Phosphate Additives in Food
a health hazard in CKD

Eberhard Ritz
Heidelberg (Germany)

Phosphate additives in food – a health hazard

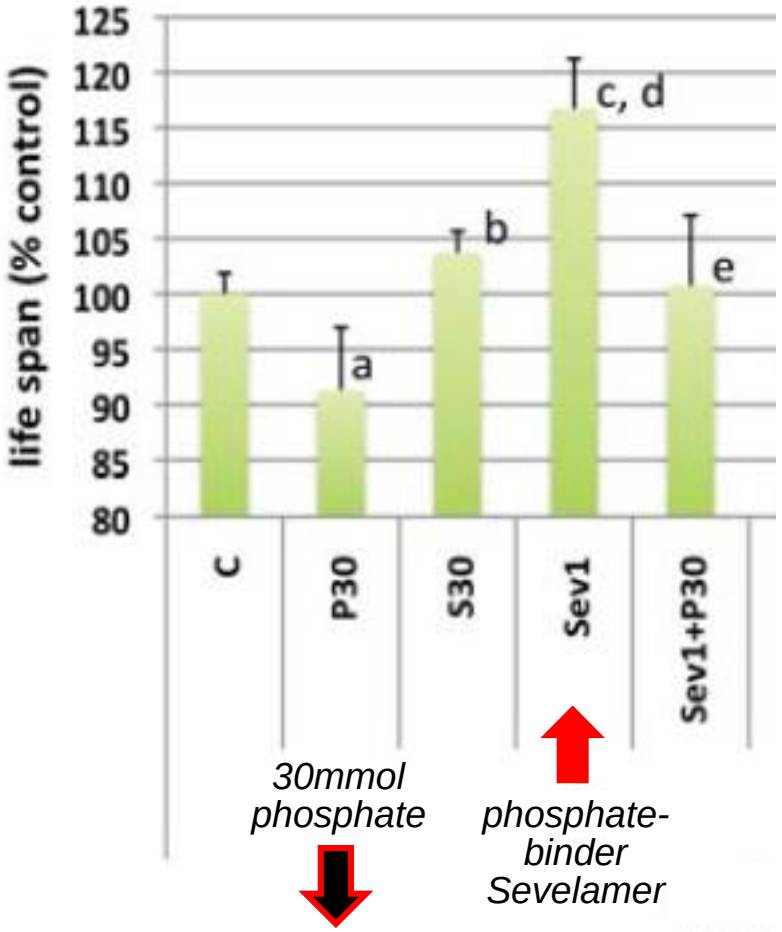
Holy-Ghost Church
(Heiliggeist-Kirche Heidelberg)

- **Phosphate-**
  what does zoology teach us ?
- **Phosphate – adverse effects in CKD and beyond kidney disease**
- **Phosphate in food items – do we know what we eat ?**
- **Not all phosphate in food is created equal**
- **Information for educated patients - labelling of P content in food items?**

Phosphate modulates life span of Drosophila

in evolution "nutrient sensing pathways" are highly conserved

restriction of phosphate supply prolongs life span



Bergwitz, Nephrol.Dial.Transplant.(2012) 27:3399

Another lection from the animal kingdom phosphate concentration and life span

Earth worm : short life span,
high S-phosphate-concentration
Tortoise: long life span,
low S-phosphate-concentration

coincidence
or are there reasonable explanations ?

Kuro-o, Mech.Aging Development (2010) 131:270

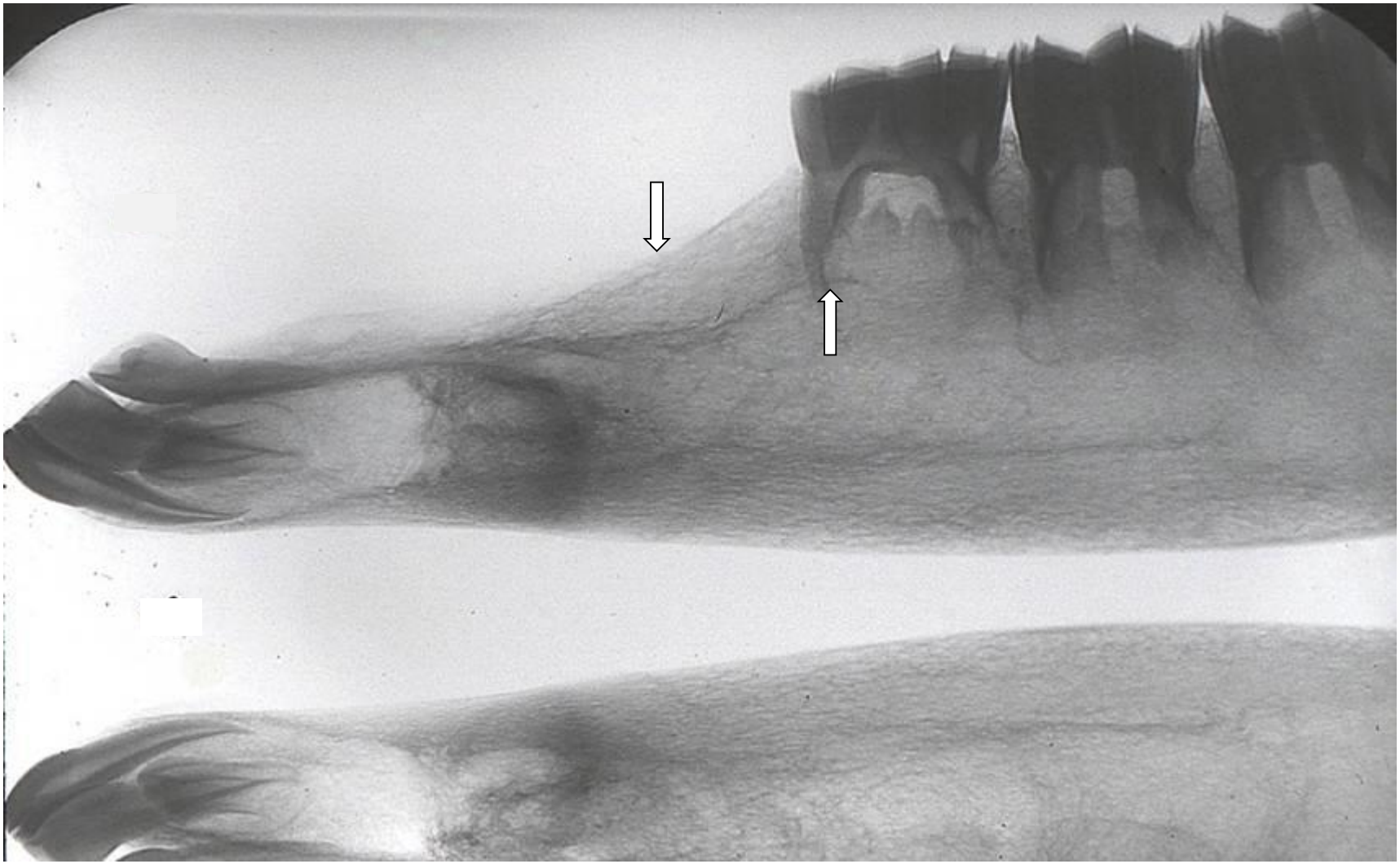
It had been known for decades :
that high phosphate intake in racing horses
has negative consequences for skeleton and muscles

When racing horses (without kidney disease)
had grazed in meadows fertilized with manure or phosphate

⇨ *secondary hyperparathyreoidism*
subperiostal resorption zones

painful tendons render the horse unfit for races during the entire racing season

for a long time this was the only known P related health hazard



Phosphate additives in food – a health hazard

Grain market

(Kornmarkt)

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What does the epidemiologist say ?

Even in "normophosphatemic" individuals the serum-phosphate-concentration is

associated with :

*- increased overall **mortality***

*- more frequent and worse outcome of **cardiovascular** and*

*- more frequent and worse outcome of **renal disease***

Tonelli, Circulation (2005) 112:2627

Kestenbaum, JASN (2005) 16:520

Dhingra, Arch Int Med (2007) 167:879

Conall, Nephrol Dial Transplant (2011) 26:2885

Serum Phosphate Predictor of ESRD

(endstage renal disease)

NHANES III

n=13 372 participants >18 years

mean age 44.3 years; 52 % women

follow-up 9.1 years

ESRD= start of dialysis

Serum Pi *(mg/dl)*

< 4 mg/dl	*>4 mg/dl*
1.0	2.41 *(95%CI 1.29-4.5)*

p< 0.007

O'Seaghdha, Nephrol.Dial.Transplant.(2011) 26:2885

Higher S-Pi concentration in the normophosphatemic range increases risk of endstage renal disease

(3rd National Health and Nutrition Examination Survey; NHANESIII)

n=13 372; follow-up 9.1 years

S-phosphate (mg/dl) at start of observation

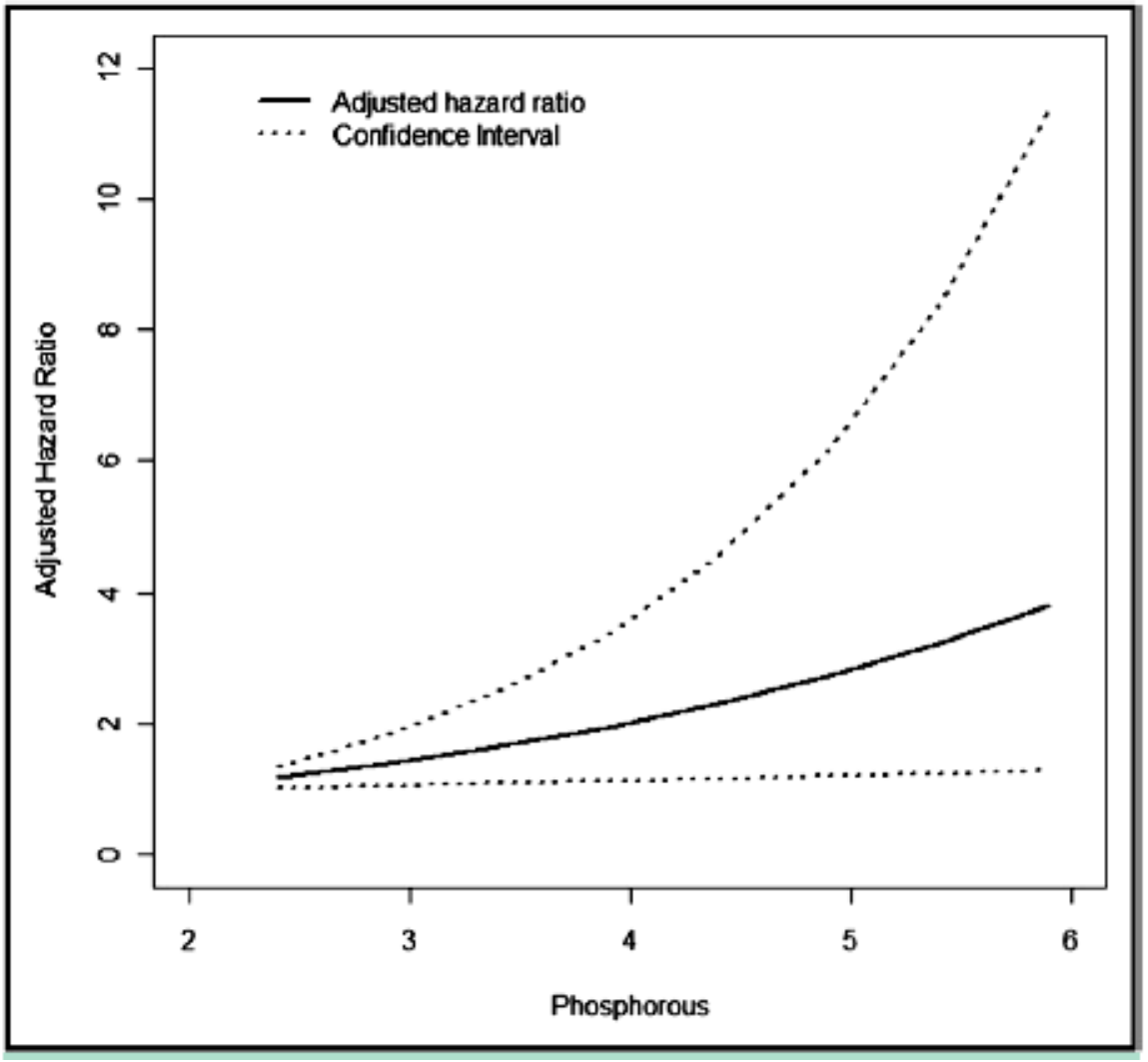
	<4.0	>4.0	p
ESRD	43 / 11‘308	22/2064	
rel.Risiko ESRD	1.0	**2.41**	*0.009*

(adjusted for age, gender, race …)

Conall, Nephrol.Dial.Transplant.(2011) 26:2885

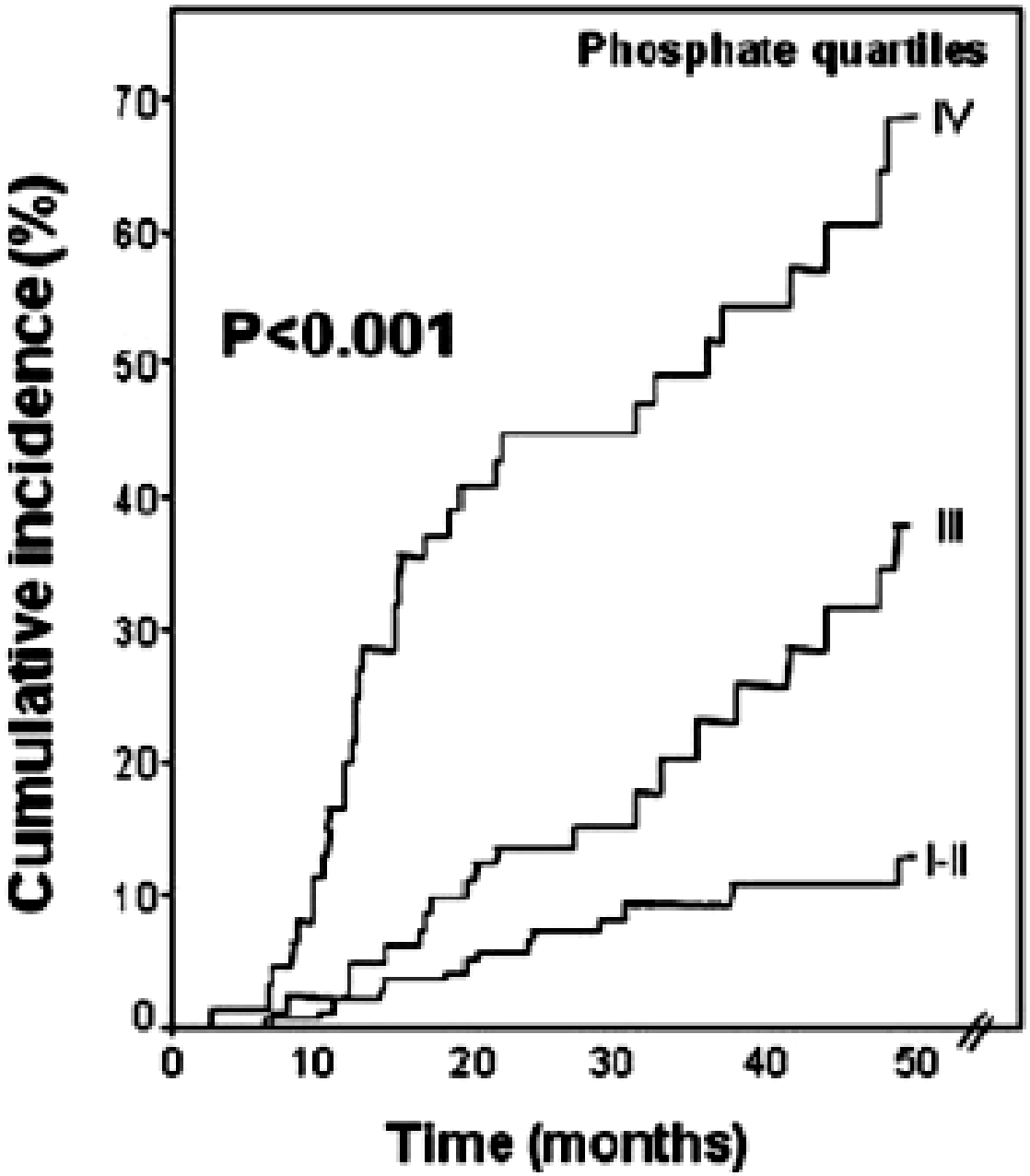
Adjusted hazard ratio *(Confidence-Interval 95%)* **:**
terminal renal failure correlated to baseline serum-phosphate

94,989 individuals without CKD, Kaiser Permanente program,11 years follow-up
mean age 50 years



Sim, Am.J.Med. (2013) 126:311

Terminal renal failure



In patients with CKD high phosphate accelerates loss of renal function

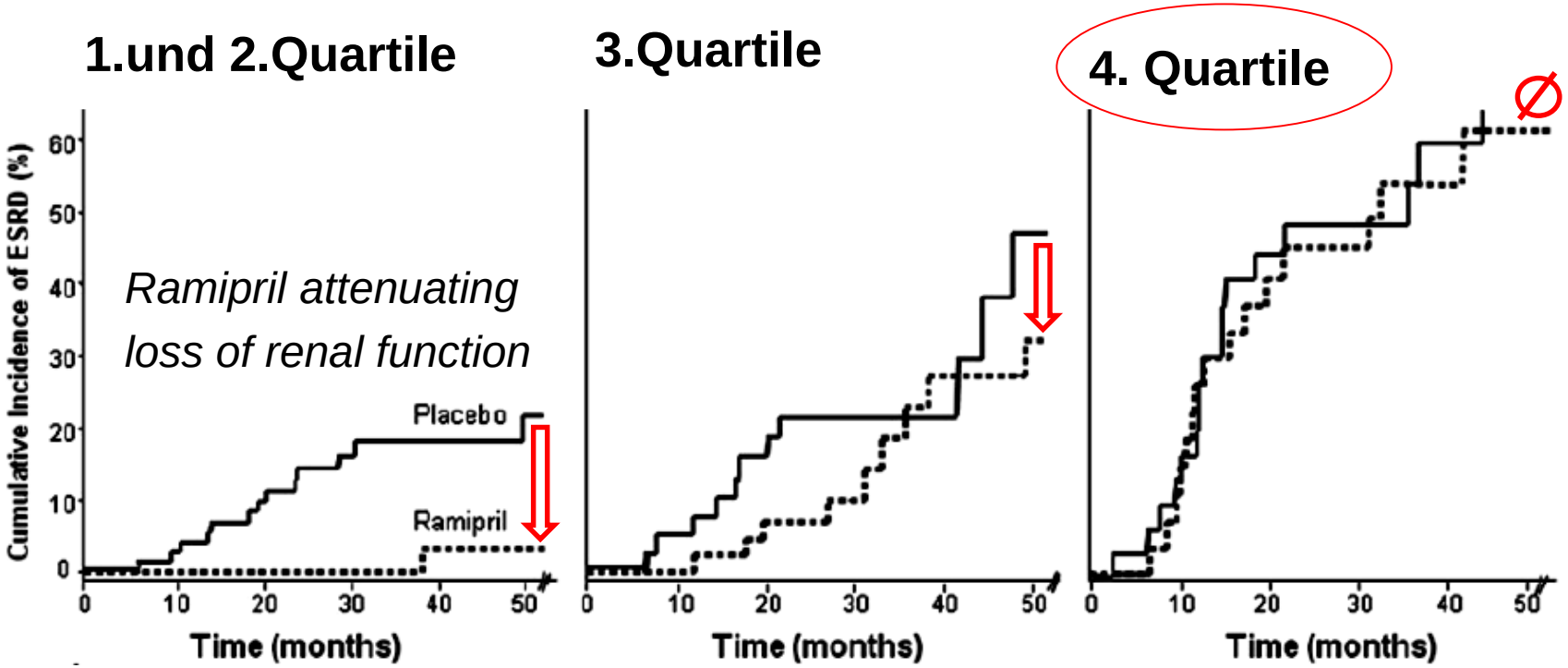
Zoccali, J.Am.Soc.Nephrol.(2011) 22:1923

High serum-phosphate-concentration

 # accelerates loss of renal function in CKD patients

 # abrogates effect of ACE inhibitors to slow down progression

S-Phosphat



Zoccali, J.Am.Soc.Nephrol.(2011) 22:1923

Metaanalysis of 17 Studies with different Cohorts

(n = 327,644)

Association between S-P and **mortality** chronic kidney disease

per **1 mg/dl** higher S-P - **18 %** higher mortality

rel. risk 1.18 *(95 % CI 1.12 – 1.25)*

Palmer, JAMA (2011) 305:1119

24h urine phosphorous excretion and all-cause mortality in CKD

880 patients
stable CKD
24h P excretion
7.4 years follow-up

Urine Phosphorous Tertiles

	Tertile 1 <508 mg/d	Tertile 2 508-748mg/d	Tertile 3 >748mg/d
Hazard ratio 95% CI unadjusted	**1.00**	**0.74**	**0.56**
adjusted	**1.00**	**0.84**	**0.72**

Palomino, CJASN (2013) 8: e-pub March 28th

High S-phosphate before renal transplantation - worse function after kidney transplantation

(longterm effects !!)

Medians within quartiles and interquartile-range *(mg/dl)*

4.2 *(3.7-4.5)*

5.4 *(5.1-5.7)*

6.4 *(6.1-6.8)*

8.5 *(7.7-9.7)*

adjusted odds ratio

1. **delayed graft function**

OR 1.68 *(95% CI 1.05-2.71)*

2. **graft-failure**

progressively higher in higher quartiles

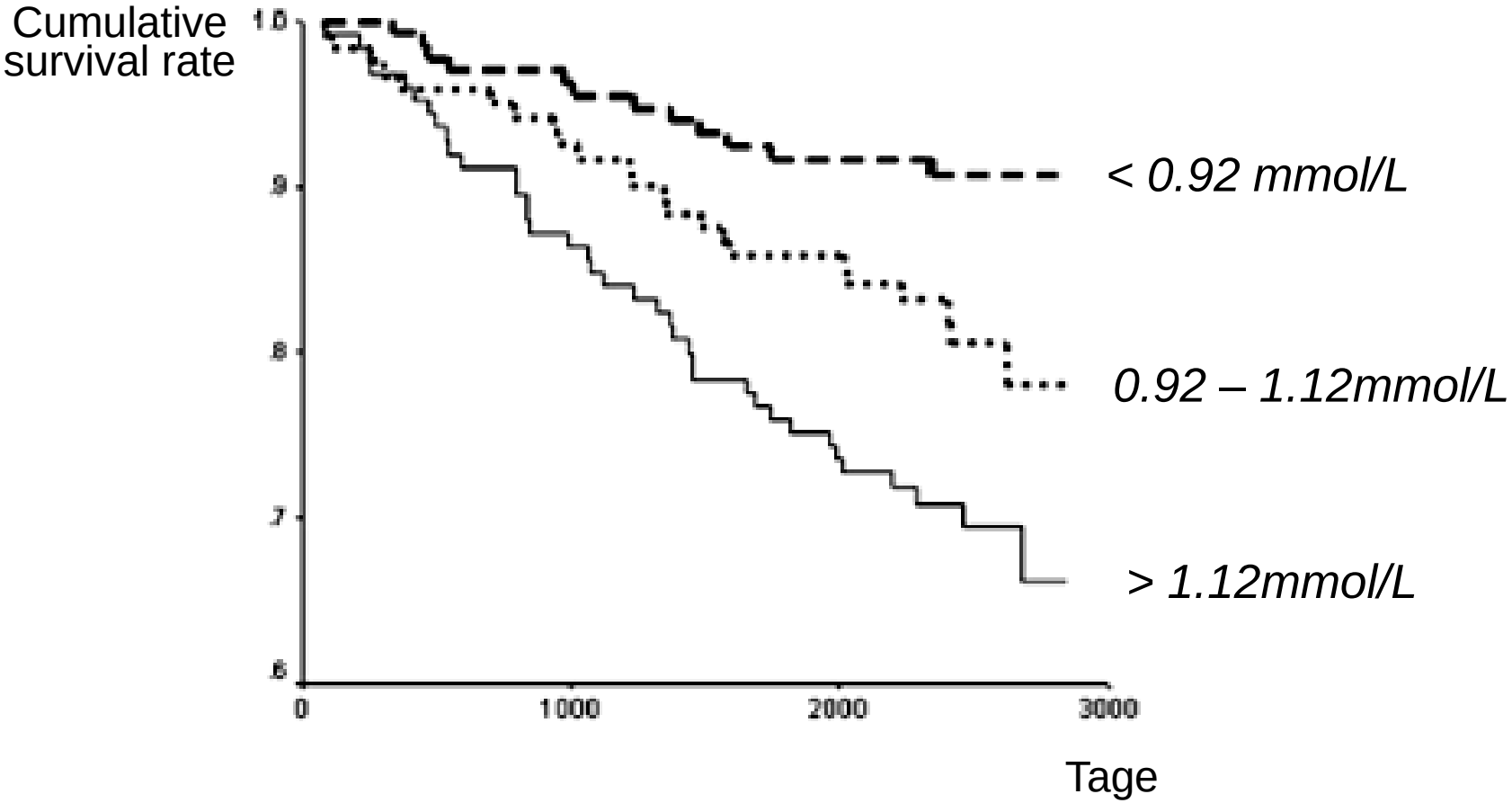
(p for trend = 0.015)

Sapir-Pichhadze, J.Nephrol. (2012) 25:1091

Serum-Phosphate

predicts mortality in kidney graft recipients

(prospective observational study; 379 patients; 6 years follow-up; corrected for eGFR)



Connolly, Transplantation (2009) 87:1040

European Heart Journal
doi:10.1093/eurheartj/ehs247

CURRENT OPINION

Phosphate: a novel cardiovascular risk factor

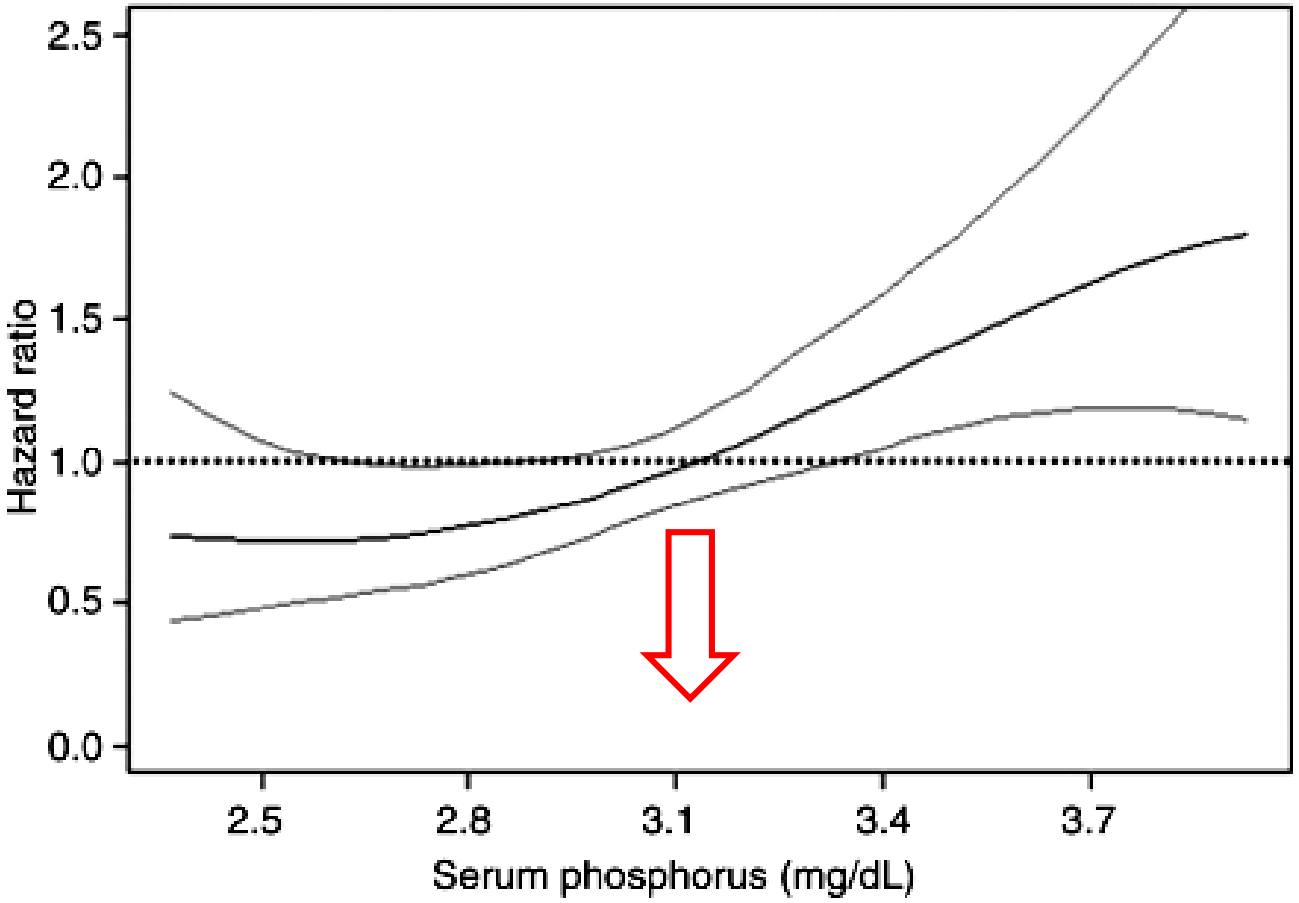
Markus Ketteler, Myles Wolf, Kai Hahn, and Eberhard Ritz*

The above findings justify the recommendation to include fasting serum phosphate as a risk predictor in patients with kidney malfunction or cardiovascular disease. In addition, dietary advice to minimize food items containing added inorganic phosphates would constitute a measure for patients with chronic kidney or cardiovascular disease. Therefore, appropriate food labelling seems warranted. Elucidation of the pathogenetic pathways triggered by phosphate will be a fascinating issue in current and future cardiovascular research.

Europ.Heart J.(2013) 34:1099

Association Serum-Phosphate and LVH (*Echo*)

3,300 participants without heart failure or CKD



Dhingra, Eur J Heart Fail (2010) 12:812

Serum Phosphate and

leftventricular hypertrophy

(Echocardiography)

4,055 young adults with

normal renal function

Odds ratio **LV mass** vs. **S-phosphate**

1.27 *(95 %, CI 1.09 – 1.47)*

Foley, JASN (2009) 20:397

Patients with chronic kidney disease
serum-phosphate is associated with LV-Hypertrophy
(cardiac magnetic resonance)

even in early stages of the disease!

208 nondiabetic patients CKD 2-4

mean GFR 50 ± 15 ml/min/1.73m²

S-phosphate 1.11 ± 0.21 mmoll

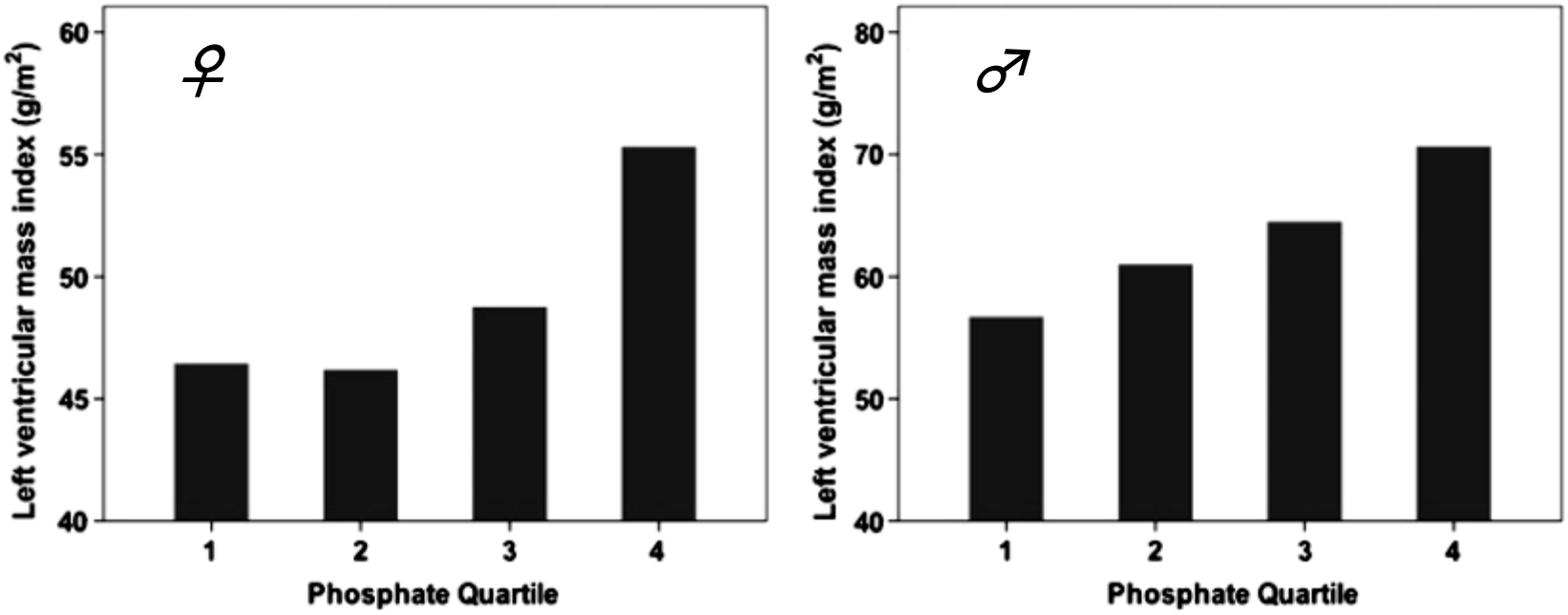
***Serum phosphate** correlated with **LVM** (r=0.173;p=0.01)*

 # LVM increasing progressively
with higher quartiles of serum phosphate concentration,

Chue, Heart (2012) 98:219

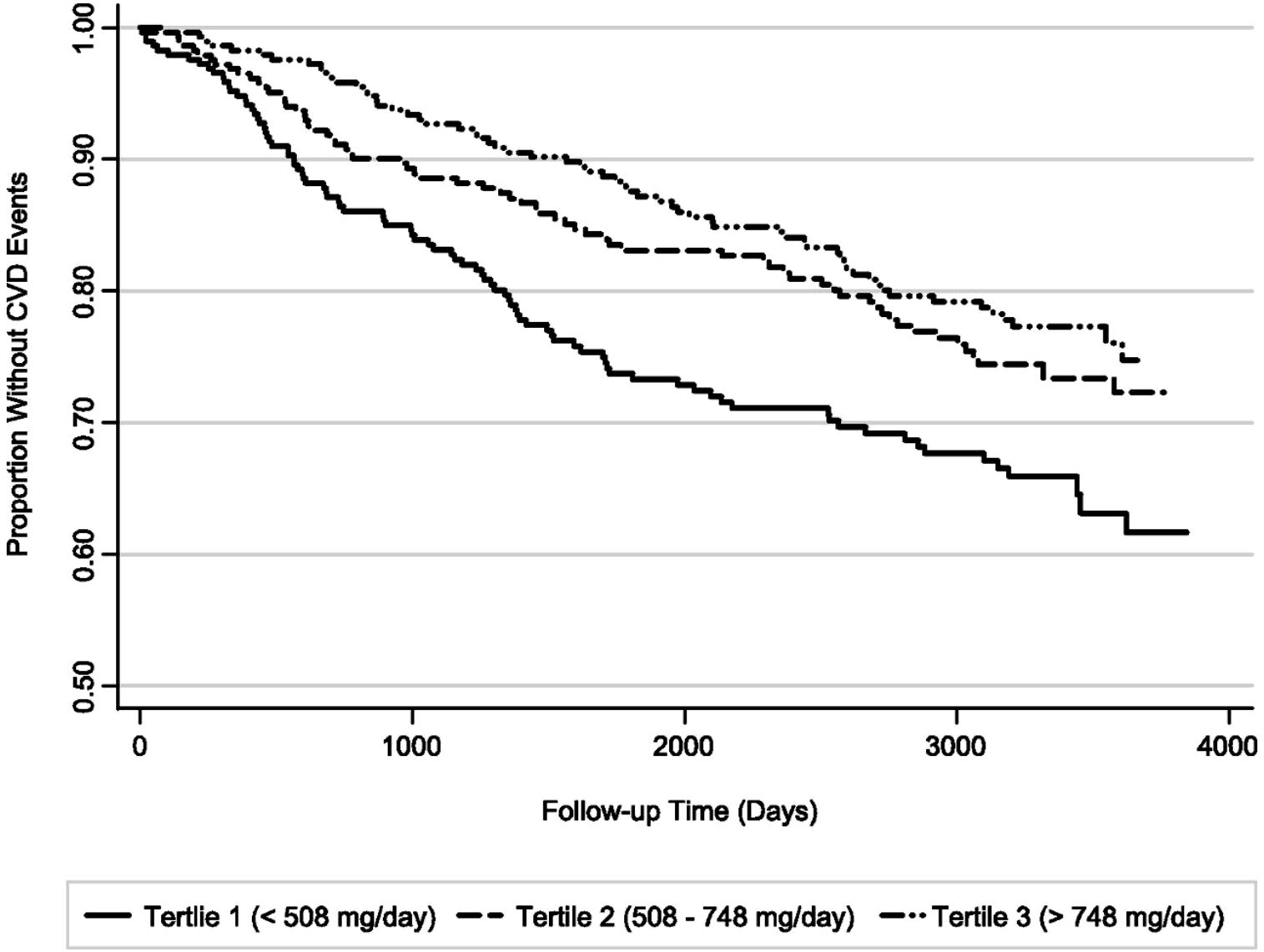
In patients with CKD
serum-phosphate is associated with LV-hypertrophy

(cardiac magnetic resonance)



Chue, Heart (2012) 98:219

24h urine phosphorous excretion and CV events in CKD

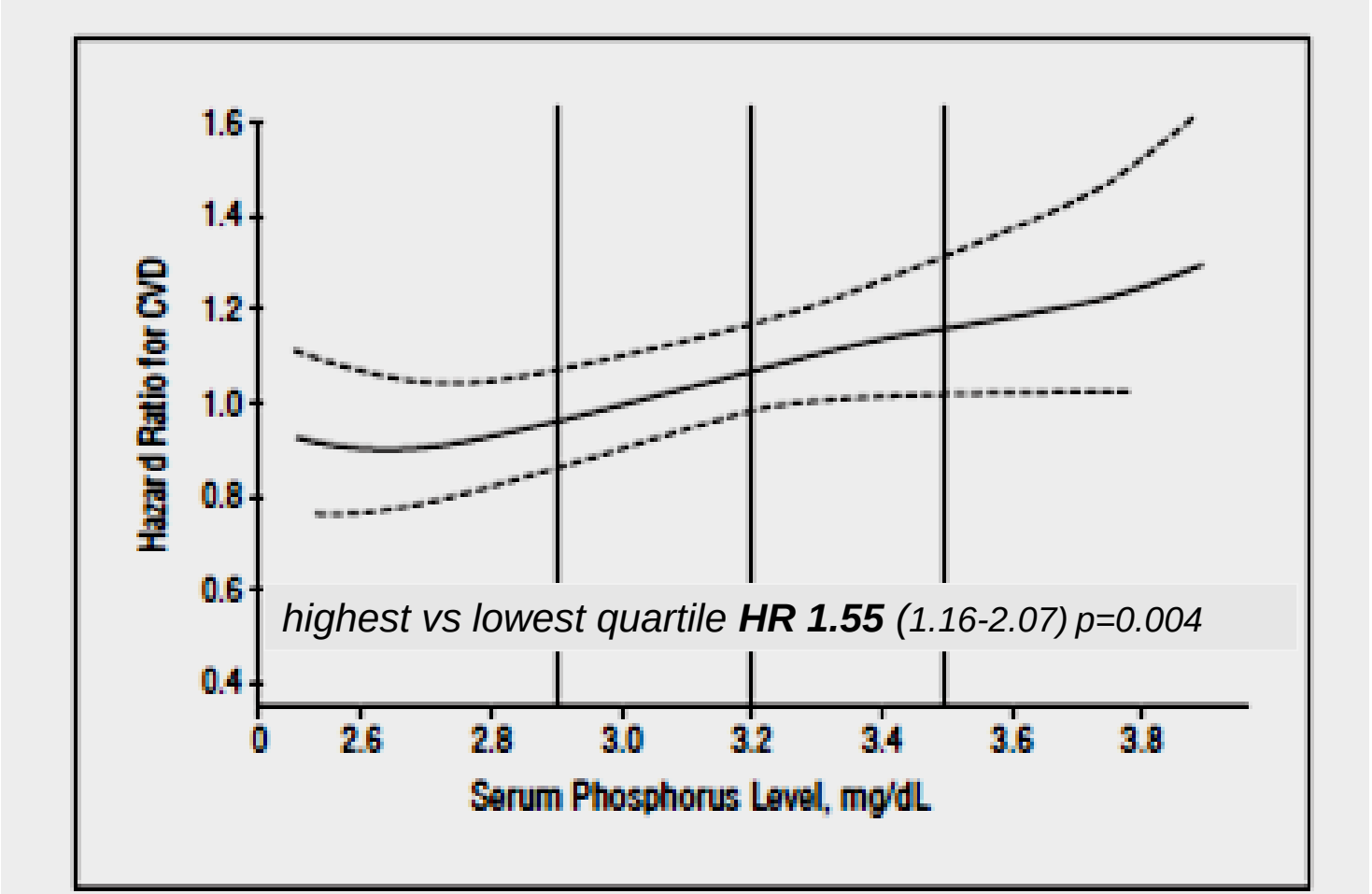


Palomino, CJASN (2013) 8: e-pub March 28th

Serum-phosphate concentration in the normal range and cardiovascular events in the general population

(Framingham offspring study)

3368 individuals, observation period 16.1 years, 524 CV events



Dhingra, Arch.Intern.Med. (2007) 167:879

Serum-Phosphate and onset of heart failure

Prospective study

3,300 participants without heart failure or CKD

17.4 years follow-up

per **1 mg/dl** Δ S-phosphate

onset of heart failure **OR 1.74**

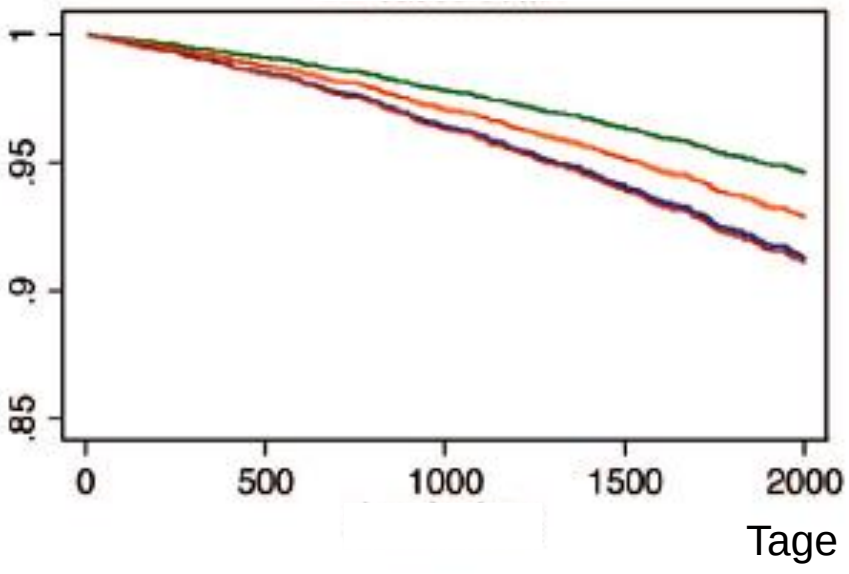
(95% CI 1.17 – 2.59)

Dhingra, Eur J Heart Fail (2010) 12:812

Serum-Pi Quartiles and Cardiovascular Events in Coronary Patients

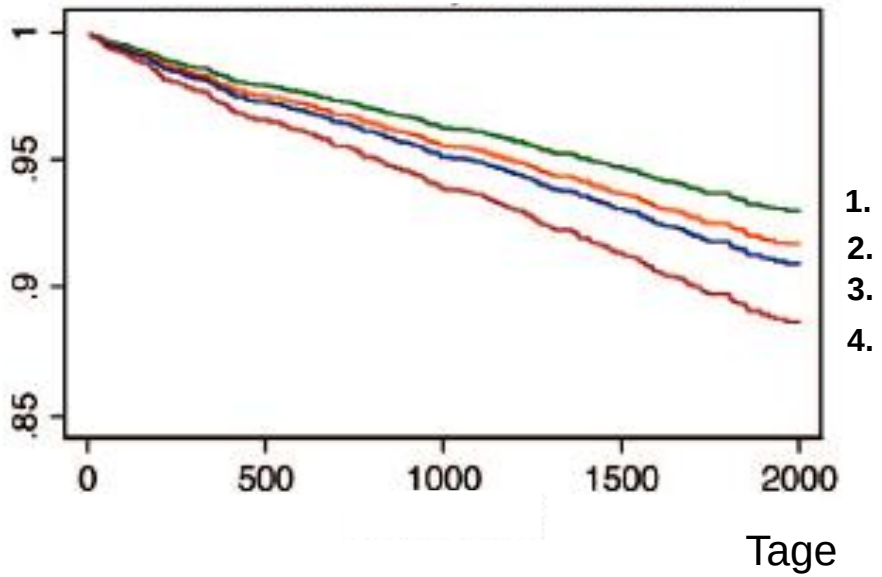
(without kidney disease !)

Overall mortality



myocardial infarction

(letan+nonletal.)



Tonelli, Circulation (2005) 112:2627

caused by P_i per se or by FGF23 triggered by Pi ?

Phosphate and cardiovascular events in patients with stabile coronary heart disease

(LURIC study)

	all patients	CV events	
Quartiles			
<3.72	358	52	1 ref
3.72–<4.03	202	23	0.82 (0.50 to 1.34)
4.03–<4.65	317	49	1.09 (0.74 to 1.61)
≥4.65	141	27	1.42 (0.89 to 2.26)
Continuous			
Per 0.81 mg/dl (SD)	1018	151	1.07 (0.93 to 1.24)

	all patients	mortality	
Quartiles			
<3.72	377	34	1 ref
3.72–<4.03	228	18	0.87 (0.49 to 1.54)
4.03–<4.65	348	43	1.41 (0.90 to 2.21)
≥4.65	157	24	1.77 (1.05 to 2.99)
Continuous			
Per 0.81 mg/dl (SD)	1110	119	1.15 (1.00 to 1.31)

Grandi, Heart (2012) 98:926

“Phosphate toxicity“

Direct effects:

vascular calcification

endothelial cell dysfunction

Di Marco, Kidn.Internat. (2013) in press

Effects mediated **via hormones**:

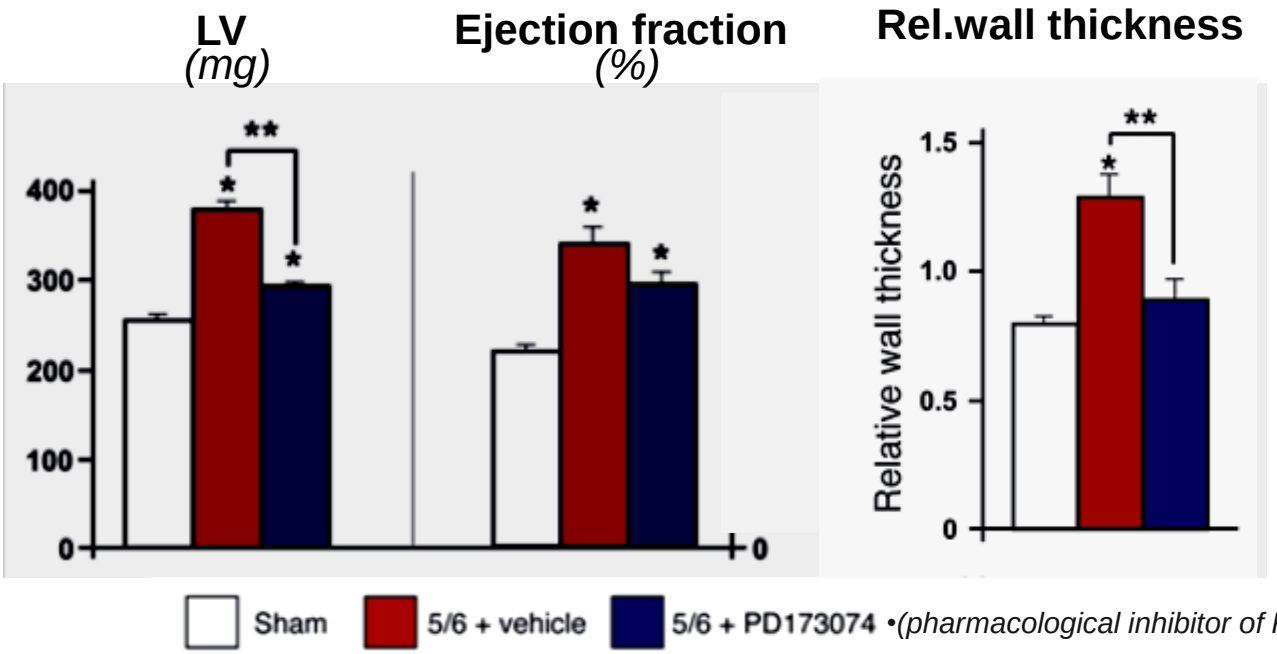
FGF23/klotho, PTH

Toussaint, Nephrology (2012) 17:433

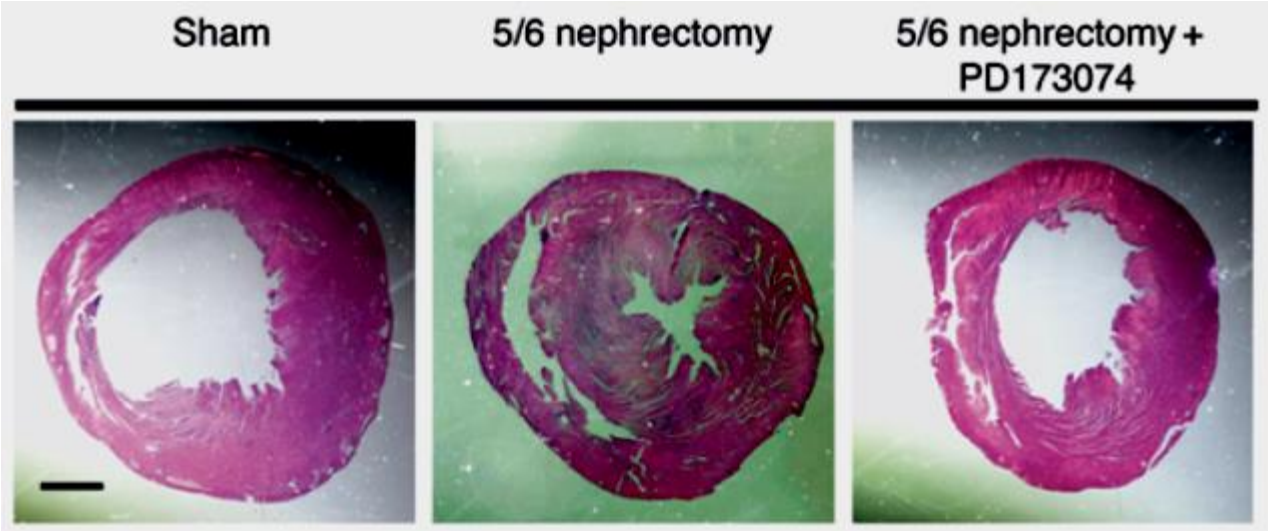
5/6 nephrectomy ⇨ cardiac hypertrophy and insufficency

heart pathology reduced by blockade of the FGF23 receptor;

FGF23 (in response to phosphate retention) **is the culprit**



•*(pharmacological inhibitor of FGF23 receptor)*



Faul, J.Clin.Invest. (2011) 121: 4393

FGF23

- Increases in early stages of chronic kidney disease

- Strongly associated with
  - *death*
  - *CVD*
  - *LVH*
  - *vascular calcification*

Toussaint, Nephrology (2012) 17:433

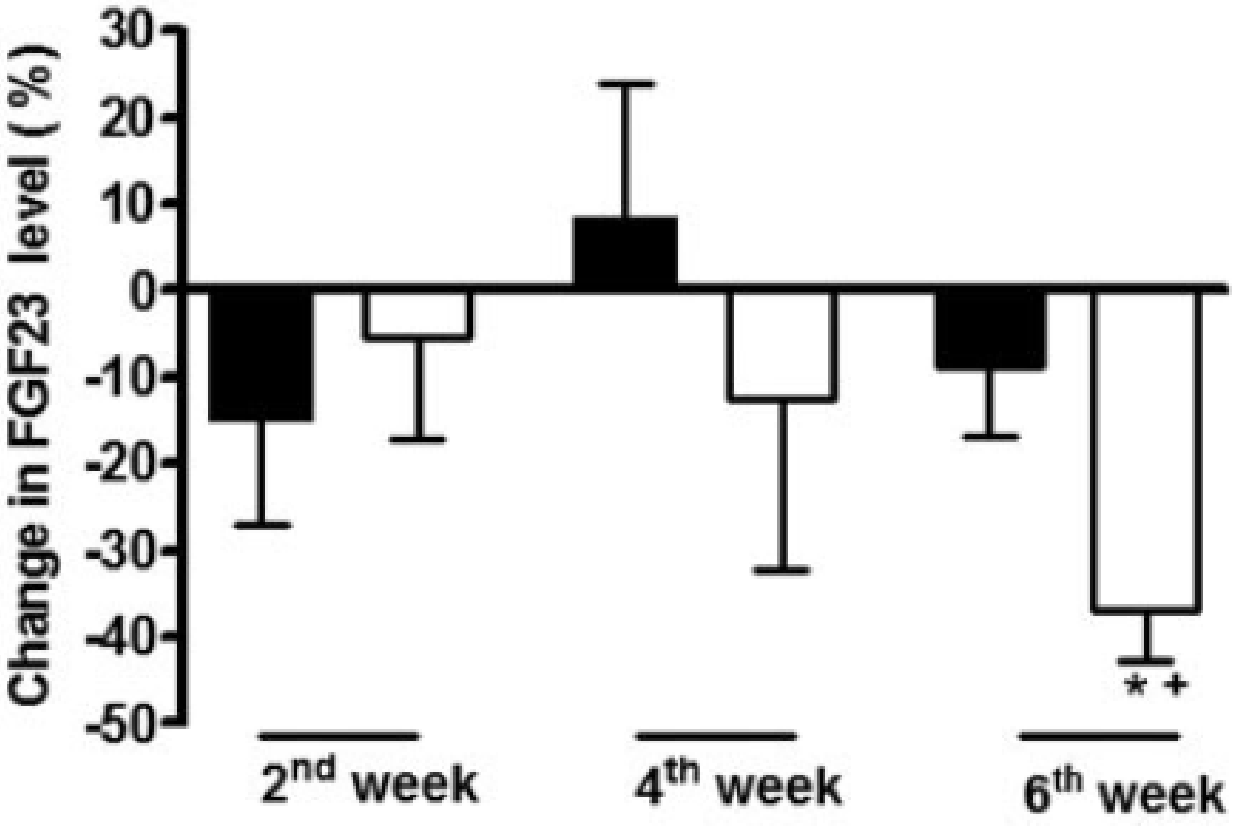
Even in normophosphatemic ! patients in

early stages of chronic kidney disease

the serum concentration of FGF23 decreases

when phosphate binders ☐ Sevelamer or ■ Calcium

(this finding suggests that it is high FGF23 which keeps S-Pi within the normal range)



Oliveira, CJASN (2010) 5:286

Phosphate additives in food – a health hazard

Old University
(Alte Universität Heidelberg)

- **Phosphate-**
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Phosphate Additives in Food—a Health Risk

ÜBERSICHTSARBEIT

Gesundheitsrisiko durch Phosphatzusätze in Nahrungsmitteln

Eberhard Ritz, Kai Hahn, Markus Ketteler, Martin K. Kuhlmann, Johannes Mann

Schlussfolgerung: Obwohl für die Allgemeinbevölkerung noch keine prospektiv kontrollierten Studien vorliegen, sollte einerseits schon allein angesichts der Häufigkeit chronischer Nierenerkrankungen und andererseits aufgrund der potenziellen Schädlichkeit einer hohen Phosphatzufuhr auch für Nierengesunde, der Phosphatgehalt von Nahrungsmitteln gekennzeichnet werden. Zudem sollten die Bevölkerung und die Ärzteschaft über die Rolle der Phosphatzusätze als Risikofaktor aufgeklärt werden.

Ritz E, Hahn K, Ketteler M, Kuhlmann MK, Mann J: Phosphate additives in food—a health risk. Dtsch Arztebl Int 2012; 109(4): 49–55.

Phosphate Industry Responds to "Phosphate Additives in Food – a Health Risk" by Ritz et al

International Food Additives Council, Atlanta Georgia

It is well documented that phosphorous, a component of food phosphates, is an essential nutrient….

The review by Ritz et al … focused on a small subset of the general population… i.e. chronic renal disease..

Humans require dietary phosphate for proper functioning of the body; in healthy individuals exccess phosphorous is excreted

IFAC and PAPA …agree with the large body of scientific and regulatory evidence that inorganic phosphates are safe and provide nutritional and functional benefits (!!!) in foods

ELSEVIER

Trends in Food Science & Technology 24 (2012) 92–102

TRENDS IN FOOD SCIENCE & TECHNOLOGY

Review

Phosphorus-containing food additives: An insidious danger for people with chronic kidney disease

Ray J. Winger[a,*], Jaime Uribarri[b] and Lyn Lloyd[c]

or absence of biomarkers in blood or urine and the level of Glomerular Filtration Rate (GFR). The level of kidney function tends to decline progressively over time in many people and kidney failure is the adverse outcome. CKD is classified in 5 stages (Table 1).

Recent regulatory changes, which require the mandatory labelling of sodium and salt, have greatly increased consumers' knowledge about sodium in food and health professionals' ability to advise dietary sodium intake. However, people with CKD stage 5, defined as End-Stage Renal Disease (ESRD), need to control their intake of a number of nutrients, including sodium, potassium and phosphorus (P) to optimise their health. The use and bioavailability of P in our processed foods is increasing and these foods are particularly dangerous to people with ESRD. There is little transparency within the food industry to identify the quantitative usage of P, which effectively

In which food items are phosphate additives ?

- *meat products and seafood*
- *pasta (to decrease cooking time)*
- *instant pudding*
- *non-dairy creamers*
- *spreadable cheese (aged cheeses have none)*
- *fortified orange juice*
- *baked goods (high in additives : leavening agents and dough conditioners)*
- *soft ice cream*
- *chicken (for "plumping") and pork (for “moisture")*

Calvo, Nephrology News and Issues 2012, July p6

Typical phosphate content of some commercial food items

(“processed foods“)

Winger,Uribarri,Lloyd;

Trends in Food Science and Technology (2012) 24:92-102

Product	P content (mg/100g food item)
Meat products	
corned beef	*1298*
bacon fried	*450*
sausages	*160-214*
Pasta	
noodle, rice	*6*
noodle wheat	*40-52*
pasta,wholemeal, boiled	*140*
Snack foods	
corn chips	*291*
popcorn	*358*

Typical phosphate content of some commercial food items

("processed foods")

Winger,Uribarri,Lloyd;

Trends in Food Science and Technology (2012) 24:92-102

Product	P content *(mg/100g food item)*
Beverages	
coffee whitener	*420*
Cereal Products	
biscuits	*155-304*
bread gluten-free	*242*
bread wholemeal	*173*
Milk Products	
cheese, processed	*552*
Yoghurt (no added calcium)	*96-195*

What are the motivations of food industry to add phosphate to food items ?

one additional incentive :

phosphate “binds“ water,

thus increasing weight

⇨ incentive for food industry:

water in food items guarantees easy money

Limited efficacy of phosphate binders

1 Sevelamer 800 mg - 1 tablet binds 27 mg phosphate
1 Calcium acetate tablet - 1 tablet binds 30 mg phosphate
1 Phosphoenol 1000 mg - 1 tablet binds 90 mg phosphate

…

Calvo, Nephrology News and Issues 2012, July p6

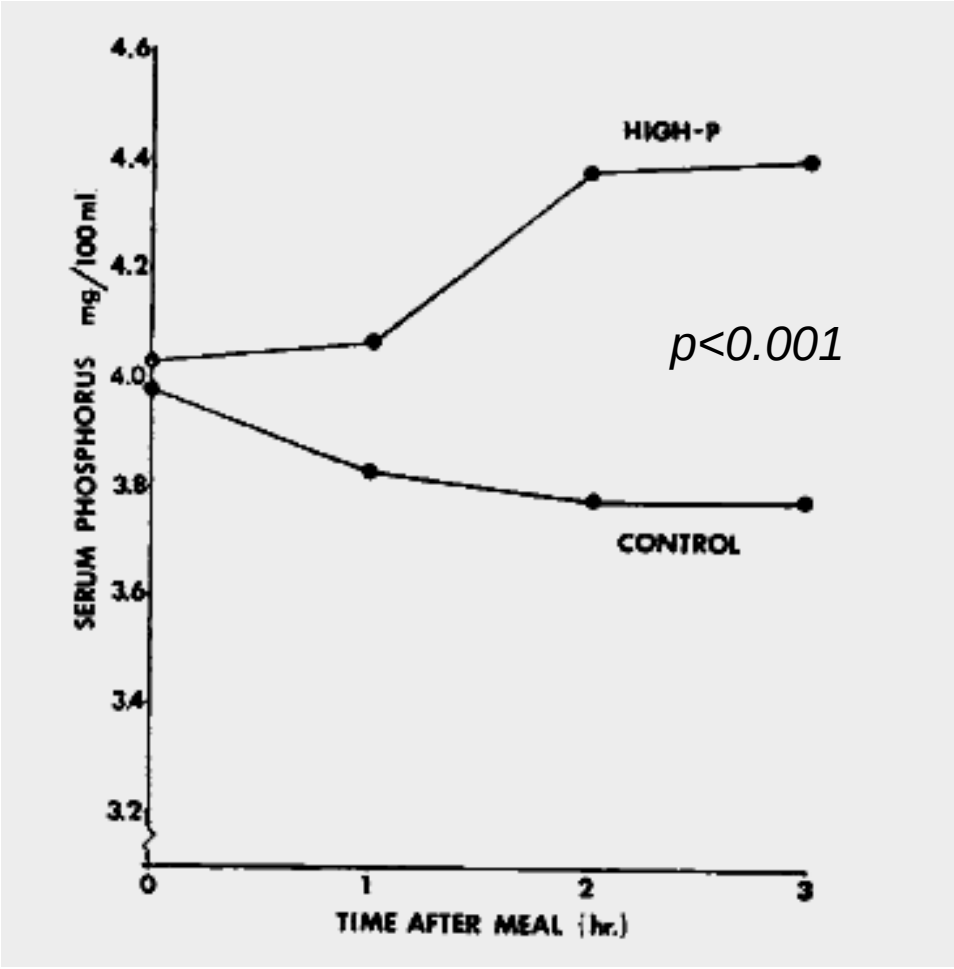
How long has all this been known ?

(we are reinventing the wheel !!!“)

Bell, J.Nutr.(1977) 107: 42

Postprandial serum-P concentration in healthy volunteers : food items with/without phosphate additives

4 weeks diet containing1g phosphate without phosphate additive
4 weeks the same diet wirh addition of sodium-phosphate
resulting in total P intake of 2.1 g/day



"the contribution to serum phosphate from P in food additives is greater than the contribution of P in the diet"

Bell, J.Nutr.(1977) 107: 42 !

Postprandial Serum-P in Healthy Volunteers
food with/without added phosphate

Serum calcium and phosphorus concentrations

Subject	Calcium[1]		Phosphorus[1]	
	Control	High-phosphorus	Control	High-phosphorus
	mg/100 ml	*mg/100 ml*	*mg/100 ml*	*mg/100 ml*
1	11.11	10.38	4.56	4.96
2	10.34	10.31	3.44	4.62
3	10.58	10.61	3.55	4.44
4	10.65	10.30	3.94	4.36
5	10.47	10.21	3.82	4.55
6	10.61	10.13	3.84	3.94
7	10.85	10.33	3.46	4.20
8	10.69	10.23	3.46	4.36
Mean ± SD	10.66 ± 0.24	10.31 ± 0.14[2]	3.76 ± 0.38	4.43 ± 0.30[2]

without *with*

added phosphate

increase : 0.67 mg/dl
27%

Bell, J.Nutr.(1977) 107:42

Urinary phosphate excretion in healthy volunteers *food with/without added phosphate*

% increase higher than % increase of S-phosphate

Urinary phosphorus excretion

Subject	Phosphorus excreted[1] Control Week 1	2	3	4	Avg.	High-phosphorus 5	6	7	8	Avg.	Significance[2]	Increase
												%
1	460	358	474	220	378	1,598	1,113	1,030	1,136	1,219	$P < 0.001$	222
2	308	625	434	244	403	611	999	1,099	1,603	1,078	$P < 0.05$	168
3	382	680	625	340	507	749	1,920	1,785	2,091	1,636	$P < 0.02$	222
4	392	474	673	569	527	897	417	684	646	661	NS	25
5	449	501	461	453	466	1,096	1,549	1,307	1,850	1,450	$P < 0.001$	211
6	264	657	580	396	474	968	872	1,016	797	913	$P < 0.01$	92
7	127	540	579	298	386	436	735	380	583	534	NS	38
8	512	218	229	148	277	525	731	451	664	593	$P < 0.05$	114
Overall mean ± SD			427 ± 156					1,010 ± 477			$P < 0.001$	137 %

resulting from.added phosphate

Bell, J.Nutr.(1977) 107:42

⇨ *serum-phosphate underestimates P-load*

Phosphate additives in food – a health hazard

Powder tower
(Pulverturm Heidelberg)

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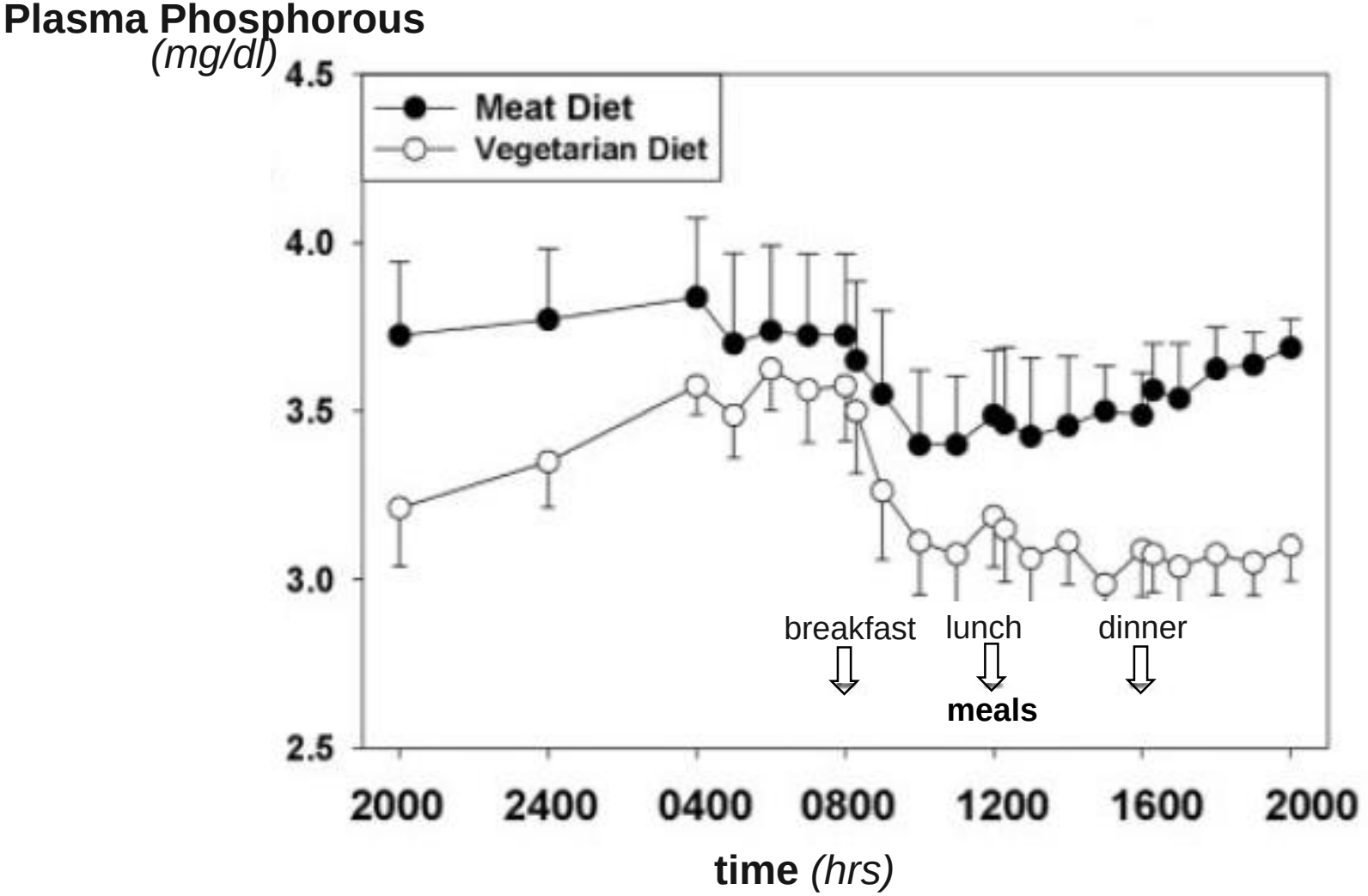
Diurnal variation of plasma phosphorous concentration

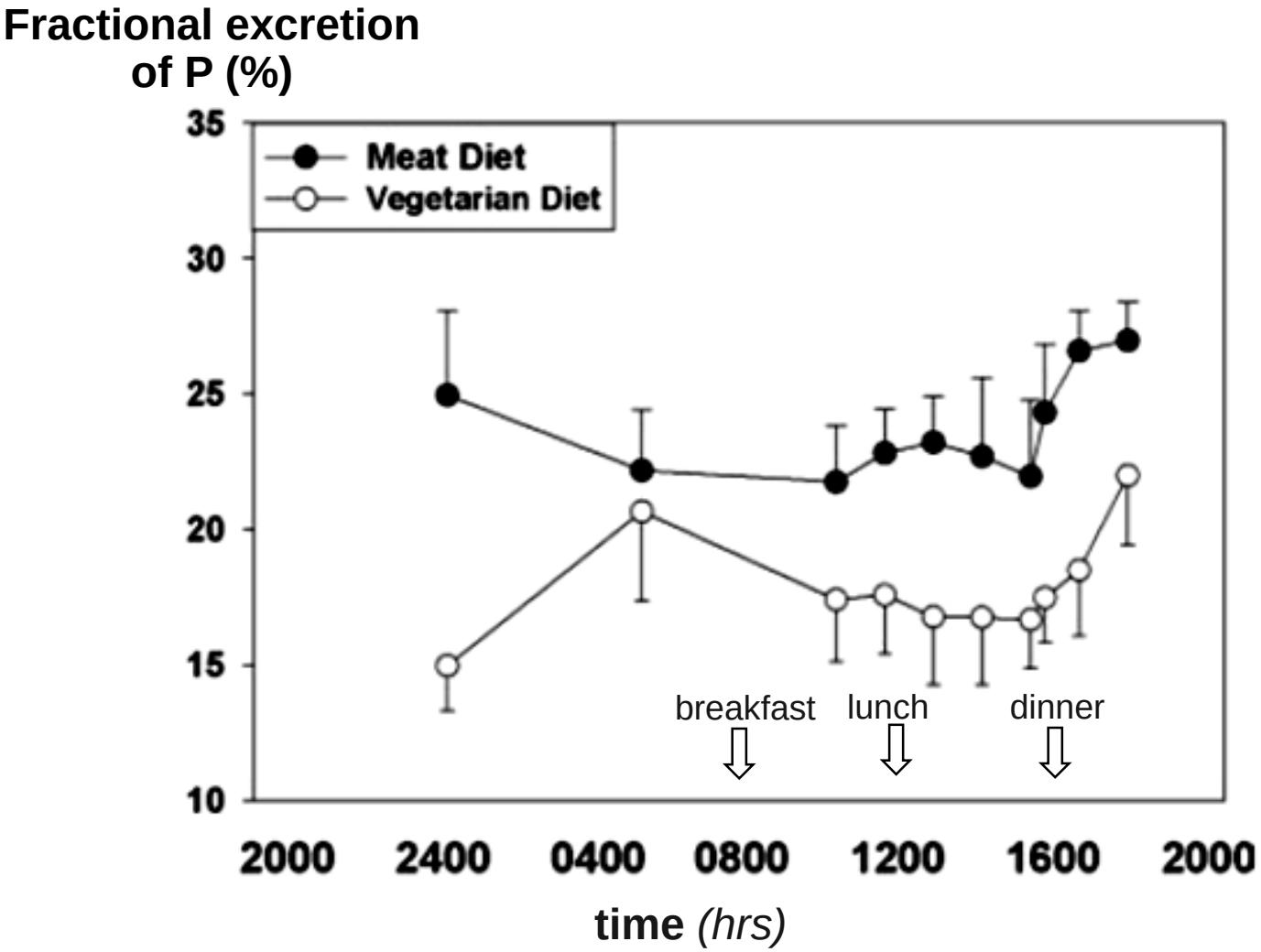
9 patients, eGFR32 ml/min; 7 days vegetarian diet, 7 days meat diet



Moe, CJASN (2011) 6:257

FE *(fractional excretion)* of P - diurnal variation

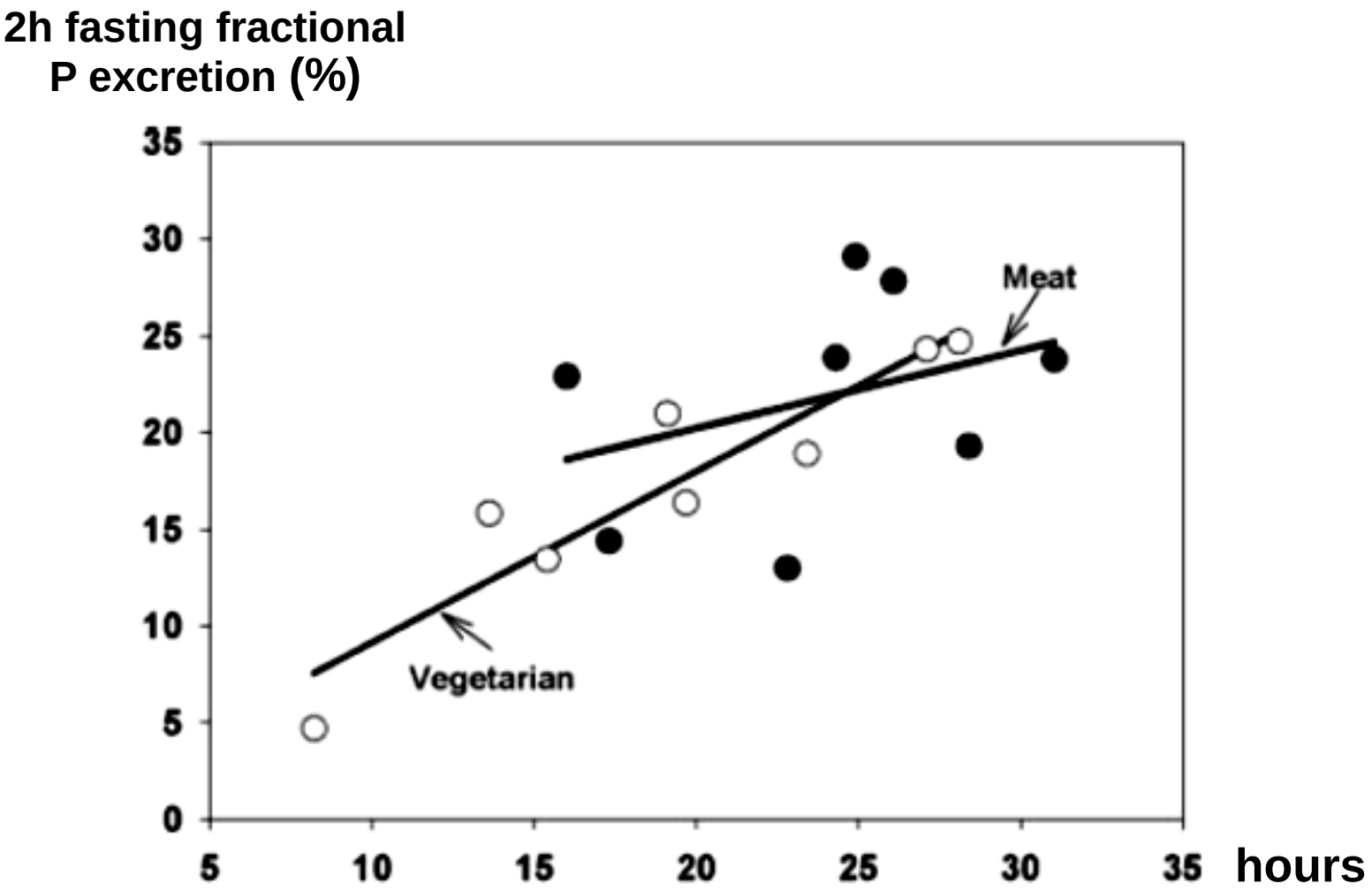
9 patients, eGFR32 ml/min; 7 days vegetarian diet, 7 days meat diet



Moe, CJASN (2011) 6:257

Diurnal variation of fractional P excretion

9 patients, eGFR32 ml/min; 7 days vegetarian diet ○, 7 days meat diet ●



Moe, CJASN (2011) 6:257

Conclusion :

“not all phosphate is created equal“

there are major differences between covalently bound and free phosphate

Phosphate additives in food – a health hazard

Elisabeth Palace
(Elisabethenbau)

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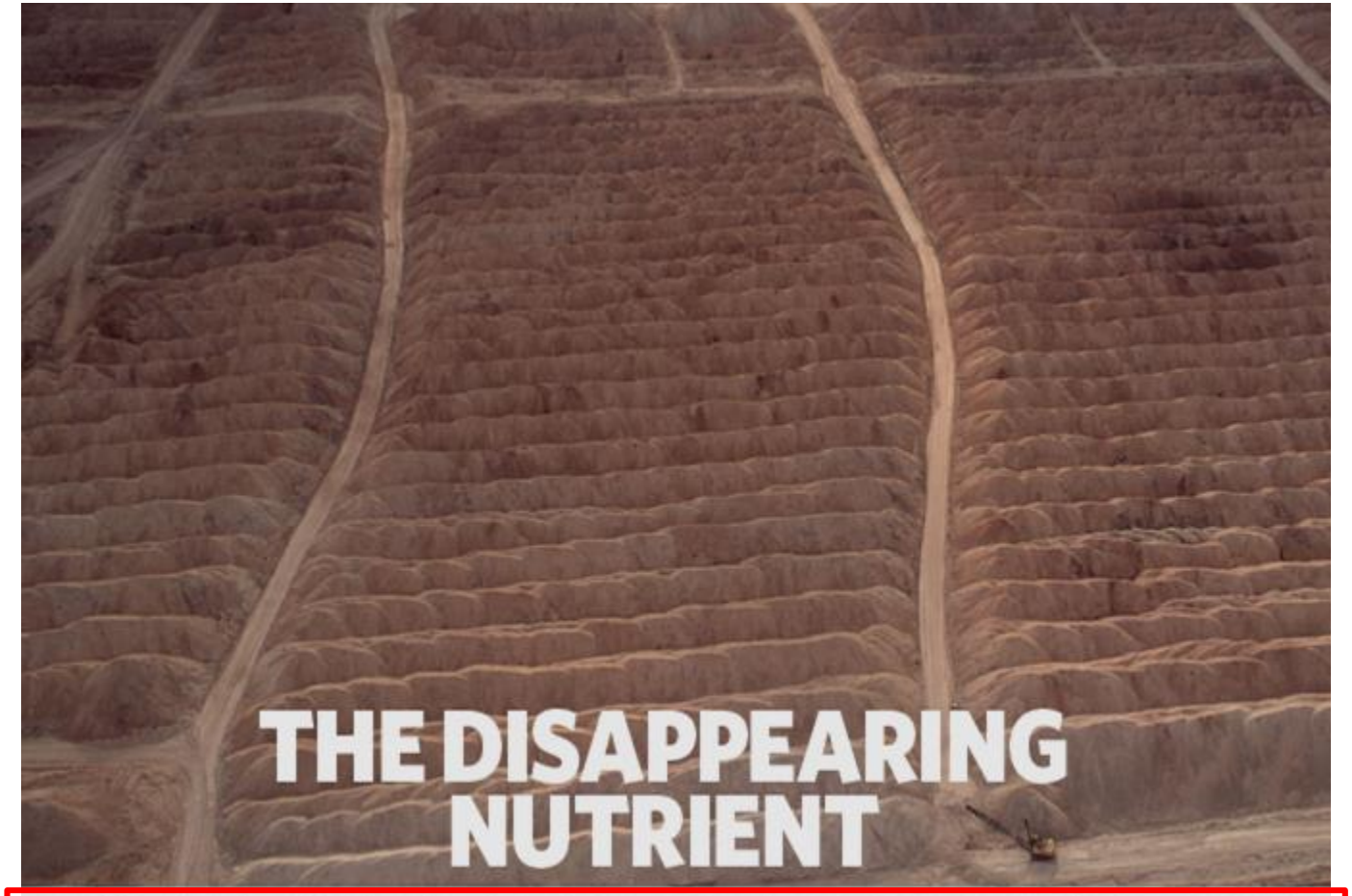
- **Not all phosphate in food is created equal**
- **Beyond patient education – we need appropriate labelling of P content in food items ?**



Gilbert N., Nature (2009) 461:716

Synthesis of P requires extreme conditions which are not available in the solar system
All phosphorous on earth is derived from sources outside of the solar system,
loss of P from available P stock (mainly Marocco, US, China) is not renewable,
thus potenitially constraining world food supplies

Phosphate additives in food – a health hazard

- Phosphate-
  what does zoology teach us ?

phosphate impacts on life span

- Phosphate in food items –
  do we know what we eat ?

no; phosphate additives are not disclosed

- Not all phosphate in food is
  created equal

P additives are <u>preferentially</u> absorbed

- Information for educated patients -
  labelling of P content in food items ?

P additives in food <u>must</u> be labeled

prof.e.ritz@t-online.de

Serum Phosphate :
predictor of chronic kidney disease and terminal renal failure

NHANES III

n=13 372 individuals age >18 years

mean age 44.3 years; 52 % women

observation 9.1 years

ESRD= start of dialysis

Serum Pi (mg/dl)

< 4 mg/dl	*>4 mg/dl*
1.0	2.41 *(95%CI 1.29-4.5)*

p< 0.007

O'Seaghdha, Nephrol.Dial.Transplant.(2011) 26:2885

Serum Phosphate Predictor of Future CKD

(chronic kidney disease)

Framingham Heart Study

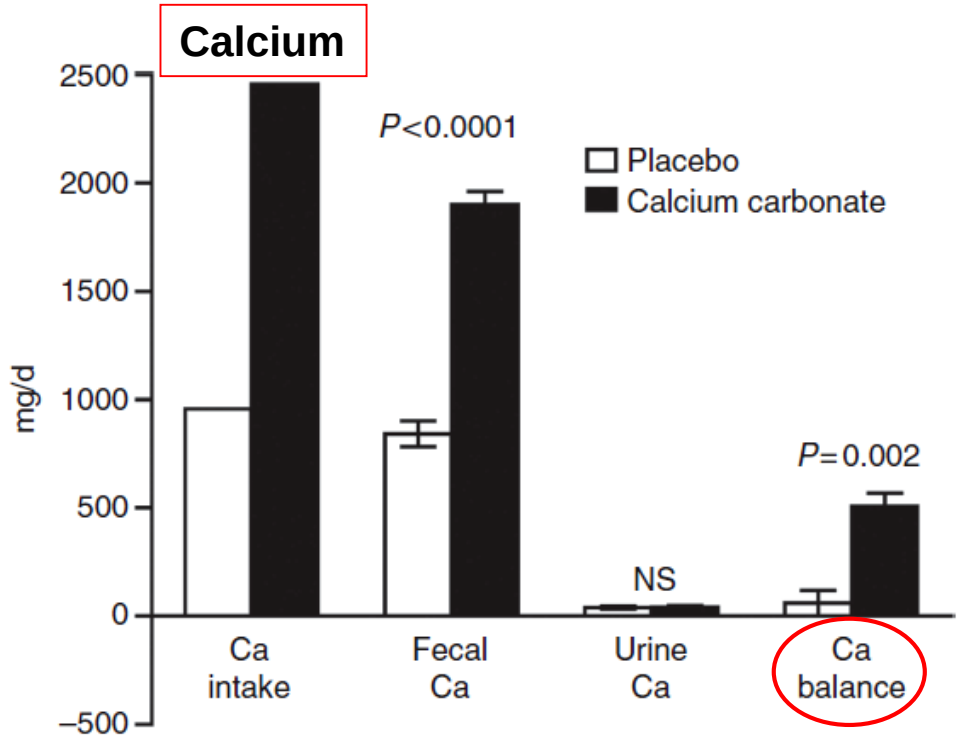
2269 participiants without CKD at start of study, 25.1 years follow-up

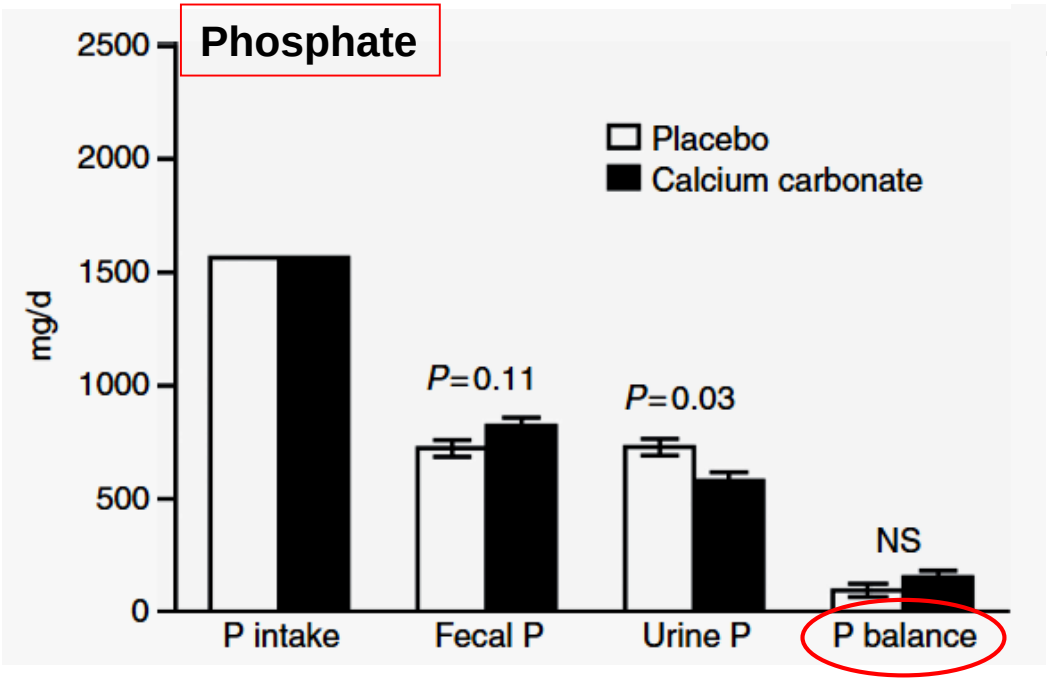
Serum P_i (mg/dl) at start and odds ratio of onset of CKD

	< 2.5	*2.5-3.49*	*3.5-3.99*	*>4*	*p<*
Odds ratio CKD	11.8	11.3	12.4	18.9	*0.0001*
Systol. BP *(mmHg)*	125	120	116	121	*0.05*
Smoking	24.4	33.4	39.7	55.4	*0.000*1
eGFR (ml/min/1.73m^2)	108	105	107	134	0.0001

Normal range : 2.7-4.5 mg/dl [0.87-1.45 mmol/L]

O'Seaghdha, Nephrol.Dial.Transplant.(2011) 26:2885





In CKD stage 3 or 4 oral calcium carbonate *(1500 mg/day)*

 # positive calcium balance

 # but no effect on P balance

Hill, Kidn.Internat.(2013) 83:959

Erstaunliches Beispiel einer Langzeitwirkung ??

Selbst S-Phosphat-Konzentration des Spenders beeinflusst Transplantationsergebnis beim Empfänger

(Lebendspender Nieren-Transplantation)

Höhere **Serumphosphat**-Konzentration des **Spenders** korreliert zu:

höherem Serumkreatinin des Empfängers

slope 0.087 *(CI:0.004-0.169); p=0.041* vergesellschaftet mit

niedrigerer eGFR des Empfängers

slope -4,32; *(CI -8.17- -0.48);p=0.028*

unabhängige Korrelation zu :

akute Transplantatrejektion *(Biopsie gesichert) und*

verzögerte Funktionsaufnahme nach Transplantation

Chang, CJASN (2011) 6:1179

Lebenserwartung

Maverick study

(Kaiser Permanente)

36,679 Patienten chronic kidney disease (CKD 3-5)

Serum – P korreliert zu :

- ***Gesamtmortalität***
- ***(Hospitalisierung wegen CV Ereignisse)***
- ***(akuter Herzinsuffizienz)***

Serum-P		**Gesamtmortalität**
4.5-4.9	*rel.Risiko*	**1.29** *(1.15-1.45)*
5.0-5.4		**1.71** *(1.46-2.0)*
> 5.5		**2.72** *(2.23-3.33)*

Gesamtmortalität progredient höher bei höherer Serum-Phosphat-Konzentration

S-Phosphate –

independent predictor of : overall mortality/ CV mortality/ atherosclerosis

 # even in patients without CKD

 # even for S-Pi values within the "normal" range

 # CARE study *(Pravastatin after MI)*

eGFR>60ml/min/1.73m²

per 1 mg/dl higher S-Pi → ***HR overall mortality 1.22*** *and* ***MI*** *1.22*

Tonelli, Circulation (2005) 112:2627

 # VA study *(Veterans with CKD, observational study)*

per 1 mg/dl higher S-Pi → ***HR overall mortality 1.2***

Kestenbaum, J.Am.Soc.Nephrol. (2005) 16:520

 # Framingham offspring study *(eGFR>60ml/min/1.73m² ,16 years)*

per 1 mg/dl higher S-Pi → ***HR 1.31*** *for* ***incident CVD event***

Dhingra, Arch.Int.Med. (2007) 167:879

 # ARIC study *(13,340 patients without CKD or cardiac disease)*

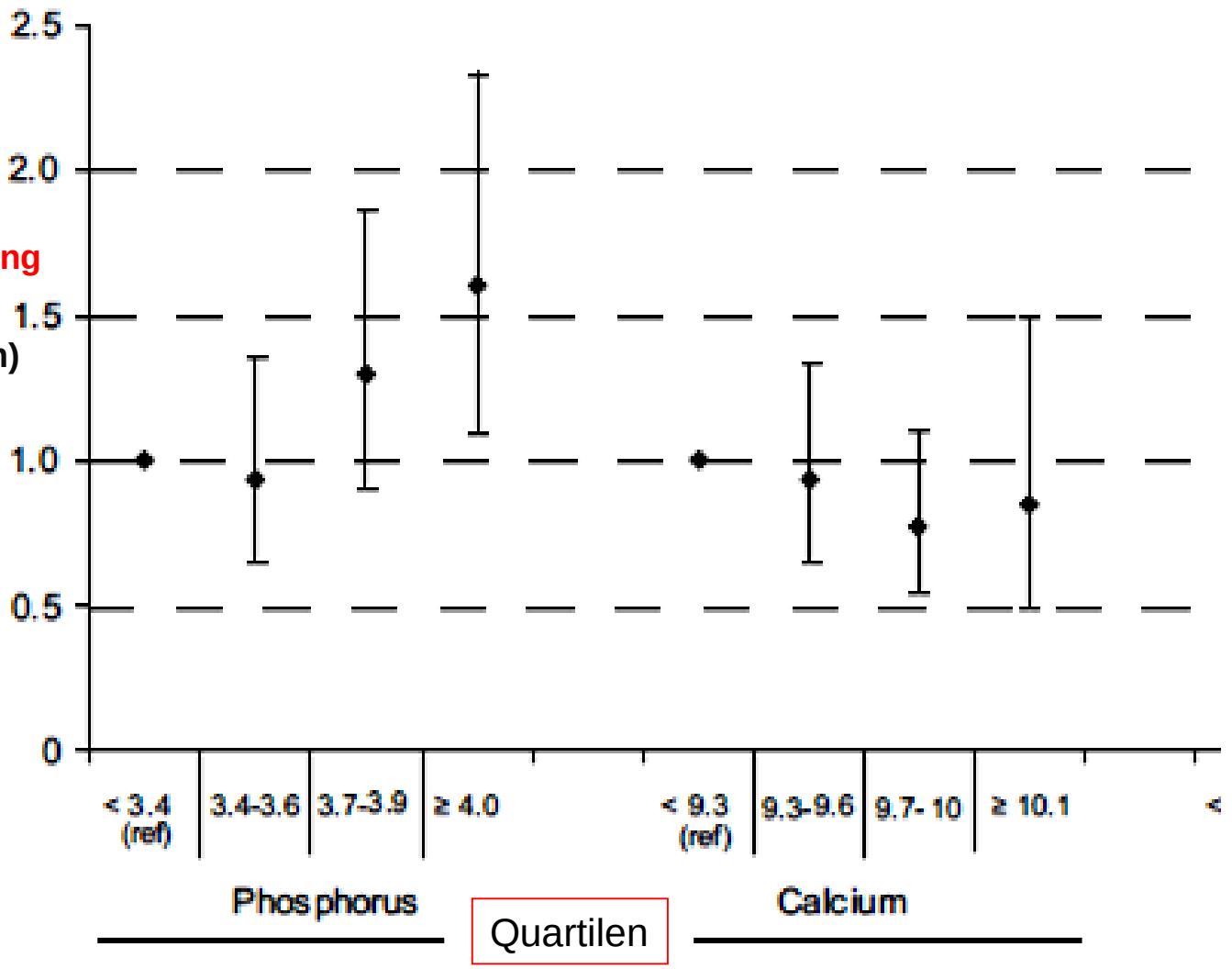
carotis intima media thickness *: higher in progressively higher S-Pi quintiles (even at GFR >90 ml/Min/1.73m²)*

Onufrak, Atherosclerosis. (2008) 199:424

Ausgangswert von S-P (aber nicht von S-Ca) korrelierte 15 Jahre später zu neu aufgetretenem Koronarkalk *(EB scan)*

(3015 gesunde junge Männer in der CARDIA Studie)

Multivariate Assoziation :
Koronararterien - Verkalkung
und
S-Phosphat (und S-Kalzium)
Quartilen



Foley,J.Am.Soc.Nephrol.(2009) 20:397