



Fosfaat en additieven

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Disclosures

- **Pharmaceutical Industries**

- Lecture fees, scientific support and advisor for: Amgen, VFMCRP, Shire, Medice, Bayer, Kissei; all companies involved in marketing or developing phosphate lowering drugs.
- Scientific support from: AbbVie and FMC.
- Advisory board of: Otsuka, Astra-Zeneca, Medice, Cablon Medical.

- **Member of**

- ERA-EDTA working group on CKD-MBD
- KDIGO committee on CKD-MBD.



VUMC and AMC merged: Amsterdam UMC



Amsterdam Cardiovascular Sciences



How does diet affect kidney outcomes?

Systematic review & meta-analysis

 18 cohort studies  630,108 adults

 Median follow up 10.4 years

 Low risk of bias in included studies

Evidence certainty

 CKD **Moderate**

 eGFR decline rate **Low**

 Incident albuminuria **Low**

Healthy dietary patterns

Encouraged higher intake of

 Fruits and vegetables

 Legumes

 Nuts

 Whole grains

 Fish

 Low-fat dairy

Encouraged lower intake of

 Red meat

 Sodium

 Processed meat

 Sugar-sweetened beverages

A healthy dietary pattern



was associated with
a lower incidence of CKD
(OR 0.71, 0.60 – 0.82)



was associated with
a lower incidence of albuminuria
(OR 0.77, 0.59-0.99)



was not associated with
rate of eGFR decline
(OR 0.70, 0.49 – 1.01)

Conclusions A healthy dietary pattern may prevent chronic kidney disease and albuminuria.

Katrina E. Bach, Jaimon T. Kelly, Suetonia C. Palmer, et al. **Healthy dietary patterns and incidence of chronic kidney disease: A meta-analysis of cohort studies.** CJASN doi: <https://doi.org/10.2215/CJN.00530119>. Visual Abstract by Michelle Lim, MBChB



Hoe beïnvloedt dieet (nier-)gezondheid?

- Minder zout?
- Minder calorieën?
- Minder fosfaat?
- Minder saturated fat?
- Een generic effect (DASH diet, vegetarisch, STOP hypertension, mediterraan)
- Het is een proxy van healthy lifestyle



Evidence based medicine?





Fosfaat is ook een noodzakelijke nutrient





Fosfaat: hoeveel nemen we in?

- Wat nemen we in, en hoeveel krijgen we binnen?
- NB:
 - Aanbevolen dagelijkse hoeveelheid: 600-700 mg (20-22 mmol in 24 uurs urine)
 - 50% van al het fosfaat komt uit additieven*
 - ADI (Acceptable Daily intake): 3000-4000 mg / dag 105-130 mmol / dag (EFSA report 2019)



ADI?

- ADI is defined as “an estimate of the amount of a substance in food or drinking water that can be consumed over a lifetime without presenting an appreciable risk to health”.

SCIENTIFIC OPINION



ADOPTED: 27 March 2019

doi: 10.2903/j.efsa.2019.5674

Re-evaluation of phosphoric acid–phosphates – di-, tri- and polyphosphates (E 338–341, E 343, E 450–452) as food additives and the safety of proposed extension of use





ADI: 40 mg/kg/day

- Gebaseerd op één “chronische” expositie studie uit 19?? (Hodge) in ratten
- Er zijn geen chronische prospective humane expositie studies
- EFSA verwijst naar nog een andere studie:

Hodge HC, 1959. Chronic Oral Toxicity Studies in Rats of Sodium Tripolyphosphate. The University of Rochester School of Medicine and Dentistry, New York.

Hodge HC, 1960. Unpublished report. Chronic oral Toxicity Studies in Rats of Sodium Hexametaphosphate. Department of Pharmacology, University of Rochester School of Medicine and Dentistry, Rochester, New York.



NB

- In deze studie was het fosfaat uit voeding (dus niet het supplement) onbekend. Dit is achterhaald door “personal communication” met een andere onderzoeker, uit een ander experiment uit 2011...



SCIENTIFIC OPINION

ADOPTED: 27 March 2019

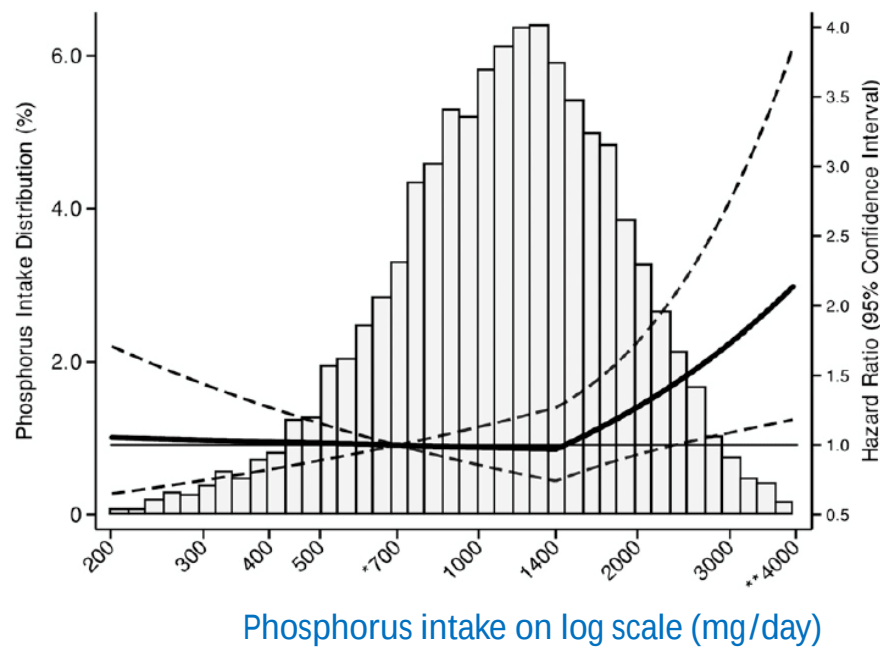
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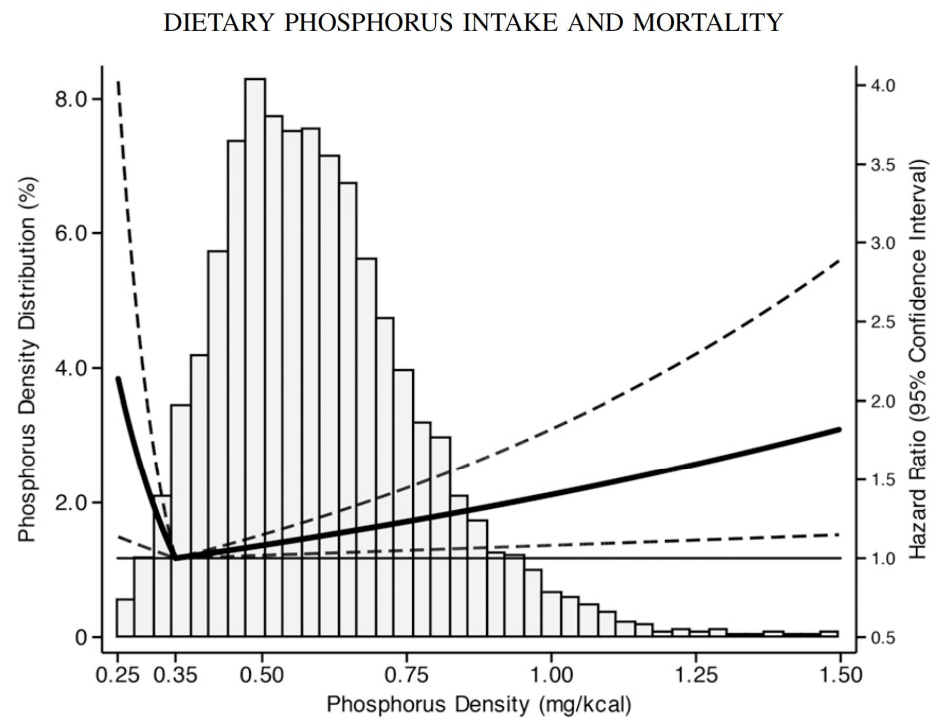


NHANES-III non-CKD, US population





Geïndexeerd naar calorie-intake

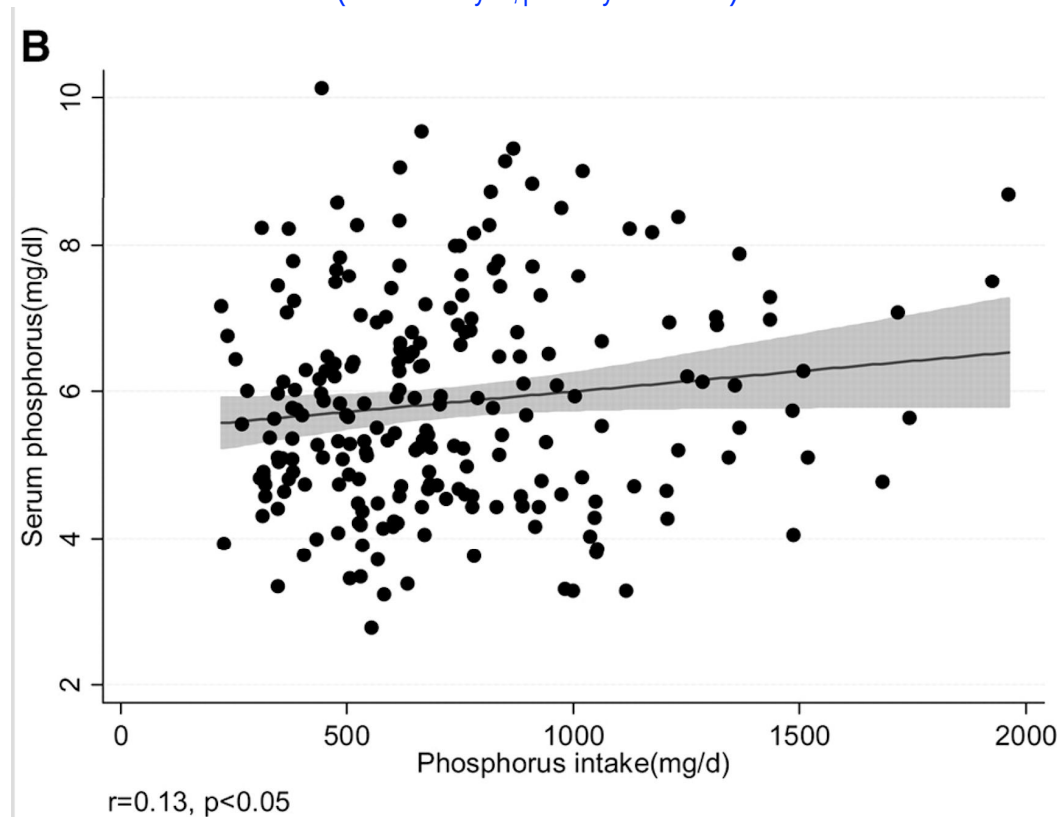


Chang A, et al. Am J Clin Nutr 2014;29:320-7



Fosfaat-inname en serum concentratie

(In hemodialyse, predialyse waarde)



Lastig....

Bewijs nodig voor :
1. P concentratie
2. P inname



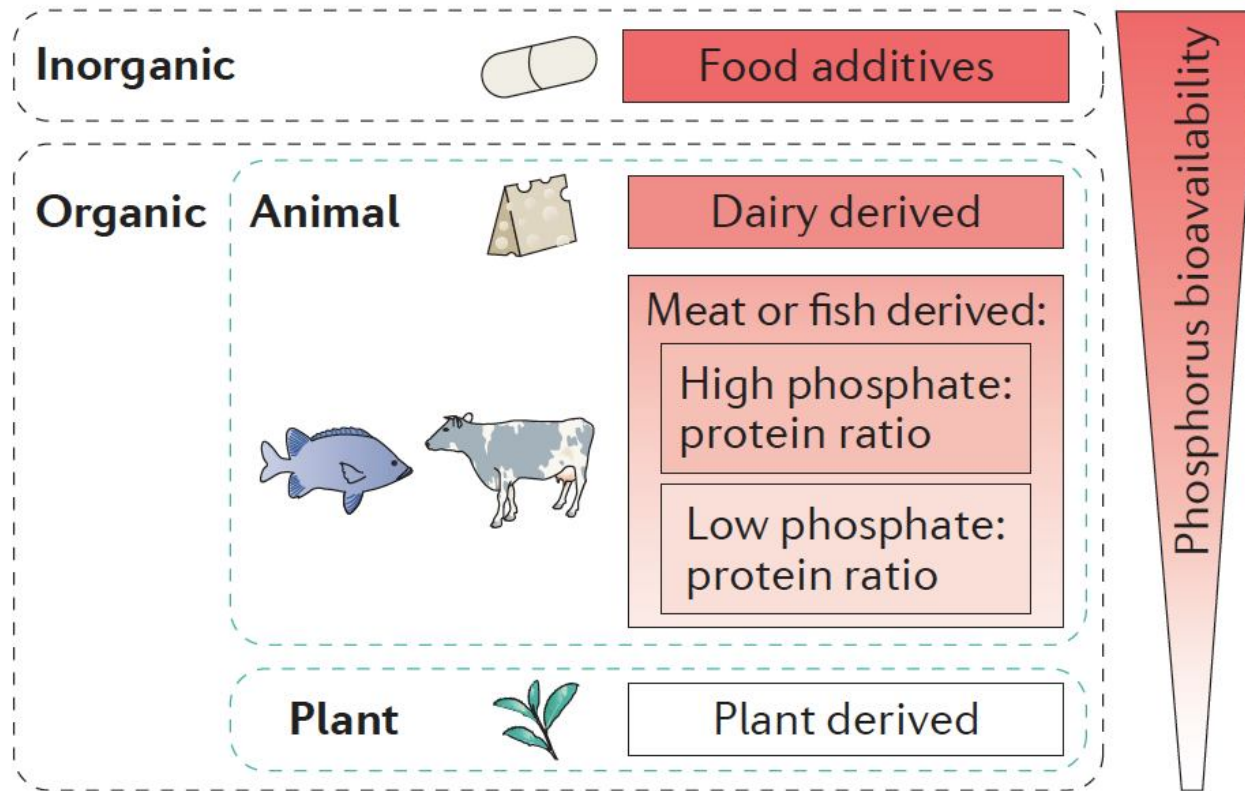
Fosfaat-inname stijgt

TABLE 4. Estimated phosphorus intakes from food¹

NHANES Years	Phosphorus Intake
	<i>mg/d</i>
Men	
2001–2002	1565 ± 24.7
2003–2004	1559 ± 22.4
2005–2006	1600 ± 24.9
2007–2008	1500 ± 26.1
2009–2010	1655 ± 18.7
10 y change	90 mg increase
Women	
2001–2002	1126 ± 18.2
2003–2004	1126 ± 17.0
2005–2006	1148 ± 22.0
2007–2008	1123 ± 22.5
2009–2010	1190 ± 11.5
10 y change	64 mg increase

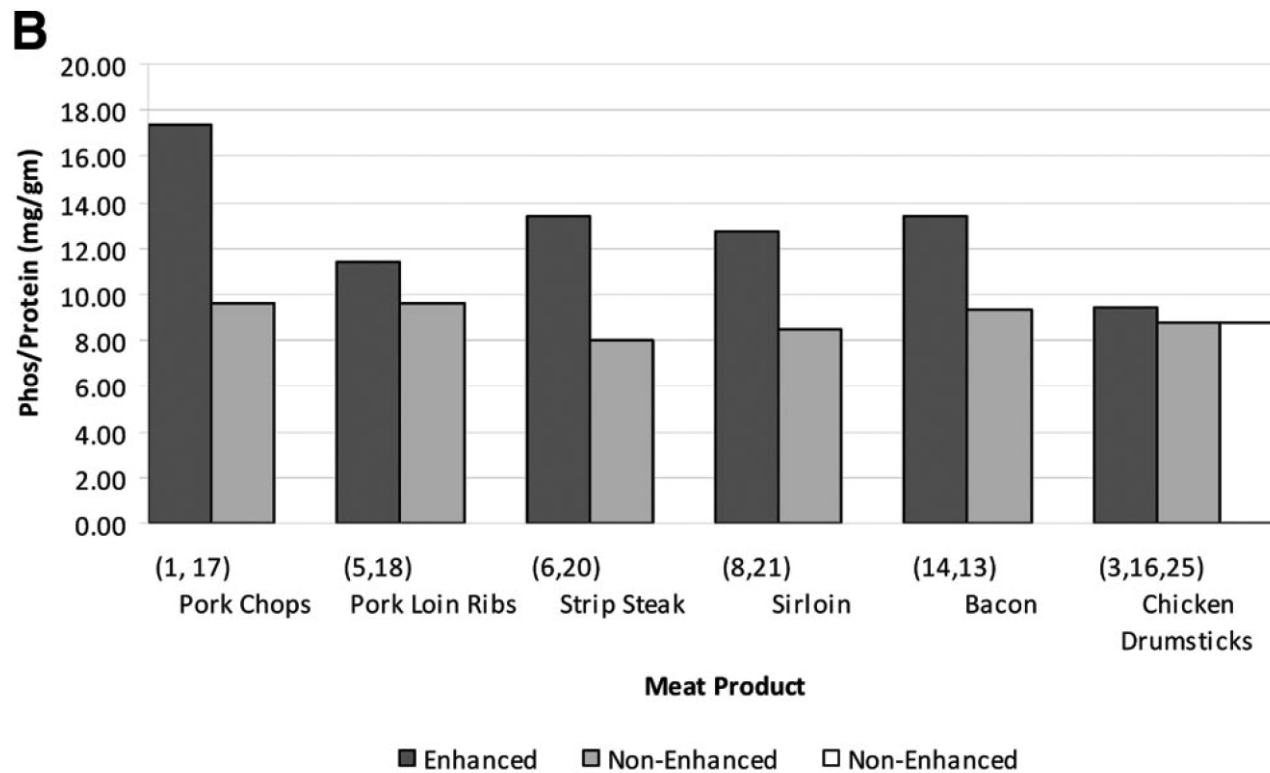


De bron van fosfaat doet er ook nog toe





Bewerkt vlees (zoals we het kopen) vs “direct” van varken of koe





Fosfaat/eiwit ratio

Table 1. Dietary P, protein, and potassium content of selected food items, ranked according to the P-to-protein ratio categories (64,65)

Parameter	Serving Amount	P (mg)	Protein (g)	K (g)	P-to-Protein Ratio (mg/g)	Comments ^a
P-to-protein ratio <5 mg						
egg white ^b	1 large	5	3.6	54	1.4	–
pork rinds	1 oz	24	17.4	36	1.4	521 mg Na
orange roughy fish	3 oz	87	19.2	154	4.5	–
P-to-protein ratio 5 to <10 mg/g						
lamb	3 oz	~170	~27.0	~203	6.3	^c
milk, low fat (2%)	1 fl cup	229	8.1	366	28.3	–
pecans ^e	20 halves	79	2.6	116	30.4	–
half and half	1 tbsp	14	0.44	20	31.8	–
cashews ^e	1 oz	139	4.3	160	32.3	–
tahini	2 tbsp	220	5.1	124	43.1	–
sunflower seeds	3 tbsp	370	6.2	272	59.7	–
liquid nondairy creamer ^d	1 oz	19	0.3	0	63.3	–



Drankjes

Table 3. P content of selected beverages, mg

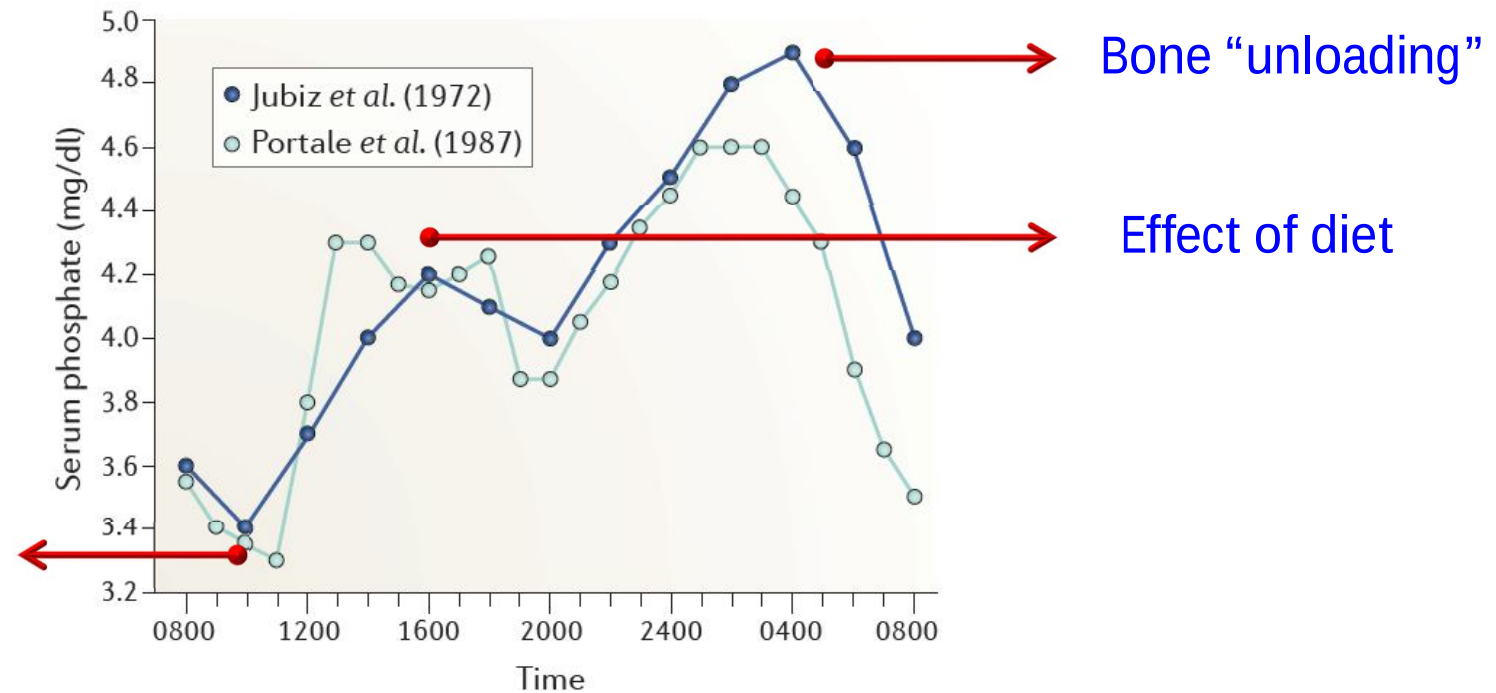
per 12-oz serving (based on 12-oz serving)

Brand Name	Specification/Flavors	P Content (mg)
Contain <10 mg of P per 12-oz serving ^a		
7 Up	All flavors	<10
Aquafina Essentials	(excluding tangerine pineapple)	<10
Barq's Root Beer	All flavors	<10
Dasani Water	All flavors	<10
Fanta	Most flavors	<10
Pepsi	Most colas (except Pepsi Natural)	54
Diet Pepsi	All flavors	41 to 68
Propel Water	All flavors	89
Tropicana Fruit Drinks	All flavors	53 to 140



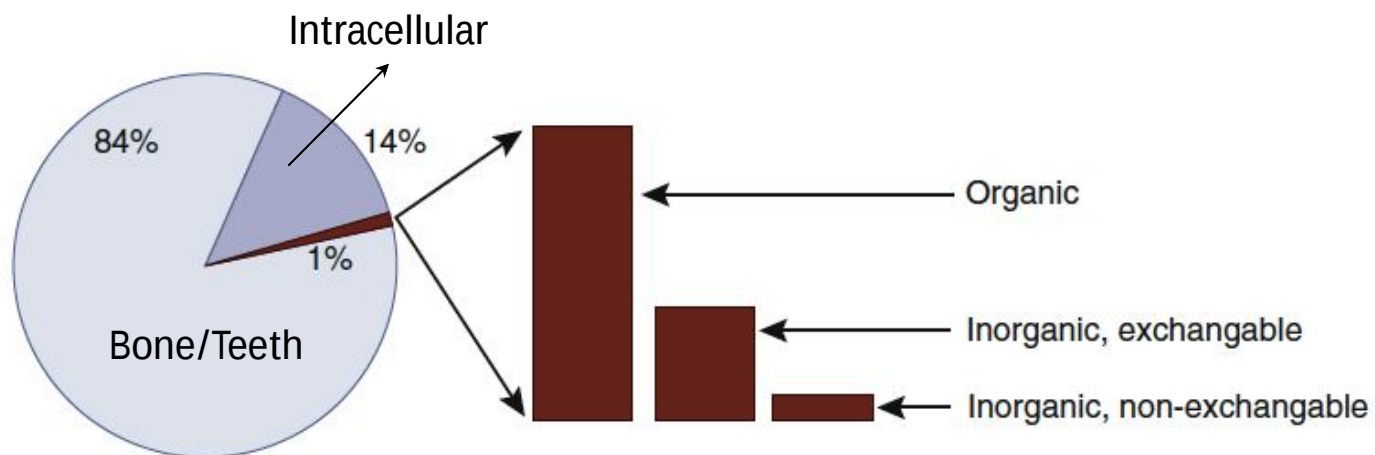
Circadian rhythm of phosphate

Effect of
phosphate
“pool”?





Phosphate pool?

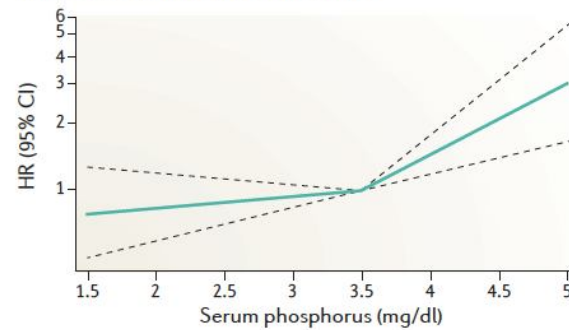




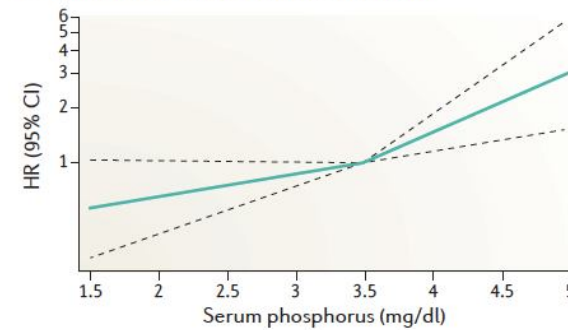
Importance of phosphate pool

NHANES
N=12984

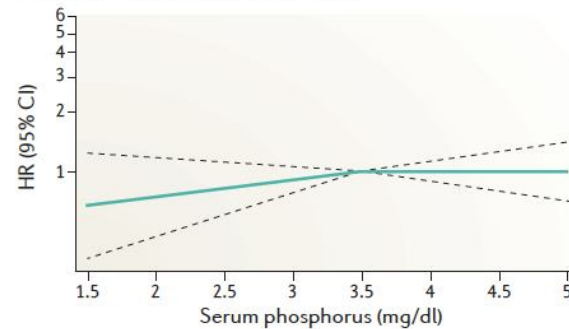
a All-cause mortality (fasted ≥ 12 h)



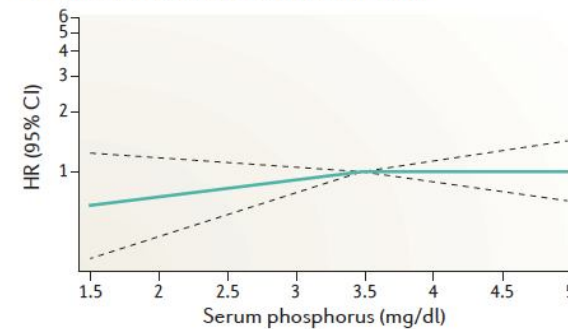
b Cardiovascular mortality (fasted ≥ 12 h)



c All-cause mortality (fasted < 12 h)



d Cardiovascular mortality (fasted < 12 h)





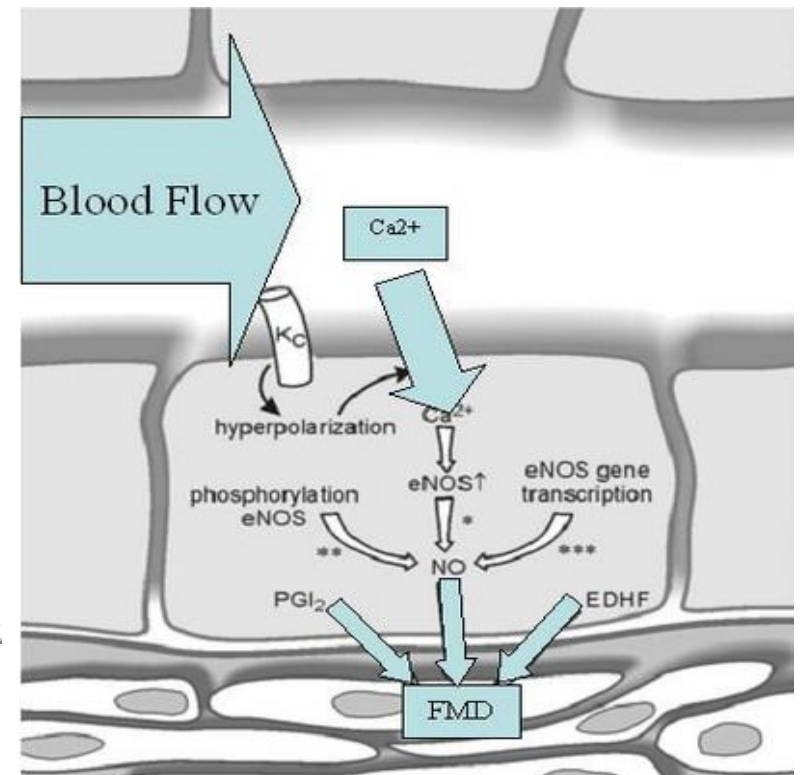
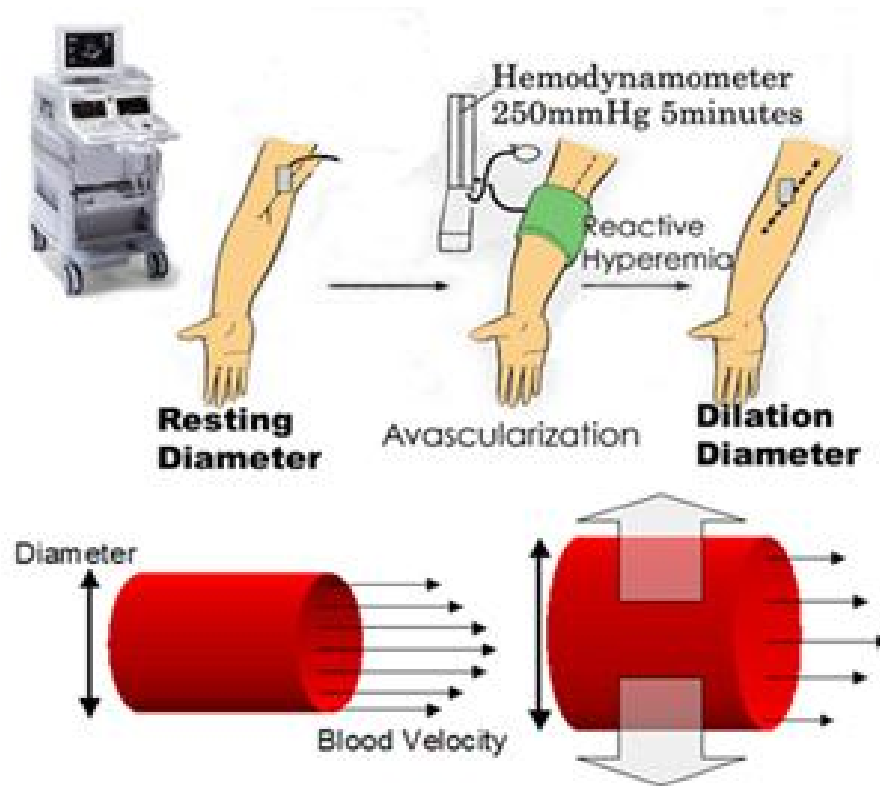
Importance of postprandial phosphate



McDonald's, New Orleans 2009



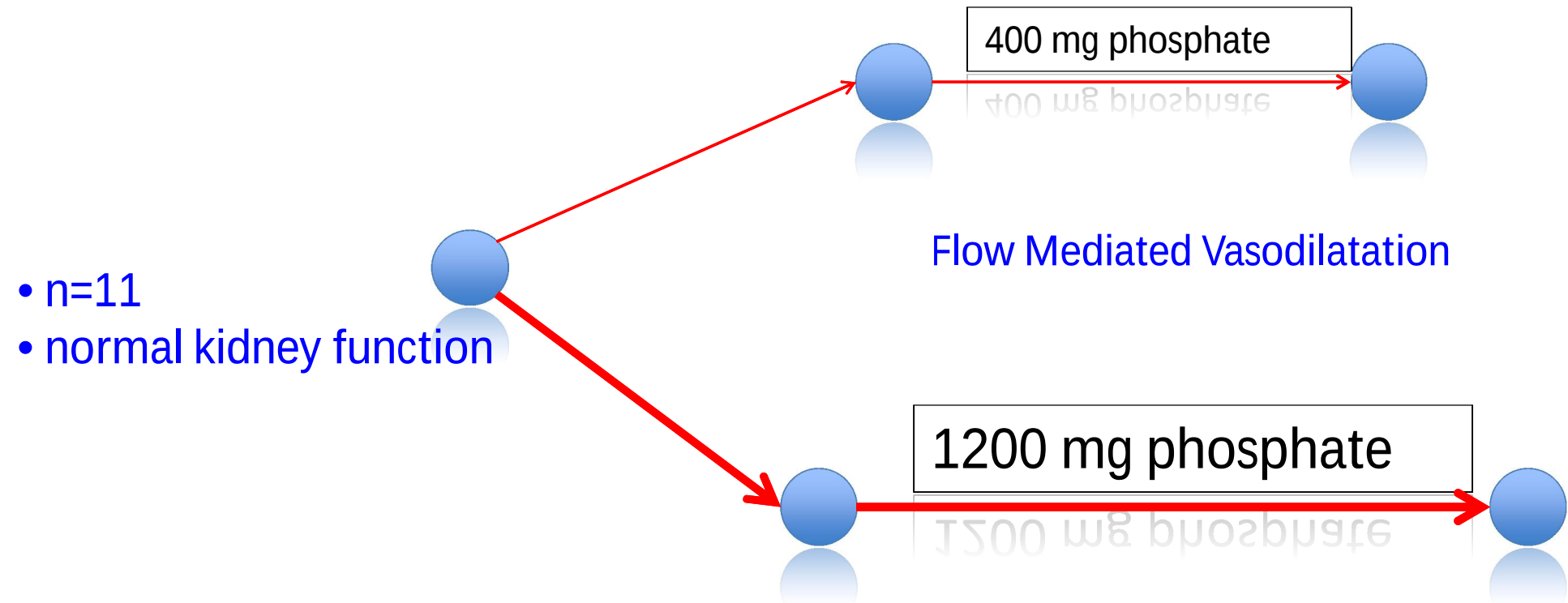
Flow mediated dilation (FMD)



Corretti MC, et al. J Am Coll Cardiol 2002;39:257–65;
Moens AL, et al. Chest 2005;127:2254–63



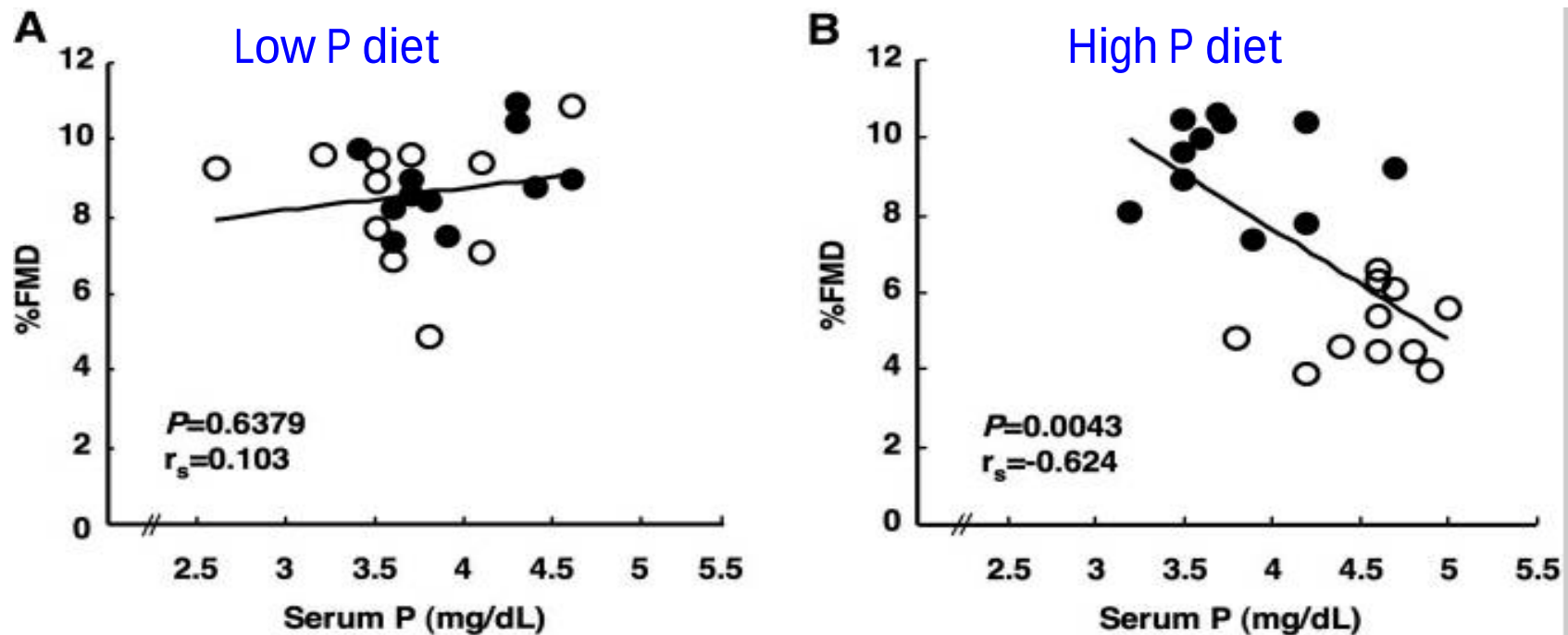
Phosphate enriched diet in healthy subjects



Shuto E, et al. J Am Soc Nephrol 2009;20:1504–12



High P diet and FMD (acute effects)

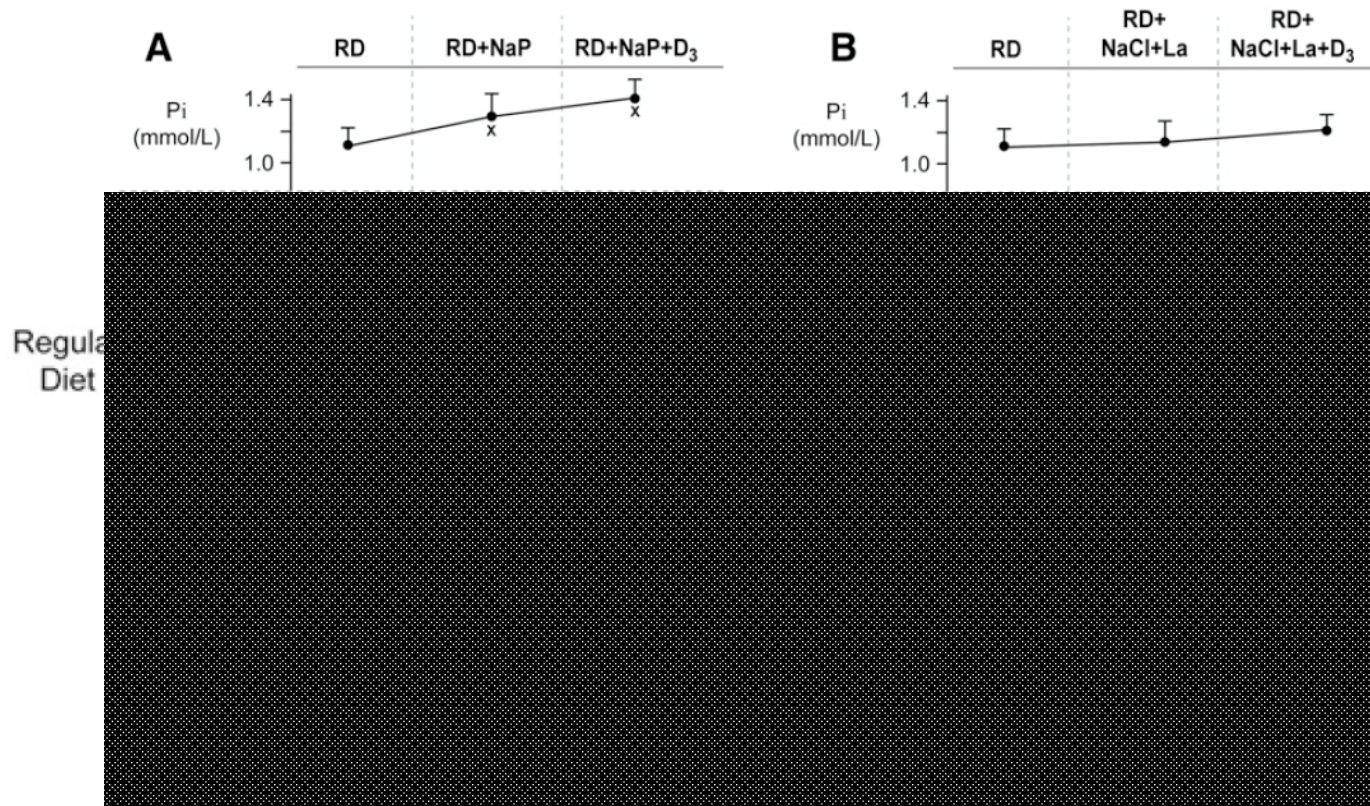


● Before meal

○ 2 hours after meal

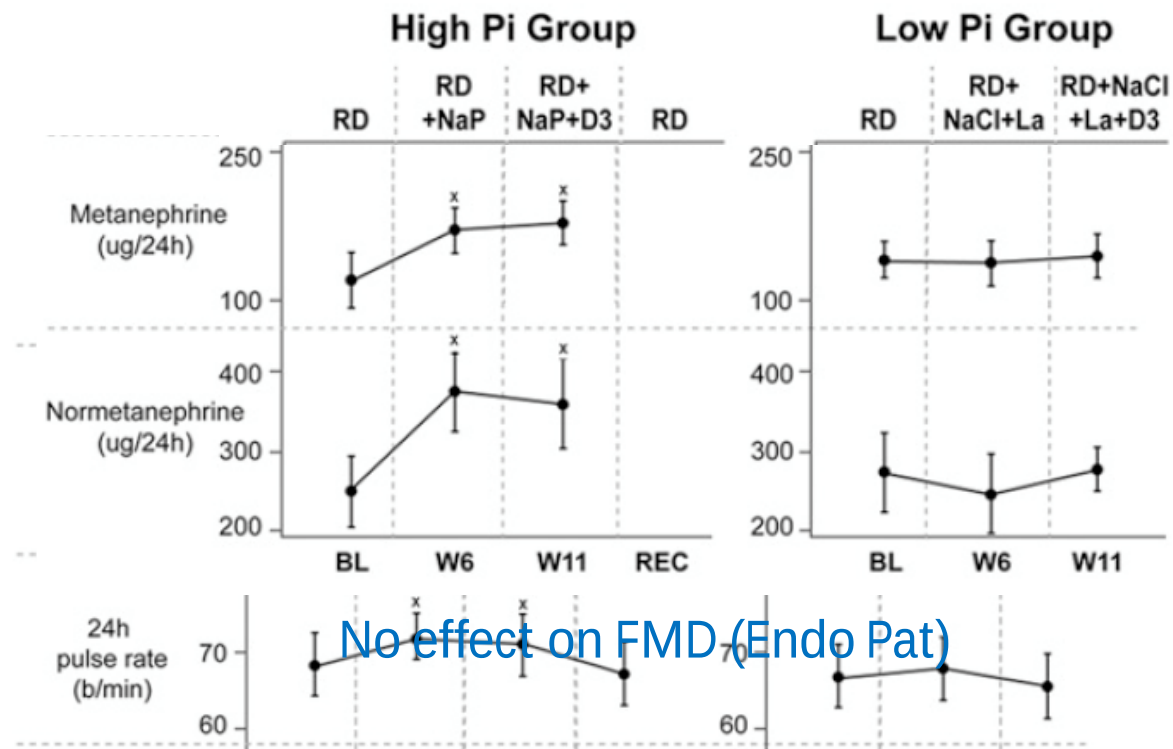


Phosphate intake and blood pressure





Phosphate intake and blood pressure





Dietary intervention

 ORIGINAL CONTRIBUTION

Effect of Food Additives on Hyperphosphatemia Among Patients With End-stage Renal Disease

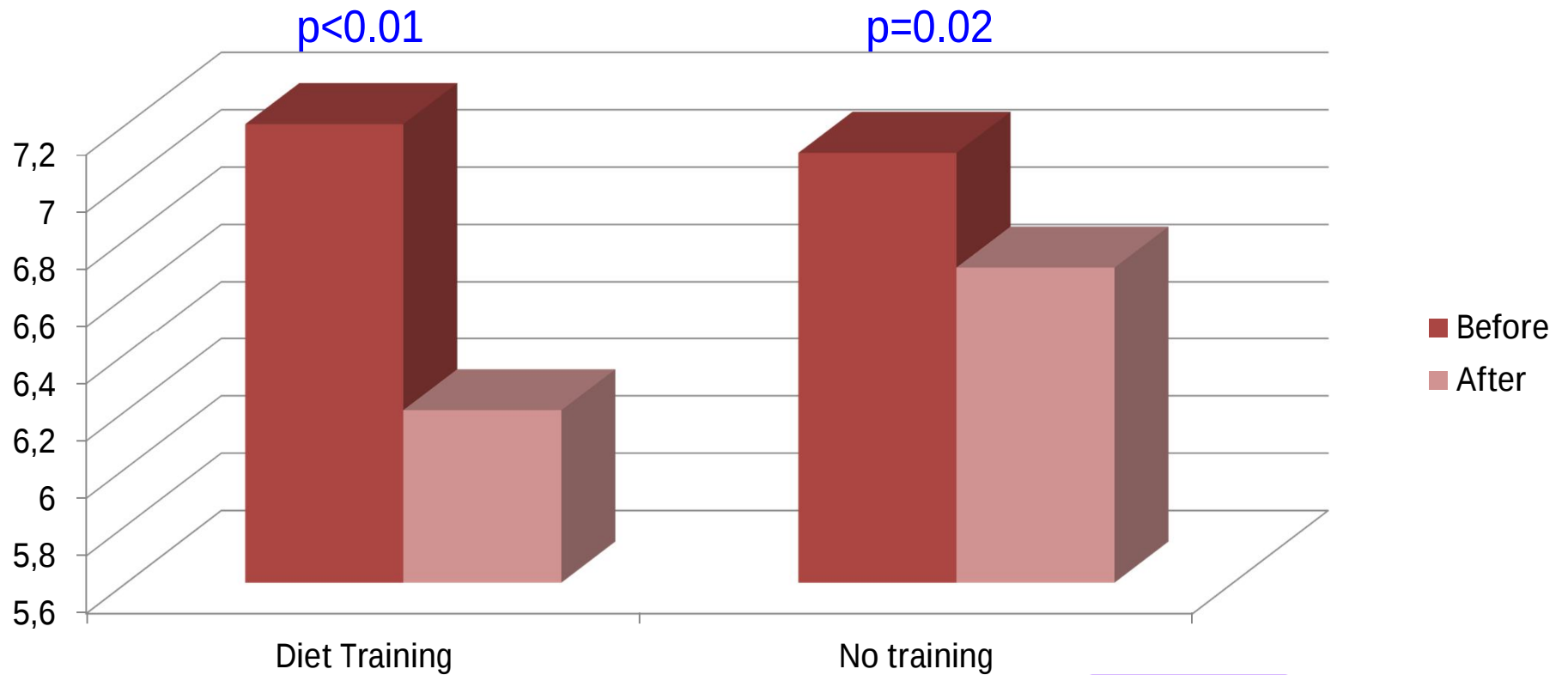
A Randomized Controlled Trial



Sullivan, JAMA 2009



Phosphate changes

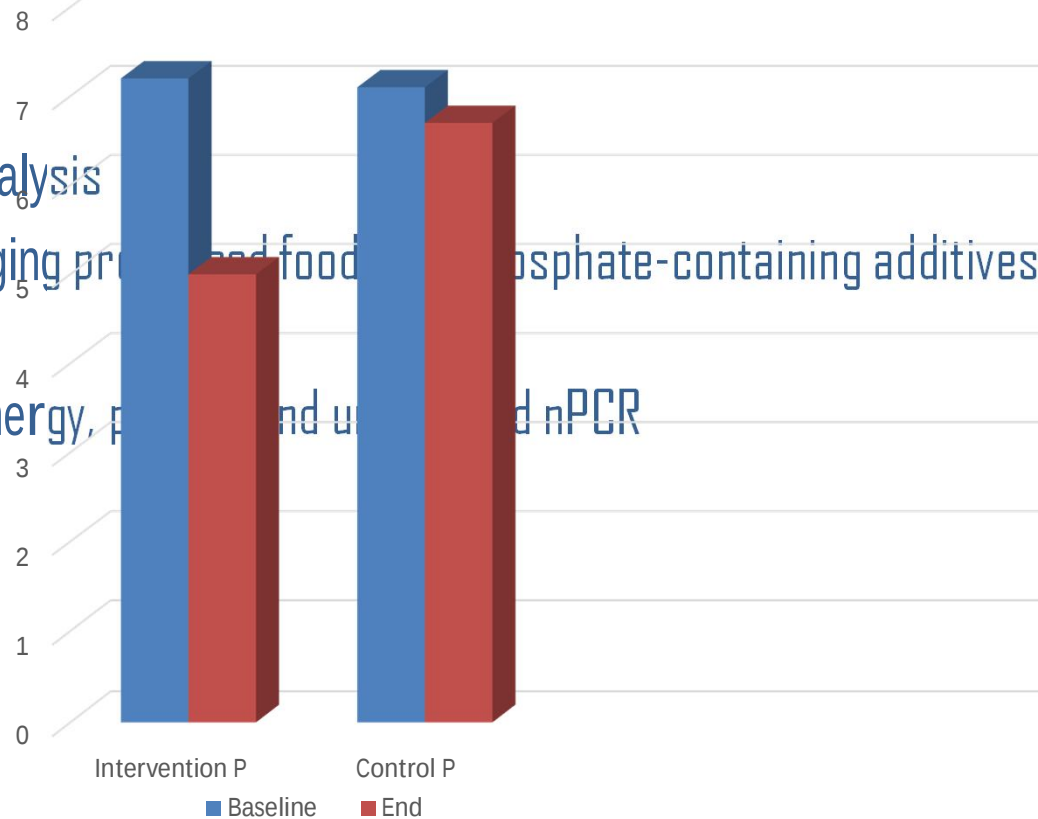


Sullivan, JAMA 2009



Randomised trial on dietary intervention

- 134 patients on hemodialysis
- Randomized to exchanging processed food for phosphate-containing additives or education only for 3 months
- Unchanged intake of energy, protein and urea index nPCR





Who should we "target"?

Patients or policymakers

Effect of 30% subsidy on



Validated simulation study among 82 million US Medicare or Medicaid participants:

- 2 – 3.3 million CVD events prevented
- 40 – 100 billion USD health care cost saving

ness of financial incentives for
t and health through Medicare
: A microsimulation study



Conclusie

- Hoge fosfaat-inname is iets anders dan hyperfosfatemie, maar waarschijnlijk ook een probleem
- Laten we ophouden met patiënten allemaal restricties op te leggen: zoutarm? Fosfaatarm? Geen rood vlees? Weinig drinken of veel drinken?
- Maar wel stimuleren gezond te eten (en te leven)
- Intussen moeten we wel werken aan beïnvloeding van overheden, voedingsmiddelenindustrie en de publieke opinie





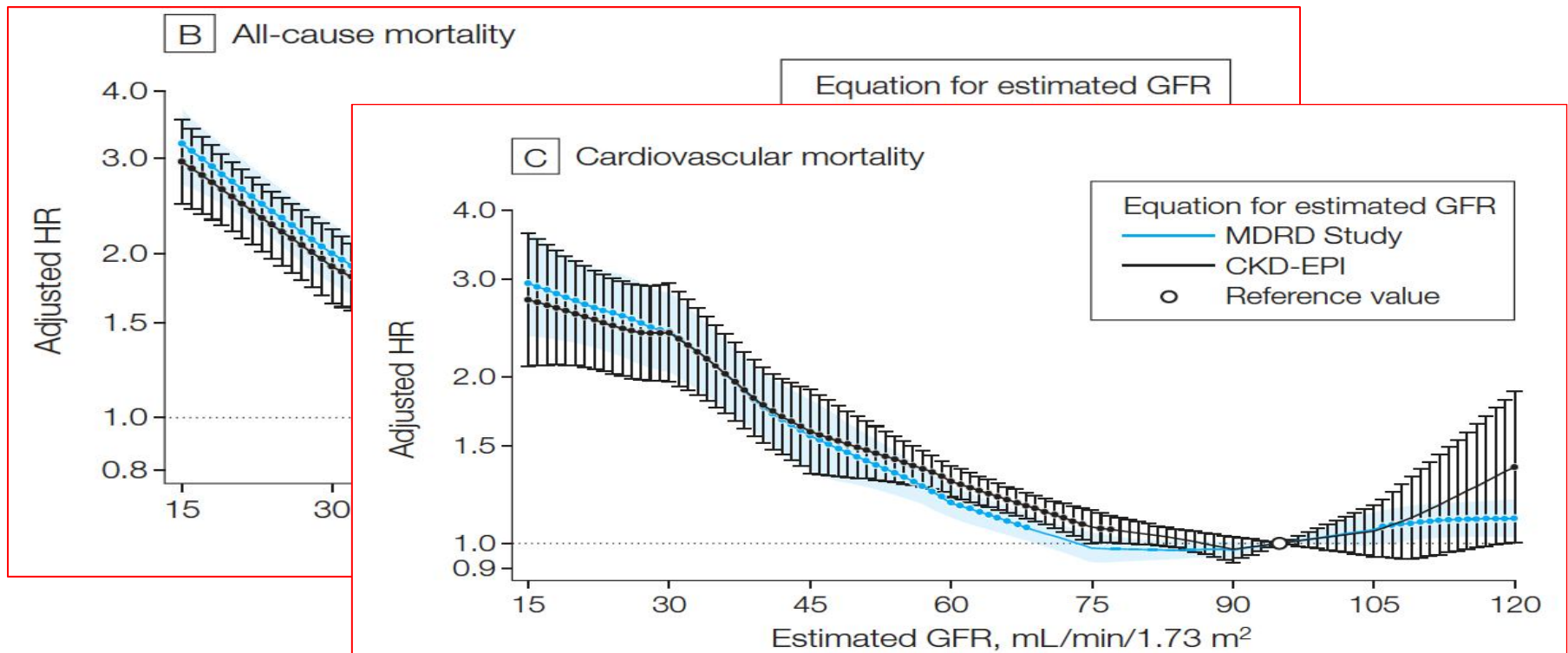


Conclusions

- Phosphate toxicity $\neq$ Hyperphosphatemia
- Hyperphosphatemia $\neq$ Phosphate toxicity
- Hence: Targeting phosphate toxicity encompasses more than treating hyperphosphatemia



Mortality in kidney disease





Risk factors for mortality

Traditional (Framingham)

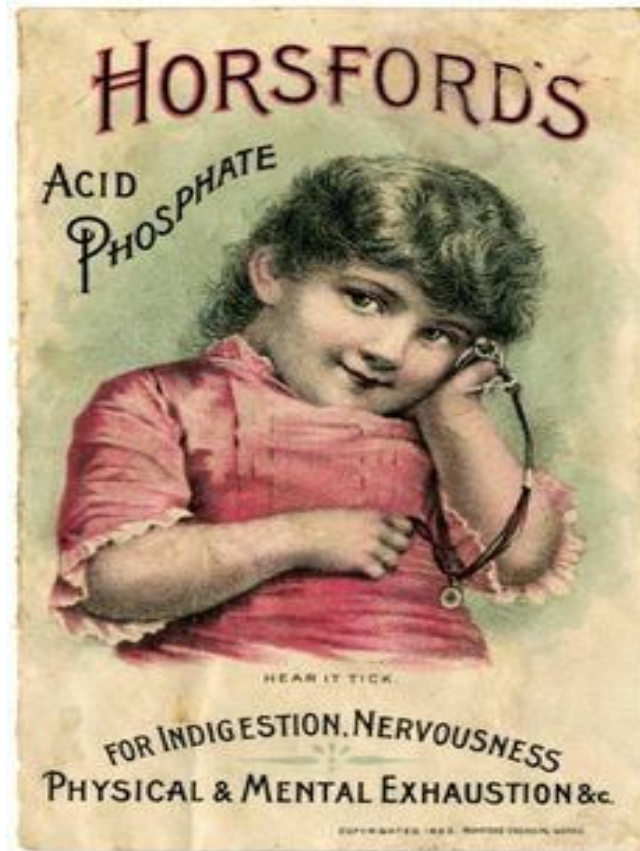
- Hypertension
- Diabetes
- Hypercholesterolaemia
- Smoking
- Obesity

CKD-related

- Proteinuria
- Volume/sodium overload
- Anaemia?
- Malnutrition
- Oxidative stress/inflammation
- **CKD-MBD**
- And several more...

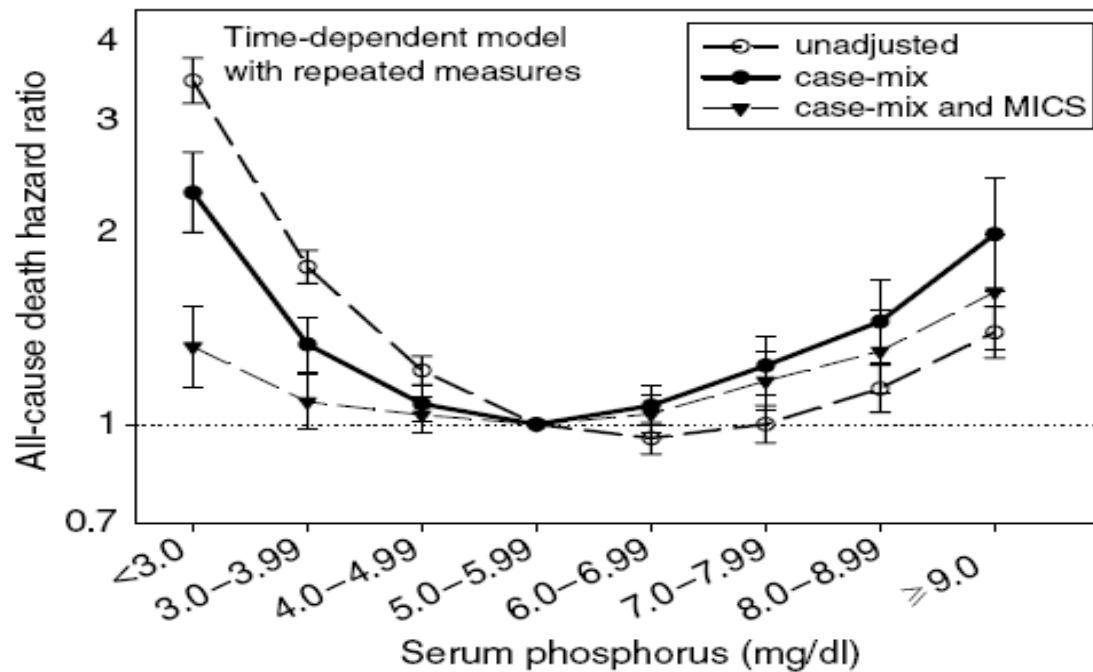


What is the rationale for targeting phosphate?





Phosphate and mortality risk





What are we measuring?



At what timepoint of day is phosphate highest?

1. Very early in the morning
2. After meals
3. End of the day



What percentage of body phosphate resides in extracellular compartment

1. 85%
2. 35%
3. 14%
4. 1%

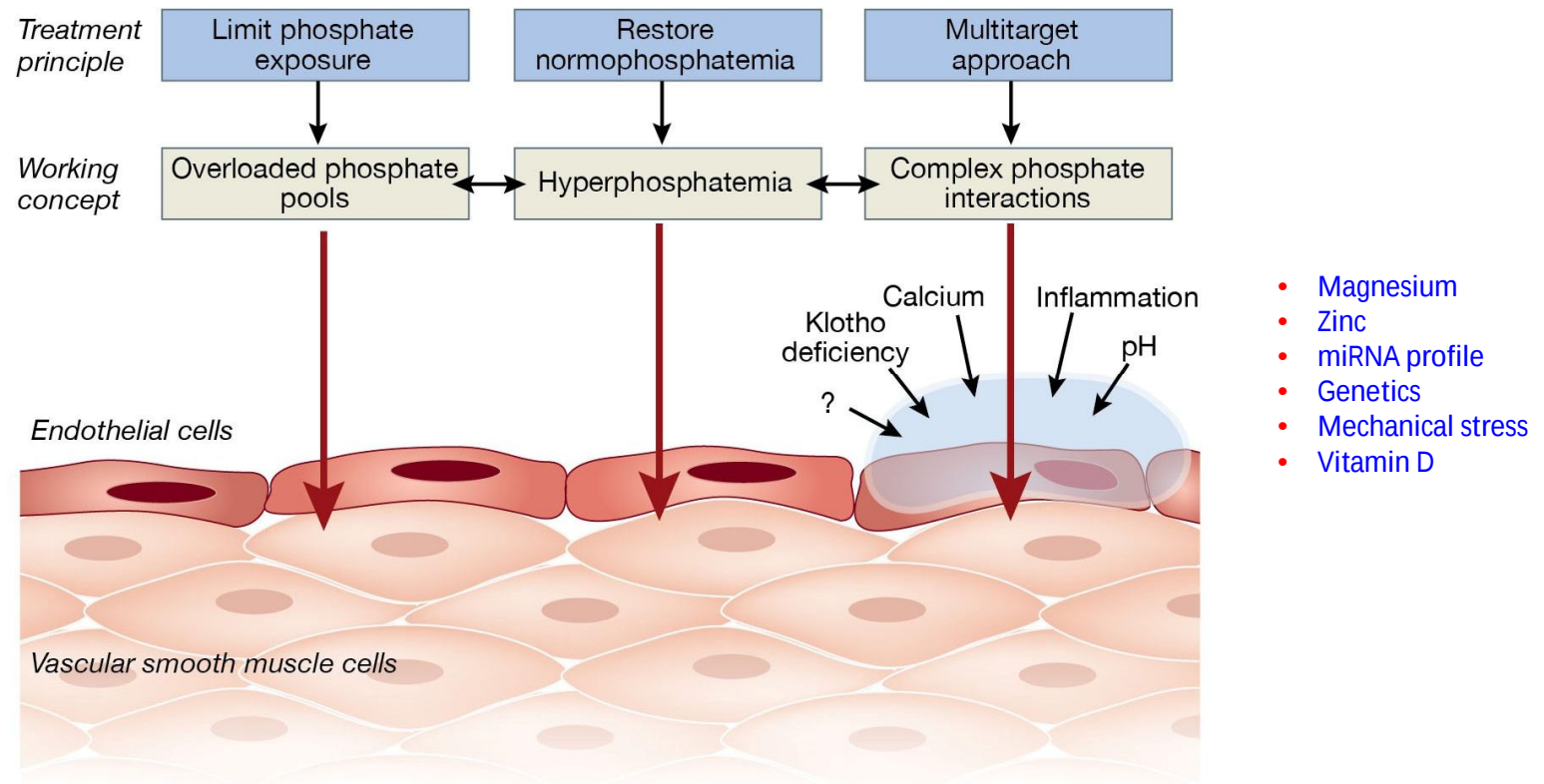


Other modifiers of phosphate toxicity

- Vascular inflammation
- Hypercalcemia, either transient/constant and local/systemic
- Mechanical stress
- Zinc deficiency
- More?



Conceptual models of phosphate toxicity





Conclusion: Treating phosphate toxicity may need to address

- Hyperphosphatemia
- Phosphate load
- Correcting acidemia
- Restoring klotho deficiency (once we know how)
- Optimizing magnesium concentration (higher than “normal”)
- Supplementing vitamin K, especially when using P-binders
- Target (secondary) calciprotein formation
- Etc.....



Einde

