0.002
Model 4	0.73 [0.61–0.87]	0.001	0.71 [0.53–0.95]	0.02
Model 5	0.73 [0.61–0.88]	0.001	0.65 [0.48–0.87]	0.004
Model 6	0.76 [0.64–0.90]	0.002	0.74 [0.56–0.97]	0.03

Model 1: urea excretion per 100 mmol/24-h + adjustments for age, sex, and waist.

Model 2: model 1 + adjustments for proteinuria and eGFR.

Model 3: model 2 + adjustment for alcohol intake.

Model 4: model 2 + adjustments for antihypertensives usage, antidiabetic drugs usage, and statins usage.

Model 5: model 2 + adjustments for sodium excretion and serum urea concentration.

Model 6: model 2 + adjustment for obesity.

eGFR, estimated glomerular filtration rate.

Table 5. Association of urea excretion with risk of mortality and graft failure and causal path analyses

Outcome	HR (95% CI) of continuous urea excretion (per 100 mmol/24-h)			
	Mortality	p	Graft failure	p
Mortality, n (%)	133 (22.0)		53 (8.8)	
Person-years	3860		3710	
Model 1	0.75 [0.63–0.89]	0.001	0.67 [0.52–0.87]	0.002
Model 2	0.75 [0.63–0.90]	0.001	0.73 [0.56–0.97]	0.03
Model 3	0.97 [0.77–1.21]	0.79	0.74 [0.52–1.03]	0.07
3a	0.76 [0.64–0.90]	0.002	0.75 [0.57–0.98]	0.03
3b	0.98 [0.78–1.23]	0.87	0.74 [0.53–1.04]	0.09
Model 4	0.76 [0.63–0.91]	0.002	0.72 [0.55–0.95]	0.02
Model 5	0.79 [0.66–0.95]	0.01	0.76 [0.57–1.00]	0.05
Model 6	0.82 [0.68–0.99]	0.03	0.74 [0.54–1.01]	0.06

Model 1: urea excretion per 100 mmol/24-h + adjustments for age, sex, and waist.

Model 2: model 1 + adjustments for proteinuria and eGFR.

Model 3: model 2 + adjustment for malnutrition: serum albumin and creatinine excretion. 3a: model 2 + adjustment for serum albumin; and 3b: model 2 + adjustment for creatinine excretion.

Model 4: model 2 + adjustment for inflammation: CRP, blood leukocyte, procalcitonin, sICAM-1, and sVCAM-1 concentrations.

Model 5: model 2 + adjustment for markers of heart failure: pro-ANP and pro-BNP.

Model 6: model 2 + adjustment for physical activity: MET.

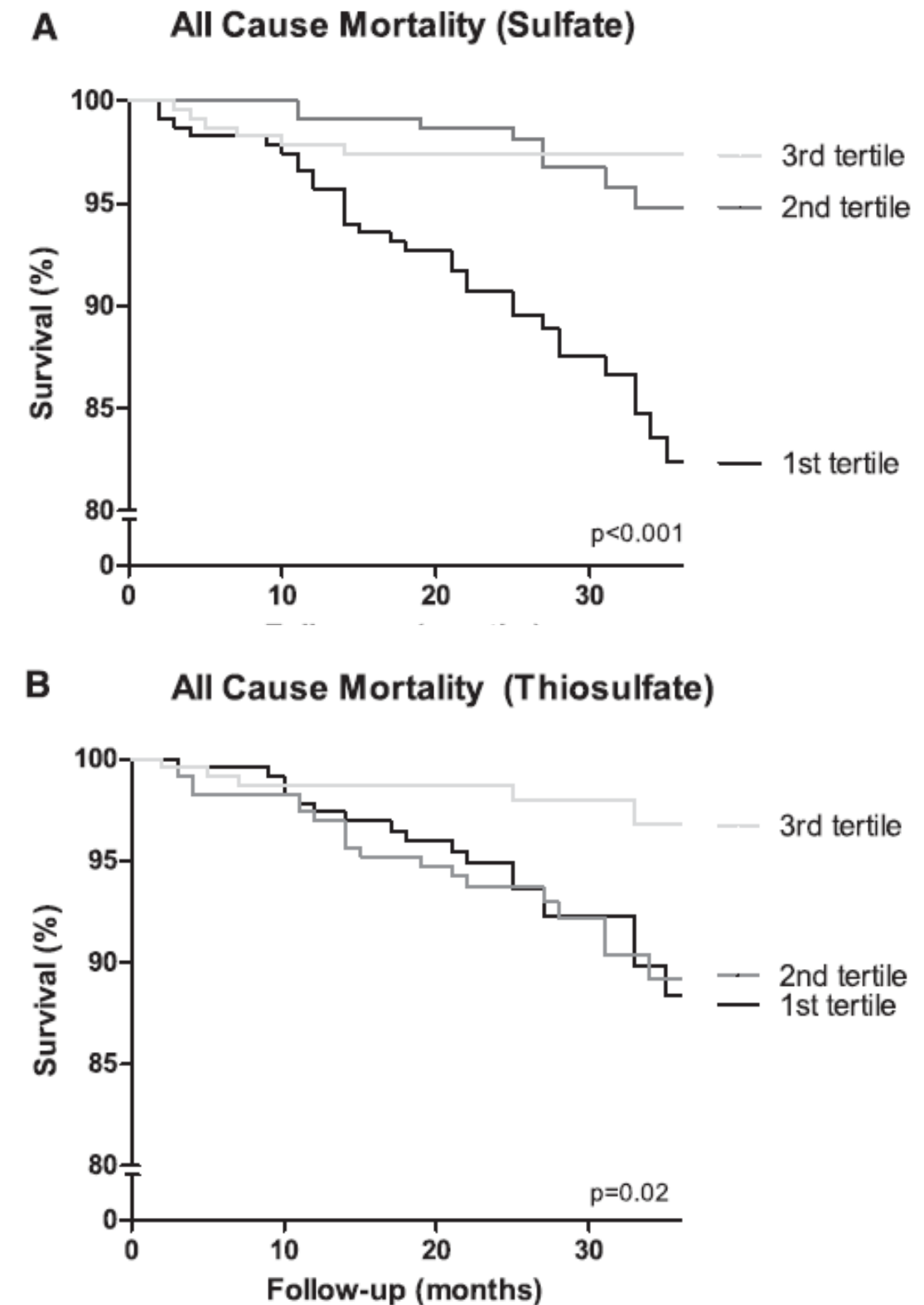
eGFR, estimated glomerular filtration rate; CRP, C-reactive protein; sICAM-1, soluble intracellular adhesion molecule 1; sVCAM-1, soluble vascular cell adhesion molecule 1; pro-ANP, pro-atrial natriuretic peptide; pro-BNP, pro-brain natriuretic peptide; MET, metabolic equivalent of task (h/wk).

# Urine zwavel metabolieten bij niertransplantatiepatiënten

Table 4. Regression coefficients for the association of protein intake with urinary sulfate and thiosulfate excretion in 637 RTRs

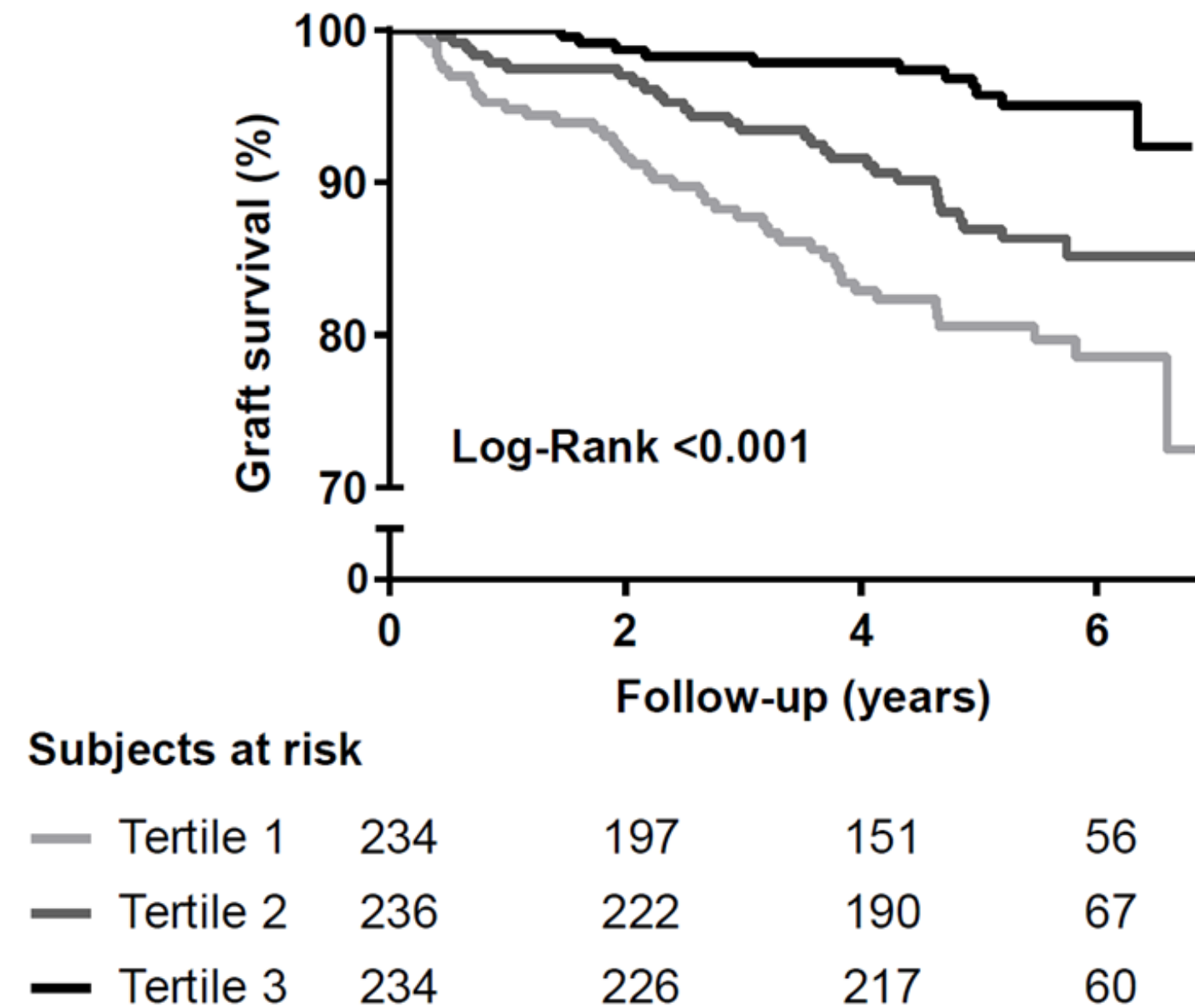
Variable	Model 1		Model 2		Model 3	
	$\beta$	P Value	$\beta$	P Value	$\beta$	P Value
<b>Sulfate</b>						
Total protein, g/d	0.25	<0.001	0.23	<0.001	0.22	<0.001
Animal protein, g/d	0.27	<0.001	0.24	<0.001	0.23	<0.001
Plant protein, g/d	0.10	0.01	0.09	0.02	0.08	0.03
Methionine, mg/d	0.27	<0.001	0.24	<0.001	0.24	<0.001
Cysteine, mg/d	0.23	<0.001	0.21	<0.001	0.20	<0.001
Methionine plus cysteine, mg/d	0.25	<0.001	0.23	<0.001	0.22	<0.001
<b>Thiosulfate</b>						
Total protein, g/d	0.01	0.85	0.02	0.72	0.01	0.85
Animal protein, g/d	-0.02	0.66	-0.01	0.80	-0.01	0.74
Plant protein, g/d	0.05	0.28	0.05	0.26	0.04	0.37
Methionine, mg/d	-0.02	0.67	-0.01	0.79	-0.02	0.68
Cysteine, mg/d	0.01	0.81	0.02	0.72	0.01	0.88
Methionine plus cysteine, mg/d	0.01	0.92	0.01	0.81	0.002	0.96

Coefficients are provided as standardized  $\beta$  values, referring to the number of SDs sulfate or thiosulfate changes, per SD increase of the nutrient. Model 1, adjusted for age and sex; model 2, additionally adjusted for BSA; and model 3, additionally adjusted for eGFR (Chronic Kidney Disease Epidemiology Collaboration equation).



# Urine sulfaat excretie en graft failure

Figure 2. Kaplan-Meier analyses of the associations of sex-specific tertiles of urinary sulfate excretion with graft failure.

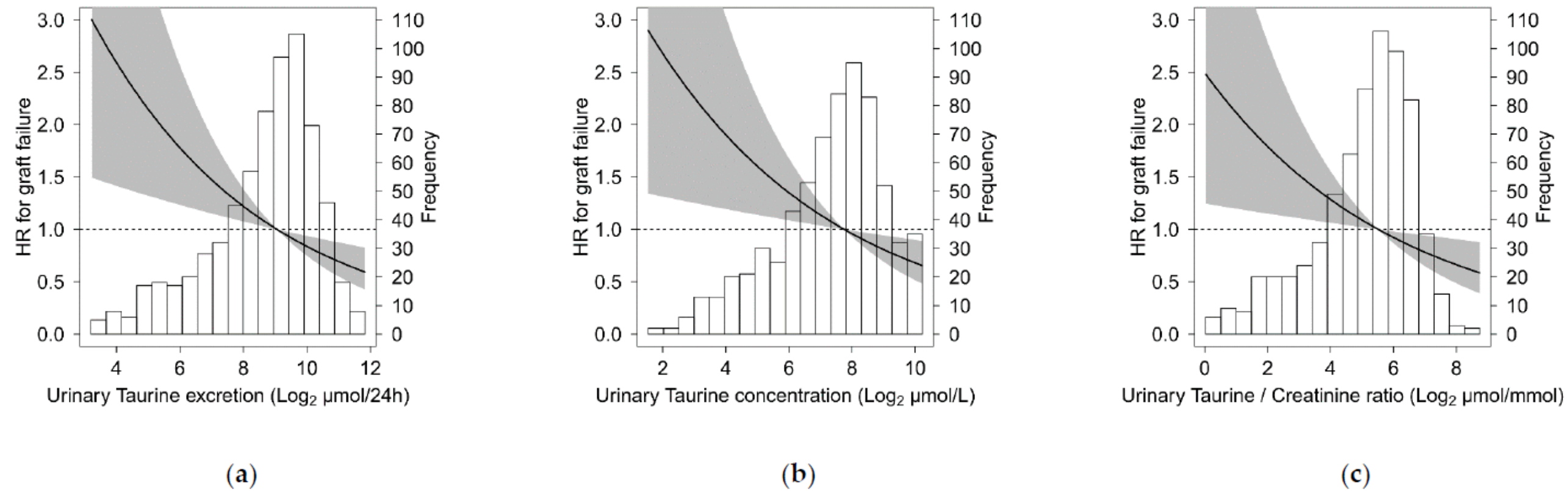


# Urine Taurine Excretion

Variable	RTR Cohort ( <i>n</i> = 678)	Range	Model 1		Model 2	
			Std. $\beta$	<i>P</i> value	Std. $\beta$	<i>P</i> value
<b>Urinary excretion</b>						
Sodium, mmol/24 h	158 ± 62	24–374	0.288	<0.001	0.179	<0.001
Chloride, mmol/24 h	138 (108–181]	28–391	0.268	<0.001	0.151	<0.001
Sulfate, mmol/24 h	17.6 ± 6.4	1.8–62.4	0.324	<0.001	0.199	<0.001
Thiosulfate, mmol/24 h	7 (4–12]	0–108	0.285	<0.001	0.170	<0.001
Creatinine, mmol/24 h	11.7 ± 3.4	2.9–23.3	0.397	<0.001	0.265	<0.001
<b>Dietary intake <sup>c</sup></b>						
Energy intake, kcal/24 h	2172 ± 619	658–4871	0.126	0.002	−0.038	0.34
Total protein intake, g/24 h	82 ± 12	26–144	0.190	<0.001	0.060	0.14
Animal protein intake, g/24 h	51 ± 13	18–110	0.133	0.001	0.085	0.03
Methionine intake, mg/24 h	1871 ± 327	687–3510	0.176	<0.001	0.077	0.05
Cysteine intake, mg/24 h	1187 ± 172	436–2296	0.238	<0.001	0.072	0.08
Meat intake, g/24 h	96 ± 38	0–275	0.223	<0.001	0.151	<0.001
Fish intake, g/24 h	11 (4–20)	0–134	0.104	0.01	0.096	0.008
Milk intake, g/24 h	117 ± 83	0–521	−0.005	0.90	0.016	0.66
Plant protein intake, g/24 h	31 ± 6	7–72	0.110	0.006	−0.077	0.06
Vegetable intake, g/24 h	93 ± 57	0–412	0.021	0.61	0.034	0.35
Fruit intake, g/24 h	152 ± 114	0–621	−0.117	0.004	−0.072	0.05
Total fat intake, g/24 h	88 ± 16	21–256	0.212	<0.001	−0.005	0.91
Saturated fat intake, g/24 h	31 ± 7	7–97	0.119	0.003	−0.021	0.59
Monounsaturated fat intake, g/24 h	30 ± 7	7–97	0.237	<0.001	0.016	0.72
Polyunsaturated fat intake, g/24 h	19 ± 6	4–74	0.151	<0.001	−0.026	0.52
Total carbohydrate intake, g/24 h	249 ± 63	16–537	0.186	<0.001	0.037	0.35
Mono and disaccharides intake, g/24 h	121 ± 34	9–301	0.106	0.008	−0.006	0.87
Polysaccharides intake, g/24 h	127 ± 28	8–297	0.190	<0.001	−0.009	0.83

Model 1: Crude, Model 2: Crude with adjustment for age, sex and eGFR. Urinary taurine excretion was log<sub>2</sub>-transformed for analysis. Regression coefficients are given as standardized beta values (Std.  $\beta$ ), the latter referring to the number of standard deviations a dependent variable changes per standard deviation increase of the independent variable, thereby allowing for comparison of the strength of the associations of different variables. <sup>a</sup> Low alcohol intake was defined as 0–5 g/24 h in females, and 0–10 g/24 h in males. High alcohol intake was defined as >5 g–24 h in females and >10 g–24 h in males). <sup>b</sup> For eGFR, model 2 was adjusted only for age and sex. <sup>c</sup> Dietary intake was adjusted for energy intake through the residual method. Dietary intake range was shown for the unadjusted values. Abbreviations: BMI: body mass index; BSA: body surface area; CVA: cerebrovascular accident; TIA: transient ischemic attack; HDL: high-density lipoprotein; LDL: low-density lipoprotein; HLA: human leukocyte antigen; eGFR: estimated glomerular filtration rate; hsCRP: high-sensitivity C-reactive protein.

# Urine Taurine Excretion en Graft Failure

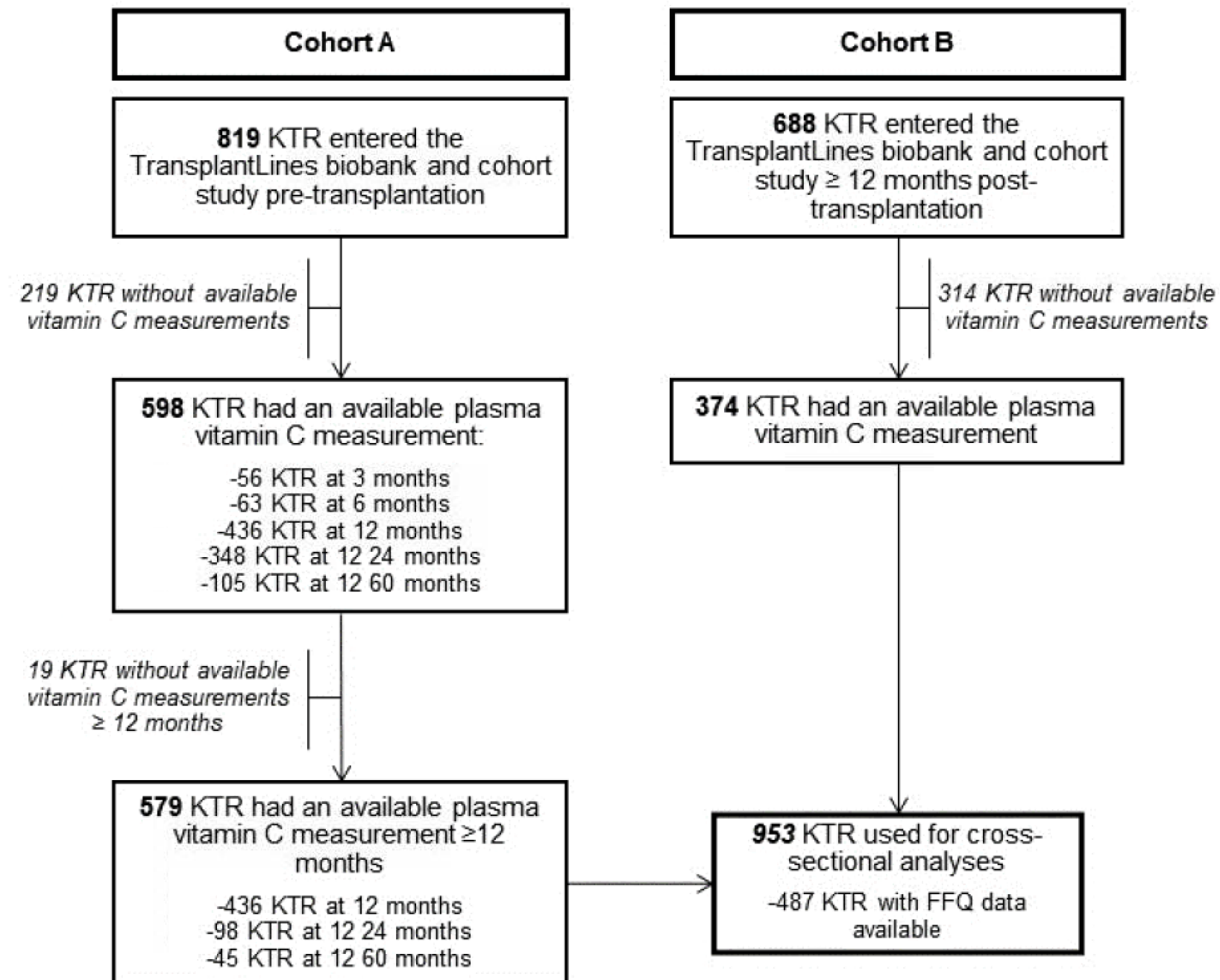


**Figure 1.** Continuous association of urinary taurine excretion (a), urinary taurine concentration (b) and urinary taurine/creatinine ratio (c) with death-censored graft failure. Urinary taurine excretion, urinary taurine concentration and urinary taurine/creatinine ratio were  $\log_2$ -transformed for prospective analysis. The histograms depict the distribution of urinary taurine excretion, urinary taurine concentration and urinary taurine/creatinine ratio. The black line shows the adjusted hazard ratio (HR) and the gray areas correspond to the 95% confidence interval (CI). The adjusted association was adjusted for age, sex, weight, height, eGFR and proteinuria. *P* values were 0.002, 0.007 and 0.01, respectively.

# Vitamin C

- Water oplosbaar
- Klein moleculair
- Het menselijk lichaam kan het niet zelf maken
- Essentieel vitamine
  
- Wat zal er gebeuren als de nierfunctie afneemt?
- En waarom?

# TransplantLines Biobank and Cohort Study



Supplemental Figure 1. Flow diagram of study population

# Patient characteristics

Table 1. Patient characteristics of the study population

Patient characteristics	Overall KTR	Plasma vitamin C concentration		P value
		≤28 μmol/L	>28 μmol/L	
<i>n</i>	953	322	631	
Vitamin C, μmol/L	37 (24-53)	18 (13-24)	47 (37-60)	<0.001
<b>Demographics</b>				
Age, years	55 ± 14	57 ± 13	55 ± 14	0.007
Sex (male), <i>n</i> (%)	590 (62)	226 (70)	364 (58)	<0.001
Body mass index, kg/m <sup>2</sup> <sup>a</sup>	27.5 ± 4.7	28.3 ± 4.8	27.0 ± 4.6	<0.001
<b>Graft function</b>				
eGFR, mL/min/1.73 m <sup>2</sup>	55 ± 19	52 ± 20	57 ± 18	<0.001
Urinary protein excretion, g/24-h <sup>b</sup>	0.2 (0.1-0.3)	0.2 (0.1-0.4)	0.2 (0.1-0.3)	0.02
Urinary potassium excretion, mmol/24-h	71.9 ± 24.4	67.8 ± 24.5	73.7 ± 24.2	0.02
<b>Transplant characteristics</b>				
Pre-emptive transplantation, <i>n</i> (%)	304 (32)	92 (29)	212 (34)	0.13
Dialysis duration, months <sup>c</sup>	9 (0-28)	14 (0-30)	6 (0-25)	0.01
Time after transplantation, years <sup>d</sup>	1 (1-6)	1 (1-4)	1 (1-7)	0.01
<b>Cardiovascular history</b>				
Systolic blood pressure, mmHg <sup>e</sup>	134 ± 16	135 ± 16.6	134 ± 14.9	0.54
Active smoking (yes), <i>n</i> (%) <sup>f</sup>	138 (15)	65 (20)	73 (12)	0.001
Diabetes, <i>n</i> (%) <sup>g</sup>	264 (28)	133 (42)	131 (21)	<0.001
Statine use, <i>n</i> (%)	548 (58)	199 (62)	349 (55)	0.07
Antihypertensive use, <i>n</i> (%)	803 (84)	284 (88)	519 (82)	0.02

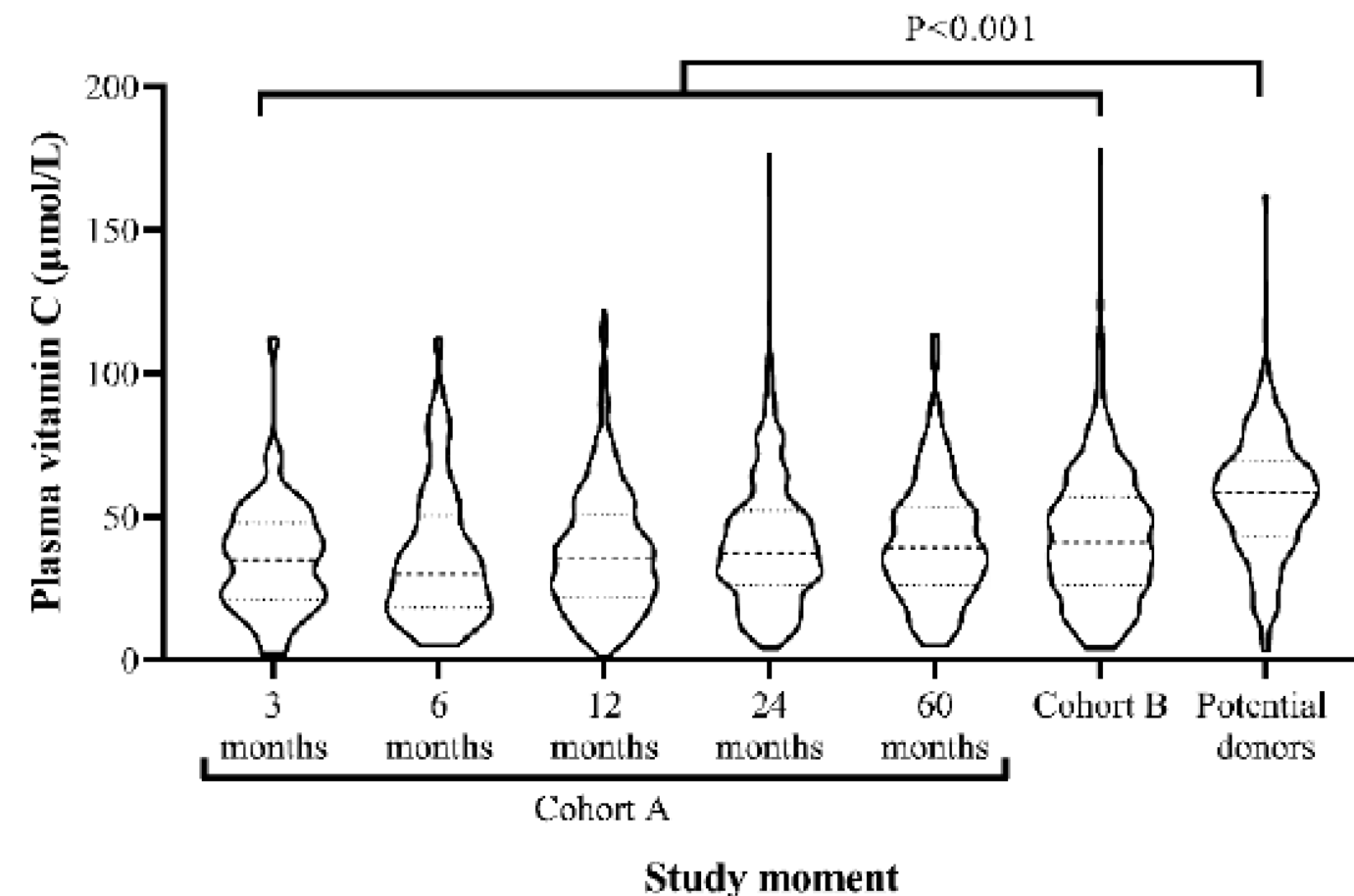
# Patient characteristics continued

Table 1. Patient characteristics of the study population

Patient characteristics	Overall KTR	Plasma vitamin C concentration		P value
		≤28 μmol/L	>28 μmol/L	
<i>n</i>	953	322	631	
Vitamin C, μmol/L	37 (24-53)	18 (13-24)	47 (37-60)	<0.001
<b>Laboratory</b>				
Glycated hemoglobin, % <sup>h</sup>	5.8 (5.4-6.4)	6.0 (5.6-6.8)	5.7 (5.4-6.2)	<0.001
hs-CRP, mg/l <sup>i</sup>	1.9 (0.8-4.7)	2.5 (1.0-6.0)	1.7 (0.6-4.2)	<0.001
Albumin, g/l <sup>i</sup>	43.6 ± 2.9	43.2 ± 3.0	43.8 ± 2.9	0.002
Total cholesterol, mmol/l <sup>h</sup>	4.61 ± 0.99	4.51 ± 1.03	4.65 ± 0.97	0.04
HDL cholesterol, mmol/l <sup>i</sup>	1.38 ± 0.42	1.27 ± 0.38	1.44 ± 0.42	<0.001
<b>Immunosuppression</b>				
Prednisolone use, <i>n</i> (%)	928 (98)	314 (98)	614 (97)	1.00
Cyclosporine use, <i>n</i> (%)	104 (11)	23 (7)	81 (13)	0.01
Tacrolimus use, <i>n</i> (%)	736 (77)	274 (85)	462 (73)	<0.001
Mycophenolic acid use, <i>n</i> (%) <sup>k</sup>	770 (81)	264 (82)	506 (80)	0.50
Everolimus use, <i>n</i> (%)	44 (5)	16 (5)	28 (4)	0.84
Azathioprine use, <i>n</i> (%)	63 (7)	16 (5)	47 (7)	0.19
<b>Other medication</b>				
Proton pump inhibitor use, <i>n</i> (%)	684 (72)	250 (78)	434 (69)	0.01
Iron supplementation, <i>n</i> (%)	70 (74)	24 (7)	46 (7)	1.00
<b>Diet</b>				
Fruit, g/d <sup>l</sup>	163 ± 123	137 ± 110	175 ± 127	0.001
Vegetable, g/d <sup>l</sup>	115 ± 79	112 ± 84	116 ± 76	0.69
Dairy, g/d <sup>l</sup>	349 ± 239	362 ± 247	343 ± 236	0.41
Meat, g/d <sup>l</sup>	117 ± 74	111 ± 68	119 ± 76	0.20
Fish, g/d <sup>l</sup>	24 ± 34	20 ± 29	26 ± 35	0.07
Nuts, g/d <sup>l</sup>	5 (0-18)	4.6 (0-16)	5 (0-19)	0.20
Bread, g/d <sup>l</sup>	156 ± 90.7	156 ± 90.7	156 ± 90.9	0.98
Coffee, mL/d <sup>l</sup>	420 (240-561)	420 (200-561)	420 (240-561)	0.83
Tea, mL/d <sup>l</sup>	291 (30-510)	243 (8-510)	291 (79-510)	0.08
Dietary vitamin C intake, mg/d <sup>m</sup>	97 ± 48	84 ± 44	103 ± 48	<0.001
Vitamin C supplementation, <i>n</i> (%) <sup>n</sup>	69 (10)	7 (3)	62 (13)	<0.001

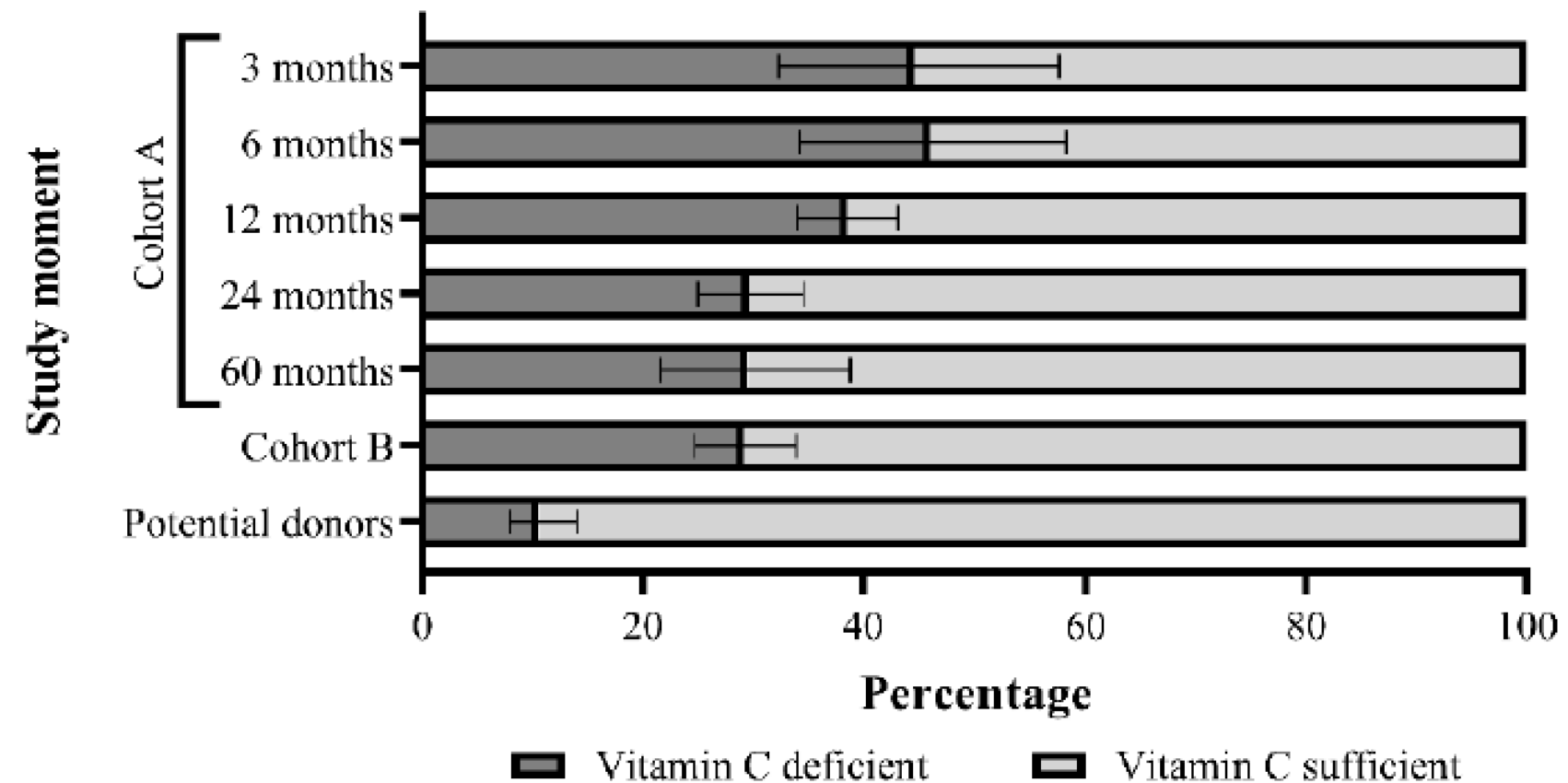
\*Differences were tested by ANOVA for continuous variables with normal distribution, Kruskal–Wallis test for continuous variables with non-normal distribution, and by  $\chi^2$  test for categorical variables. Data available in <sup>a</sup>939, <sup>b</sup>848, <sup>c</sup>779, <sup>d</sup>911, <sup>e</sup>936, <sup>f</sup>942, <sup>g</sup>928, <sup>h</sup>949, <sup>i</sup>920, <sup>j</sup>950, <sup>k</sup>952, <sup>l</sup>500, <sup>m</sup>487 and <sup>n</sup>688 KTR.

# Plasma vitamin C concentration in KTR and donors



**Figure 1. Vitamin C concentration in KTR.** Dashed and dotted lines represent the median and first and third quartile, respectively, and the width of the sections represent the probability that members of the population will take that given value. The median (IQR) plasma vitamin C concentration was 35 (21-48), 30 (18-50), 35 (22-51), 37 (26-52), 39 (26-54), 41 (26-57), and 58 (43-69) µmol/L at 3, 6-, 12-, 24- and 60-month post-transplantation, among prevalent KTR of cohort B and among potential donors, respectively.

# Vitamin C deficiency in KTR and donors



**Figure 2. Vitamin C status in KTR.** The percentage of vitamin C deficient KTR was 45, 46, 39, 30, 30, 30 and 11% at 3-, 6-, 12-, 24- and 60-month post-transplantation, among prevalent KTR of cohort B and among potential donors, respectively.  $P < 0.001$  for  $\chi^2$  test.

# Clinical determinants of vitamin C deficiency

**Table 2.** Clinical determinants of vitamin C deficiency

Patients characteristics	Vitamin C deficiency		
	Odds ratio	95% CI	P value
Diabetes, yes	2.67	1.84-3.87	<0.001
Active smoking, yes	1.84	1.16-2.91	0.01
HDL cholesterol, per SD increase	0.67	0.55-0.82	<0.001
eGFR, per SD increase	0.76	0.63-0.91	0.003
Plasma albumin, per SD increase	0.83	0.69-0.99	0.04
Time since transplantation, years	0.94	0.90-0.99	0.02

Logistic regression analyses with backward selection were performed (Pin 0.05, Pout 0.10). Age, sex, body mass index, estimated glomerular filtration rate, urinary protein excretion, pre-emptive transplantation, dialysis duration, systolic blood pressure, statin use, antihypertensive use, glycated hemoglobin, hs-CRP, total cholesterol, prednisolone use, cyclosporine use, tacrolimus use, mycophenolic acid use, azathioprine use, proton pump inhibitor use, and iron supplementation use were eliminated from the final model.

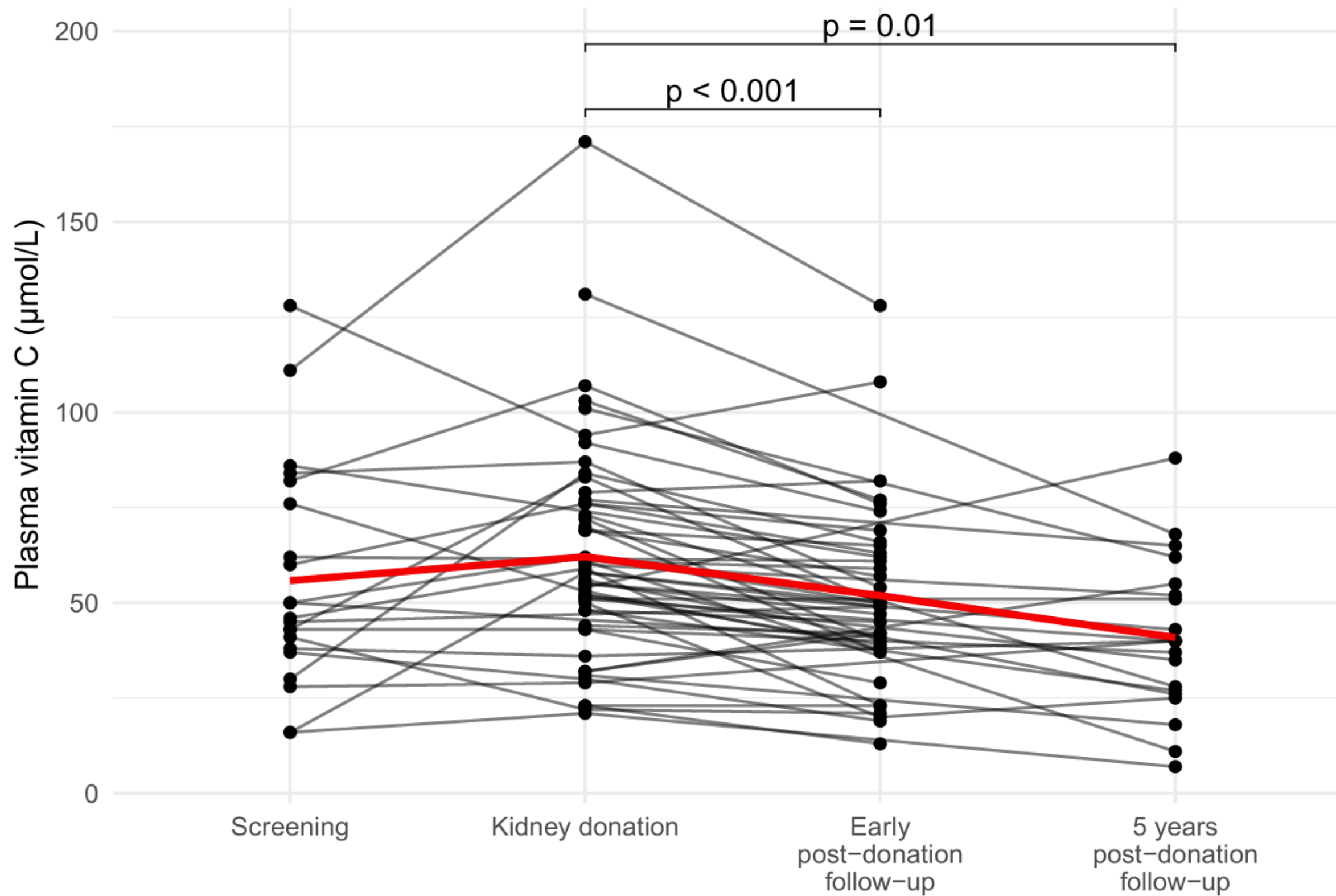
# Dietary determinants of vitamin C deficiency

**Table 3.** Dietary determinants of plasma vitamin C deficiency in KTR

Diet	Vitamin C deficiency					
	Crude			Adjusted <sup>†</sup>		
	Odds Ratio	95% CI	P value	Odds Ratio	95% CI	P value
Fruit, 100 g/d	0.75	0.62-0.89	0.002	0.78	0.64-0.94	0.01
Vegetable, 100 g/d	0.95	0.74-1.21	0.68	0.97	0.74-1.27	0.84
Dairy, 100 g/d	1.03	0.96-1.12	0.40	1.01	0.92-1.10	0.88
Meat, 100 g/d	0.85	0.65-1.10	0.22	0.84	0.62-1.12	0.24
Fish, 100 g/d	0.58	0.30-1.05	0.09	0.62	0.31-1.19	0.17
Nuts, 100 g/d	0.30	0.09-0.86	0.03	0.52	0.16-1.62	0.28
Bread, 100 g/d	1.00	0.81-1.23	0.98	1.01	0.79-1.28	0.95
Coffee, 100 ml/d	0.99	0.93-1.07	0.97	0.99	0.92-1.08	0.90
Tea, 100 ml/d	0.98	0.93-1.03	0.42	1.00	0.94-1.06	0.96
Vitamin C intake, 100 mg/d	0.38	0.24-0.61	<0.001	0.44	0.26-0.72	0.002
Vitamin C supplementation use, yes	0.21	0.09-0.44	<0.001	0.25	0.10-0.55	0.001

Univariable and multivariable logistic regression analyses were performed. <sup>†</sup>Adjustment was performed in each logistic regression analysis by history of diabetes, active smoking status, HDL cholesterol, estimated glomerular filtration rate, plasma albumin concentration, and time since transplantation.

## Longitudinal plasma vitamin C measurements before and after kidney donation



**FIGURE 2.** Plasma vitamin C concentrations at predonation screening [5.3 (2.8–8.8) mo predonation,  $n = 20$ ], at the day of donation (predonation,  $n = 51$ ), at the early postdonation follow-up visit [1.7 (1.6–2.1) mo postdonation,  $n = 35$ ], and at the 5 y postdonation follow-up visit [60.2 (59.8–60.8) mo postdonation,  $n = 20$ ]. Vitamin C concentrations at different timepoints were compared with a paired T-test. The red line represents the mean vitamin C concentration across all timepoints.

# Voeding en chronische laaggradige ontsteking zijn onafhankelijk van nierfunctie determinanten van vitamine C concentraties

**TABLE 3**

Results of univariable and multivariable linear regression analyses in the chronic kidney disease (CKD) population (dialysis group, the CKD stage 4/5 group, and the kidney transplant recipients group combined), with log<sub>2</sub>-transformed plasma vitamin C concentrations as the dependent variable. In the multivariable analysis, all potential determinants were included in the model together with additional adjustment for study group.

	Univariable	<i>P</i> value	Multivariable	<i>P</i> value
	St. β (95% CI)		St. β (95% CI)	
Age	−0.00 (−0.17, 0.16)	0.99	0.11 (−0.07, 0.29)	0.24
Female	0.23 (−0.11, 0.56)	0.18	0.23 (−0.11, 0.57)	0.19
BMI	−0.03 (−0.20, 0.13)	0.69	0.02 (−0.14, 0.18)	0.80
Smoking	0.00 (−0.41, 0.41)	0.99	0.10 (−0.34, 0.54)	0.65
CRP <sup>1</sup>	−0.21 (−0.39, −0.04)	0.02	−0.23 (−0.40, −0.06)	0.009
Vitamin C intake <sup>1</sup>	0.36 (0.20, 0.51)	<0.001	0.39 (0.20, 0.58)	<0.001
Energy intake	0.04 (−0.12, 0.21)	0.63	−0.13 (−0.31, 0.05)	0.17

Missing values: none.

Abbreviations: BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; st. β, standardized β coefficient.

<sup>1</sup> Log<sub>2</sub>-transformed.

# Hoe kan het dat vitamin C lager wordt met slechtere nierfunctie?

## THE RELATION BETWEEN THE STRUCTURE OF HALOGENATED BENZOIC ACIDS AND THE DEPLETION OF ADRENAL ASCORBIC ACID CONTENT

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Previous studies have been reported on the relationship between structural modifications of salicylic acid and the effect of these compounds in causing a depletion of adrenal gland ascorbic acid content, an effect frequently used to indicate adrenal cortical activation (Hetzl and Hine, 1951; Cronheim *et al.*, 1952; Smith, 1952; Lowenthal and Jaques, 1953). There is a disagreement between these investigators as to whether or not the property of adrenal ascorbic acid depletion is inherent in the benzoic acid molecule, there being two reports in the affirmative (Cronheim, *et al.*, 1952; Smith, 1952) and two reports in the negative (Hetzl and Hine, 1951; Lowenthal and Jaques, 1953).

The purposes of this study are to resolve this conflict, if possible, and to study the effect of halogen substituted benzoic acid derivatives on the adrenal ascorbic acid depletion in the rat.

# Wat doet benzoic acid?

## Benzoate and Sorbate Salts: A Systematic Review of the Potential Hazards of These Invaluable Preservatives and the Expanding Spectrum of Clinical Uses for Sodium Benzoate

Joseph D. Piper  and Peter W. Piper

**Abstract:** Sodium benzoate and potassium sorbate are extremely useful agents for food and beverage preservation, yet concerns remain over their complete safety. Benzoate can react with the ascorbic acid in drinks to produce the carcinogen benzene. A few children develop allergy to this additive while, as a competitive inhibitor of D-amino acid oxidase, benzoate can also influence neurotransmission and cognitive functioning. Model organism and cell culture studies have raised some issues. Benzoate has been found to exert teratogenic and neurotoxic effects on zebrafish embryos. In addition, benzoate and sorbate are reported to cause chromosome aberrations in cultured human lymphocytes; also to be potentially mutagenic toward the mitochondrial DNA in aerobic yeast cells. Whether the substantial human consumption of these

Table 1—Studies that have uncovered potentially hazardous effects of benzoate and/or sorbate in cell culture, model organisms, or isolated mitochondria

Effect	Comments	References
<b>Whole organism studies</b>		
Growth retardation and organ injury (SB)	Excess dietary benzoate leads to growth retardation, hematological abnormality, and organ injury of piglets; also Necrotic and cirrhotic changes in the livers of mice.	(Kaboglu and Aktac 2002; Shu and others 2016)
Teratogenic and neurotoxic effects (SB)	Significant developmental defects on the motor neuron axons and neuromuscular junctions in zebrafish larvae; also teratogenic effects during mouse fetal eye development. Reported to downregulate the expression of tyrosine hydroxylase and dopamine transporter in dopaminergic neurons.	(Tsay and others 2007; Chen and others 2009; Afshar and others 2013).
<b>In cell culture studies</b>		
Genotoxic effects (sorbate and benzoate)	Mutagenic to human lymphocytes <i>in vitro</i> ; also bone marrow chromosomes of mice <i>in vivo</i> , causing enhanced micronucleus formation, and/or chromosome aberrations.	(Abe and Sasaki 1977; Banerjee and Giri 1986; Yilmaz and others 2009; Zengin 2011; Mamur 2012; Pongsavee 2015)
Lowering of leptin (SB) Oxidative stress, mutagenic to mtDNA (PS and SB)	Inhibition of leptin release in cultured murine adipocytes In yeast enhances oxidative stress, causing damage to mtDNA readily identified as an increase in respiratory deficient cells. In human erythrocytes benzoic acid induces oxidative stress, causing enhanced malondialdehyde formation, symptomatic of lipid peroxidation. In cultured rat hepatocytes potassium sorbate causes decreased glutathione, another characteristic of oxidative stress.	(Ciardi and others 2012) (Kinderlerer and Hatton 1990; Piper 1999; Yetuk and others 2014; Baş and others 2014)
Loss of cell viability (SB)	Cell death, increases in intracellular Ca(2+) concentration and loss of mitochondrial transmembrane potential in cultured rat cortical neurons and in HeLa cells.	(Park 2011)
<b>In isolated mitochondria</b>		
Induction of the mitochondrial permeability transition in isolated mitochondria (SB)	Opening of a high-conductance, cyclosporin-sensitive pore in the mitochondrial inner membrane, causing mitochondrial swelling, depolarization, and uncoupling of oxidative phosphorylation.	(Trost and Lemasters 1996)

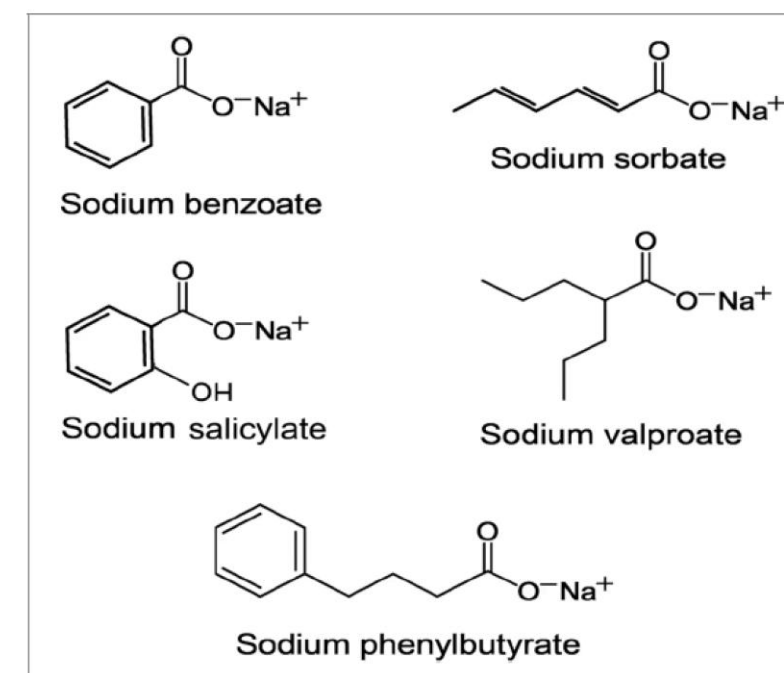


Figure 1—The monocarboxylate compounds discussed in this article, shown as their sodium salts.

# Benzoic acid

**Table 3.** Maximum allowed limits (mg/kg) of benzoic acid and its salts (Na, K, and Ca) as permitted food additives, according to Codex Alimentarius (FAO/WHO, 2014).

Product	Maximum level
<i>Beverages<sup>1</sup></i>	
Concentrates for fruit juice or nectar, fruit juice, fruit nectar, coffee or substitutes, tea, infusions, and cereal or grain beverages	1000
Concentrates for vegetable nectar, and water-based flavored drinks including "sport," "energy," or "electrolyte," particulated drinks and soft drinks with pH lower than 3.5	600
Water-based flavored drinks including "sport," "energy," or "electrolyte," particulated drinks and soft drinks with pH higher than 3.5	1000
Beer, wines, spirituous, refreshers, cider, perry, and mead	1000
<i>Bakery and sweets</i>	
Bakery wares, cereal and starch-based desserts, fat-based desserts, fruit filling for pastries, and fat emulsions	1000
Chewing gum, cocoa-based spreads and fillings, confectionery including candy and nougats, decorations, topping and sweet sauces, imitation chocolate, and chocolate substitutes	1500
Table-top sweeteners	2000
<i>Fruits and vegetables<sup>2</sup> and derivatives</i>	
Fruit: candied, cooked, fermented or in vinegar, oil, or brine; Vegetables: cooked, fried, dried, fermented, purees, spreads; Fruit pulp, fruit purees, and fruit preparations; Nut and seeds, coconut milk, seasoning, and condiments; Jam, jellies, marmalades, sauces, syrups, and vinegars	1000
Dried fruit	800
Salads and sandwich spreads	1500
Vegetables in vinegar, oil, or brine, and soybean sauce	2000
Vegetables pulps or preparations	3000
<i>Eggs and derivatives</i>	
Egg-based desserts	1000
Liquid-egg products	5000
<i>Meat and derivatives</i>	
Cured or salted and dried nonheat-treated processed meat, poultry and game products in whole pieces or cuts (added on surface)	1000
<i>Fish, seafood, and derivatives</i>	
Fish, mollusks, crustacean, and echinoderms: smoked, dried, fermented, or salted; Fish products: smoked, dried, or salted	200
Fermented fish products	1000
Fish, fish products, mollusks, crustacean, and echinoderms: semi-preserved; Mollusks, crustacean, and echinoderms: cooked	2000
Caviar	2500
Cooked shrimps	6000
<i>Dairy products</i>	
Dairy-based desserts	300
Dairy-fat spreads	1000
<i>Other products</i>	
Soups and broths	500
Pre-cooked pastas and noodles and like products	1000
Dietetic foods for medical purposes and dietetic formulas for slimming purposes	1500
Food supplements and dietetic foods	2000

<sup>1</sup>Subject to national legislation of the importing country.

<sup>2</sup>Vegetables, including fungi, roots, pulses, legumes, aloe vera, and seaweeds.

## Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: Uses, exposure, and controversy

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 Departamento de Tecnología de Alimentos, INIA, Madrid, Spain

**Table 4.** Maximum levels (mg/kg or L) reported for benzoic acid in commercial beverages.

Product	Maximum level	Reference
Apple juice	335	Lozano et al. (2007)
Apricot juice	45	Ene and Diacu (2009)
Grape juice	971	Lozano et al. (2007)
Lemon juice	997	Lozano et al. (2007)
Orange juice	902	Lozano et al. (2007)
Passion fruit juice	804	Tfouni and Toledo (2002)
Peach juice	63	Ene and Diacu (2009)
Ice tea	105	Lazarević et al. (2011)
Fruit drink	170	Pant and Trenerry (1995)
Orange soft drink	338	Tfouni and Toledo (2002)
Cola drink	170	Morales et al. (2002)
Cola light drink	160	El-Ziney (2009)
Energy drink	129	El-Ziney (2009)
Low alcohol wine	280	Pant and Trenerry (1995)
Cordial	440	Pant and Trenerry (1995)
Diet cordial	450	Pant and Trenerry (1995)
Thai rice wine	25	Techakriengkrai and Surakarnkul (2007)
Rice distillates	7	Techakriengkrai and Surakarnkul (2007)

**Table 5.** Maximum levels (mg/kg or L) reported for benzoic acid in commercial fish, seafood, and meat products.

Product	Maximum level	Reference
Canned fish	60	de Luca et al. (1995)
Dried fish	2	Nagayama et al. (1986)
Pickled herring	987	Leth et al. (2010)
Danish caviar	1032	Leth et al. (2010)
Prepared fish products	720	Mischek and Krapfenbauer-Cermak (2012)
Fish sauce	266	Lin and Choong (1999)
Tunny sauce	17	de Luca et al. (1995)
Fish pâté	26	de Luca et al. (1995)
Seafood salad	3	de Luca et al. (1995)
Surimi	890	Leth et al. (2010)
Shrimps, crustacean, and mollusks	1040	Mischek and Krapfenbauer-Cermak (2012)
Boiled shrimps in brine	932	Leth et al. (2010)
Cured duck meat	345	Lo et al. (2001)
Cured pork meat	52	Lo et al. (2001)
Cured pork liver	933	Lo et al. (2001)
Pâté	260	Leth et al. (2010)

## Benzoic acid and its derivatives as naturally occurring compounds in foods and as additives: Uses, exposure, and controversy

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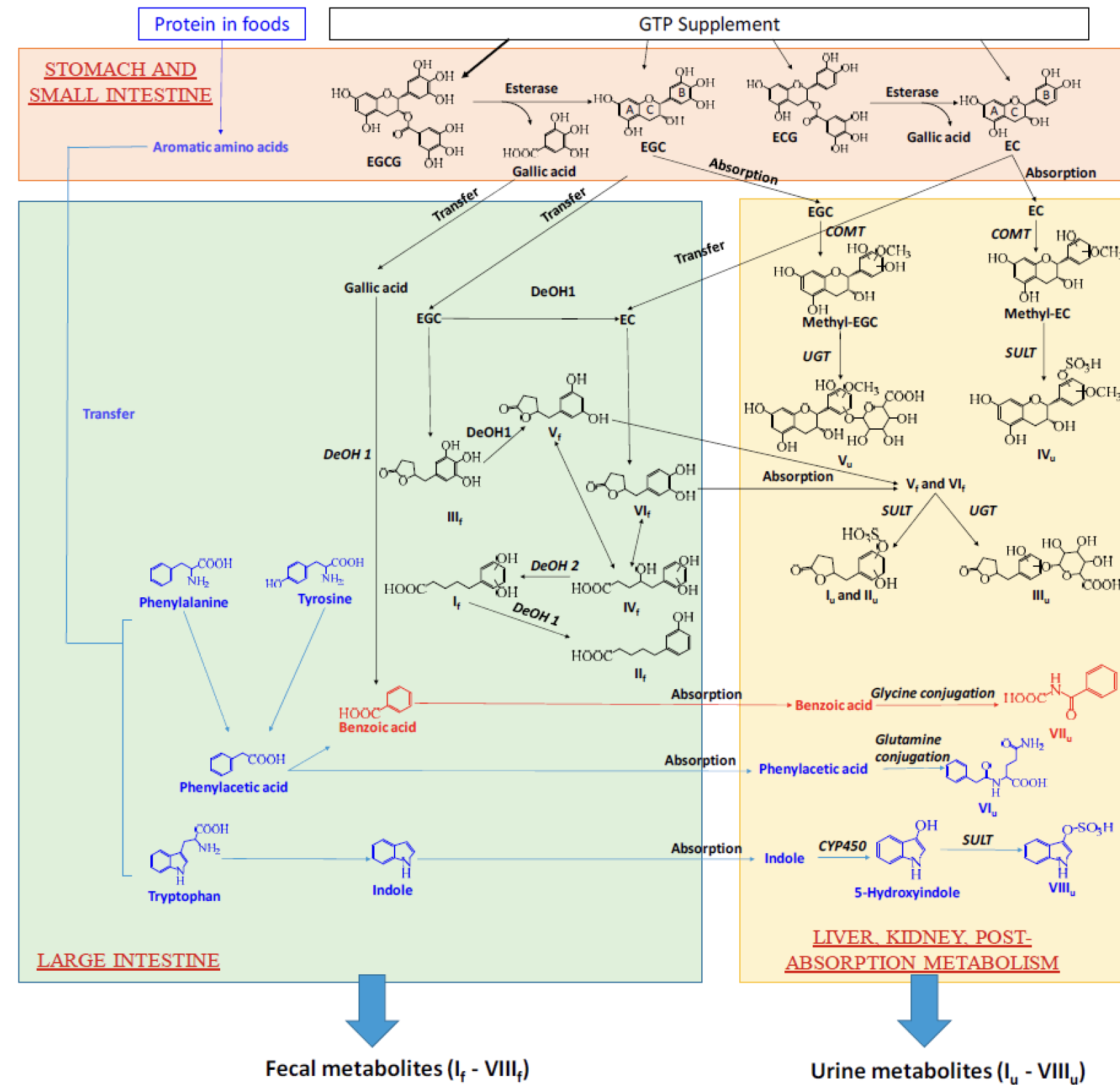
**Table 1.** Benzoic acid and some derivatives or related compounds approved as food additives by FAO/WHO (CAC/MISC 6–2013).

INS number	Compound
210	Benzoic acid
211	Sodium benzoate
212	Potassium benzoate
213	Calcium benzoate
214	Ethyl <i>p</i> -hydroxybenzoate
215	Sodium ethyl <i>p</i> -hydroxybenzoate
216*	Propyl <i>p</i> -hydroxybenzoate
217*	Sodium propyl <i>p</i> -hydroxybenzoate
218	Methyl <i>p</i> -hydroxybenzoate
219	Sodium methyl <i>p</i> -hydroxybenzoate
928	Benzoyl peroxide
1519	Benzyl alcohol

\*Currently withdrawn.

INS = International Numbering System, defined by the Codex Alimentarius.

# Endogene synthese van benzoic acid uit eiwit in voeding en thee polyfenolen



# Leidt de combinatie van benzoic acid en vitamin C tot endogene benzeen productie en toxiciteit?

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### SHORT COMMUNICATIONS

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**Benzene Production from Decarboxylation of Benzoic Acid in the Presence of Ascorbic Acid and a Transition-Metal Catalyst**

# Ultra-Processed Foods NOVA classificatie

<b>Group 4:</b>	
<b>Ultra-processed foods</b>	
<i>Products largely or entirely made from industrial food ingredients, many requiring sophisticated equipment and technology. Contain little or no whole foods, but contain additives, preservatives and are loaded with sugars, fats, and salt.</i>	
Sugar sweetened beverages	Soft drinks, light soft drinks, fruit juices, soy drinks
Starchy foods and breakfast cereals	Bread, raisin bread, buns, rusk, breakfast cereals
Dairy products other than desserts (i.e. cheeses, yogurt)	Full-fat yogurt, semi-skimmed yogurt, skimmed yogurt, full-fat quark, semi-skimmed quark, skimmed quark, grated cheese, breakfast drinks, full-fat drinks, semi-skimmed drinks, skimmed drinks
Desserts	Ice cream, whipped cream, full-fat custard and pudding, semi-skimmed custard and pudding, skimmed custard and pudding, soy desserts, soy ice cream
Sauces and fats	Mayonaise, halvanaise, ketchup, other sauces and dressings, margarine, halvarine
Prepared meals	Dutch, Italian, and Chinese ready-to-heat meals, ready-to-eat salads, ready-to-heat quiches, other ready-to-heat products, ready-to-heat fish, pizza
Cookies	Small and large cookies, biscuits
Fried foods and salty snacks	Spring rolls, snacks with meat or cheese, chips, salty snacks, French fries
Cakes and pastries	Croissants, cake and pastries, gingerbread
Toppings	Chocolate spread, sweet toppings, egg salad, fish salad or spread, meat salad, other salads and spreads
Processed meats	Sausages, smoked sausages etc., luncheon meat etc.
Liquors	Long drinks, cocktails, spirits
Candy	Candybar, chocolate bonbons, liquorice, other candy
Plant-based products	Vegetarian meat products, soy products

# Baseline characteristics (1)

UPFs	Overall RTRs (n = 632)	Sex-specific tertiles			P value
		T1 (n = 210)	T2 (n = 211)	T3 (n = 211)	
Total energy intake, kcal/d	2172.7 ± 638.3	2033.3 ± 578.7	2203.5 ± 593.3	2280.6 ± 711.9	<0.001
Weight proportion UPFs, % g/d					
Men	29.7 ± 11.8	18.1 ± 3.9	28.1 ± 3.2	43.1 ± 8.8	<0.001
Women	26.2 ± 9.9	16.3 ± 3.6	25.1 ± 2.4	37.2 ± 7.5	<0.001
Energy proportion UPFs, % kcal/d					
Men	33.9 ± 14.1	22.4 ± 5.6	31.8 ± 7.1	47.4 ± 14.1	<0.001
Women	32.9 ± 13.1	22.7 ± 6.0	31.1 ± 6.6	45.0 ± 13.6	<0.001
NOVA classification					
Unprocessed or minimally processed foods, g/d	1454.9 ± 471.2	1733.0 ± 469.5	1467.4 ± 368.0	1165.0 ± 387.4	<0.001
Percentage of total food intake	57%				
Processed culinary ingredients, g/d	26.3 ± 26.7	26.8 ± 26.4	24.9 ± 26.1	27.3 ± 27.7	0.62
Percentage of total food intake	1%				
Processed foods, g/d	365.7 ± 239.8	411.1 ± 256.0	363.8 ± 235.3	322.4 ± 219.8	0.001
Percentage of total food intake	14%				
UPFs, g/d	721.2 ± 341.1	453.0 ± 151.5	679.7 ± 193.3	1029.7 ± 346.8	<0.001
Percentage of total food intake	28%				
Sugar-sweetened beverages	163.3 [53.6–326.1]	42.9 [8.3–123.1]	153.6 [85.7–294.0]	406.7 [258.4–630.9]	<0.001
Starchy foods, breakfast cereals	115.4 [84.7–149.4]	106.4 [78.7–140.3]	125.7 [94.7–156.7]	114.8 [85.2–153.4]	0.001
Dairy products (not desserts)	85.8 [28.8–145.0]	62.1 [13.3–127.3]	92.8 [41.4–145.0]	104.6 [49.3–187.9]	<0.001
Desserts	20.7 [3.7–61.2]	9.2 [0.5–33.7]	28.3 [4.5–65.8]	27.1 [9.2–66.7]	<0.001
Sauces and fats	38.1 [24.5–52.7]	32.3 [19.3–47.6]	39.9 [28.6–53.8]	38.1 [25.4–57.3]	0.001
Prepared meals	21.9 [5.8–51.3]	12.9 [0.0–39.6]	20.8 [5.8–50.5]	40.2 [16.1–70.8]	<0.001
Cookies	21.4 [10.7–36.7]	18.5 [8.4–29.9]	23.8 [13.1–34.7]	24.6 [11.8–43.5]	0.002
Fried foods and salty snacks	16.9 [6.3–31.6]	10.7 [2.3–21.8]	16.3 [6.4–30.6]	24.9 [12.5–39.6]	<0.001
Cakes and pastries	13.8 [7.9–29.1]	13.2 [6.9–26.4]	16.0 [7.9–34.4]	13.0 [7.7–28.6]	0.10
Toppings	15.0 [5.4–30.0]	13.1 [4.5–28.8]	16.3 [6.4–32.5]	15.0 [4.3–29.8]	0.07
Processed meats	11.1 [4.5–20.0]	8.3 [1.5–16.6]	12.2 [4.6–20.2]	12.7 [7.3–21.4]	<0.001
Liquors	0.0 [0.0–3.7]	0.0 [0.0–3.7]	0.0 [0.0–4.5]	0.0 [0.0–3.7]	0.82
Candy	5.9 [1.6–13.0]	4.9 [1.2–10.6]	5.8 [1.9–11.0]	7.1 [2.2–16.8]	0.008
Plant-based products	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.0 [0.0–0.0]	0.78
Nutrients					
Carbohydrates, En%	45.9 ± 6.4	44.6 ± 6.5	45.7 ± 6.4	47.3 ± 6.1	<0.001
Protein, En%	15.5 ± 2.6	16.2 ± 2.5	15.6 ± 2.6	14.6 ± 2.4	<0.001
Animal protein, g/d	51.4 ± 14.9	50.9 ± 14.1	52.7 ± 15.4	50.5 ± 15.2	0.29
Plant protein, g/d	30.7 ± 9.9	29.5 ± 9.2	31.9 ± 10.3	30.6 ± 9.9	0.05

# Baseline characteristics (2)

UPFs	Overall RTRs ( <i>n</i> = 632)	Sex-specific tertiles			<i>P</i> value
		T1 ( <i>n</i> = 210)	T2 ( <i>n</i> = 211)	T3 ( <i>n</i> = 211)	
Fat, En%	35.8 [32.4–40.0]	35.5 [32.1–39.9]	36.1 [32.9–39.7]	35.8 [32.2–40.5]	0.66
SFAs, g/d	29.3 [22.7–37.7]	26.8 [20.9–35.2]	30.3 [24.2–38.0]	31.6 [23.7–39.4]	<0.001
MUFAs, g/d	28.2 [21.5–35.1]	25.2 [19.6–32.8]	29.9 [22.6–35.3]	29.3 [22.9–36.9]	0.001
PUFAs, g/d	17.3 [13.0–23.1]	16.3 [12.0–22.9]	18.2 [13.8–23.3]	17.5 [13.0–23.7]	0.08
Total fiber intake, g/d	22.4 ± 6.8	22.6 ± 6.8	23.3 ± 7.3	21.3 ± 6.1	0.007
Fruit consumption, g/d	123.0 [66.3–232.0]	167.4 [84.1–260.7]	128.6 [70.3–232.0]	94.4 [35.1–169.1]	<0.001
Vegetables consumption, <sup>2</sup> g/d	112.4 [76.8–158.6]	130.2 [87.0–171.6]	114.7 [80.7–163.3]	97.0 [68.4–129.9]	<0.001
Alcohol consumption, g/d	2.6 [0.0–11.1]	4.8 [0.1–15.6]	2.6 [0.1–9.7]	1.1 [0.0–6.7]	0.001
Mediterranean diet score	4.3 ± 1.7	4.8 ± 1.8	4.3 ± 1.7	3.8 ± 1.5	<0.001
DASH score	23.8 ± 4.7	25.9 ± 4.6	24.2 ± 4.2	21.4 ± 4.1	<0.001

# Contributie van “food groups” aan intake van ultra-processed foods

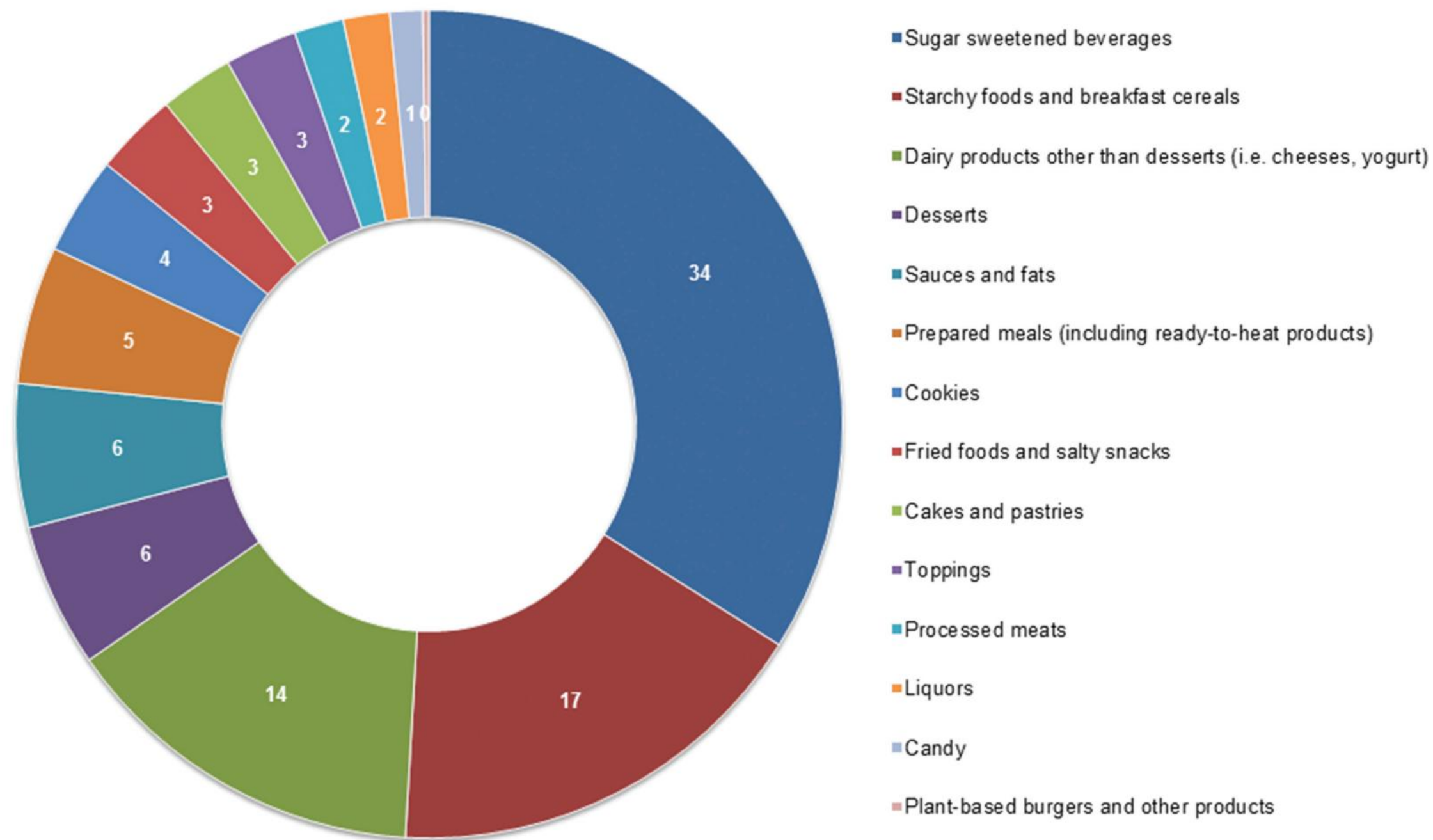


FIGURE 1 Contribution of food groups to the ultra-processed foods (group 4) according to the NOVA classification.

# Conclusie (terug naar dialyse)

Er is nog veel te leren over het optimale dieet voor dialysepatiënten

Tijd voor het opzetten van een grote cohortstudie bij dialysepatiënten met

- Objectieve metingen van voedselintake
- Vragenlijst/anamnese informatie over het dieet
- Dit alles te linken aan uitkomsten (spiermassa, spierkracht, sterfte, ziekenhuisopnames, kwaliteit van leven, cognitie)

Tijd voor DiaLines

Het **Niercongres** wordt mede mogelijk gemaakt door:



**Boehringer  
Ingelheim**



**eurocept  
homecare**  
verder in zorg dichtbij



**FRESENIUS  
MEDICAL CARE**



**MEDICE**  
THE HEALTH FAMILY



**novo nordisk**



Otsuka

