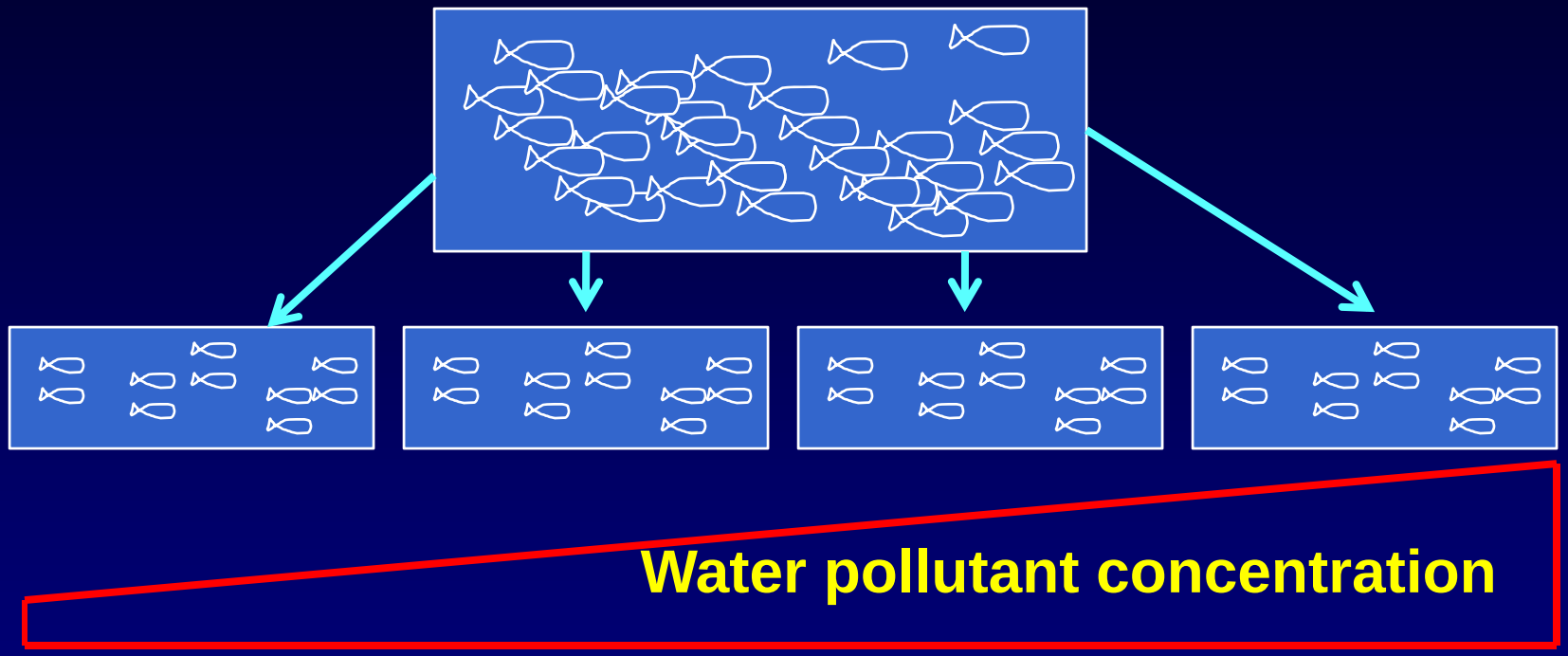
Different types of claims—equal or different standard of evidence?

- *Health claims sometimes include nutrition content and structure function statements. How does the required evidence relate to the type of claim being considered?*

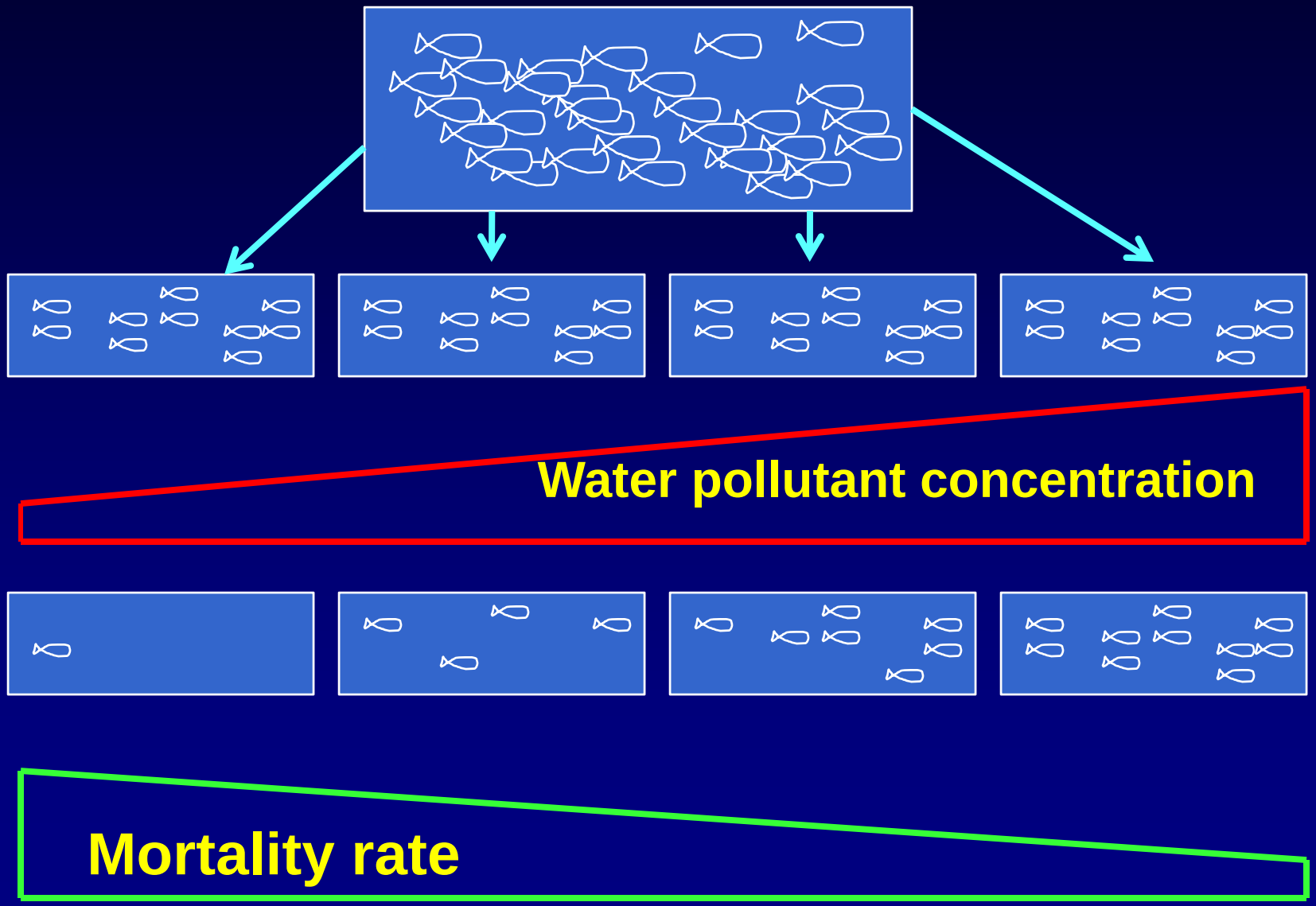
- **Hans Konrad Biesalski, University of Hohenheim, Germany**

A well designed randomized controlled trial to evaluate the mortality in guppies due to increased water pollution

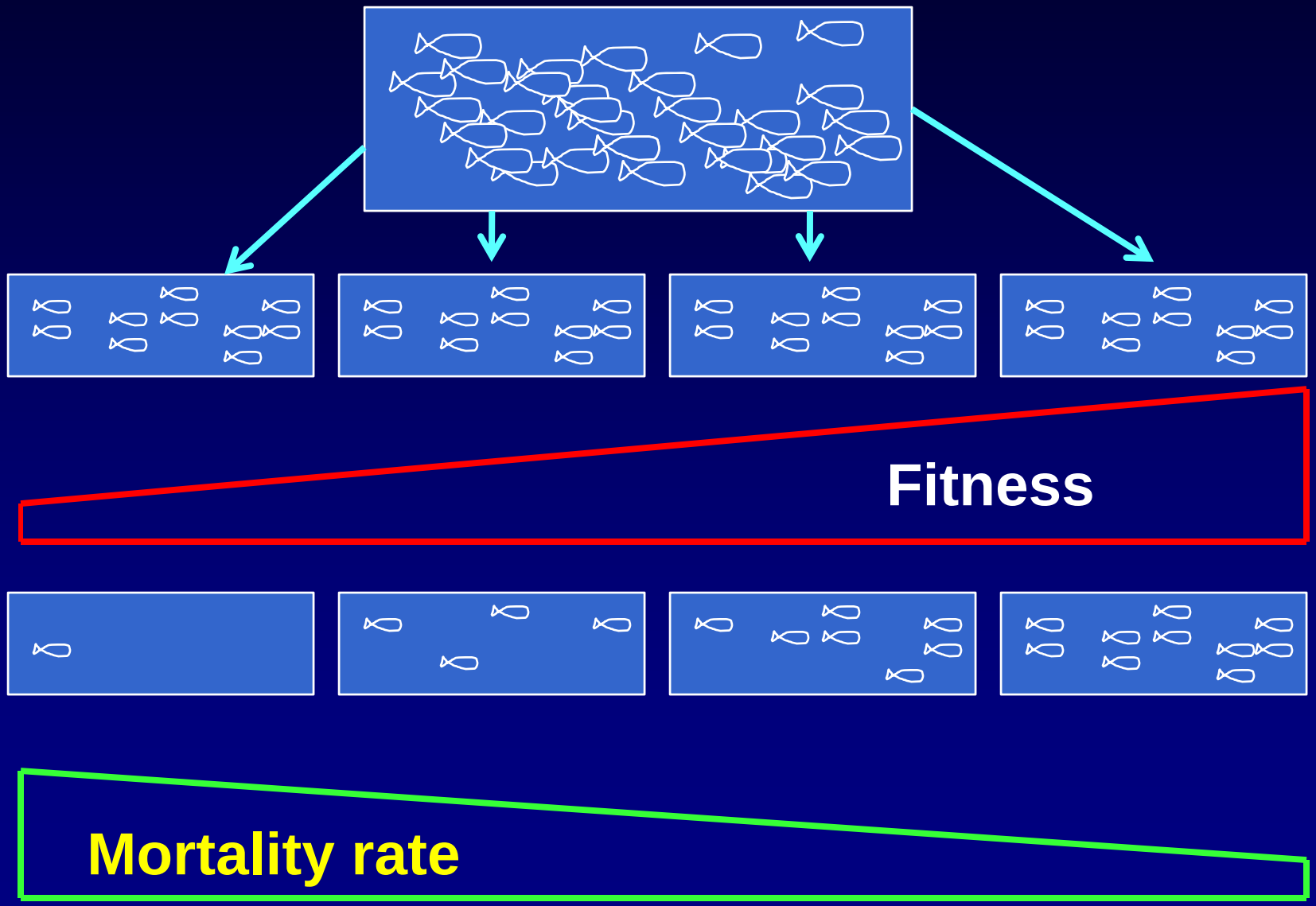


Any confounding factors?

A well designed randomized trial to evaluate the mortality in guppies



A well designed randomized trial to evaluate the mortality in guppies



Different types of claims—equal or different standard of evidence?

- Can we separate physiology (function)from pathophysiology (risk reduction)?

Health claim for fruits and vegetables?

Function claim?

- **Help to maintain body weight**
- **Help to maintain a normal digestion**
- **Improve quality of life**
- **Part of a healthy lifestyle**

Risk reduction claim?

- **Reduce risk for major chronic diseases**
- **Reduce cancer risk**

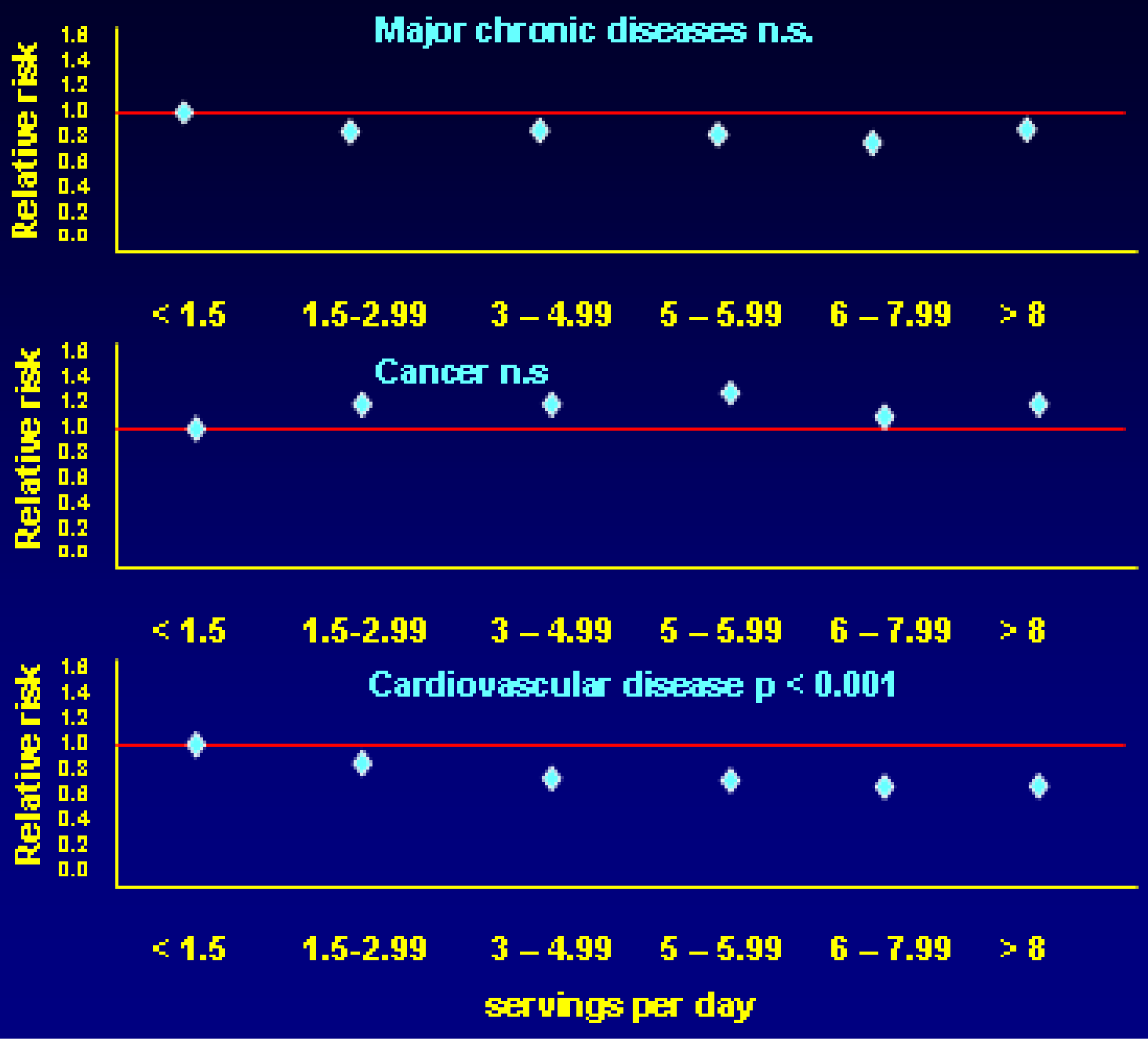
Health claim for fruits and vegetables?

Function claim?

- **Help to maintain body weight**
  - **Depends on composition**
- **Help to maintain a normal digestion**
  - **Depends on fibre content**
- **Improve quality of life**
  - **No real claim**
- **Part of a healthy lifestyle**
  - **No real claim**

Safety concern: The more fruits and vegetables are part of the diet the more harmful contaminants may be absorbed!

Fruit and vegetable intake and risk of major chronic disease



71 910 part. from NHS and 37 725 part. from PHS
Dietary quest. in 1984, 1986, 1990, 1996

Observation
May 1998
Jan 1998

Hung et al
JNCI 2004

Health claim for fruits and vegetables?

Risk reduction claim?

- **Reduce risk for major chronic diseases?**
- **Reduce cancer risk?**

Inconsistent data!

Fruits and vegetables are sources for essentiel micronutrients and phytochemicals which might be more or less involved to ensure the function of the body and by the way might prevent the development and progression of some diseases

Function: impact of a nutrient on a physiological function

Disease risk reduction : impact of a nutrient on pathophysiology

Can we separate physiology from pathophysiology?

Chronic pain of the musculoscelatal system is frequent in elderly.

It decreases mobility and quality of life and increases fracture risk.

Treatment of pain may improve QOL and reduces fracture risk

Treatment with a pain killer like Aspirin may help.

If Aspirin would be treated like a nutrient we can claim:

Pain is Aspirin-deficiency!

What to do?

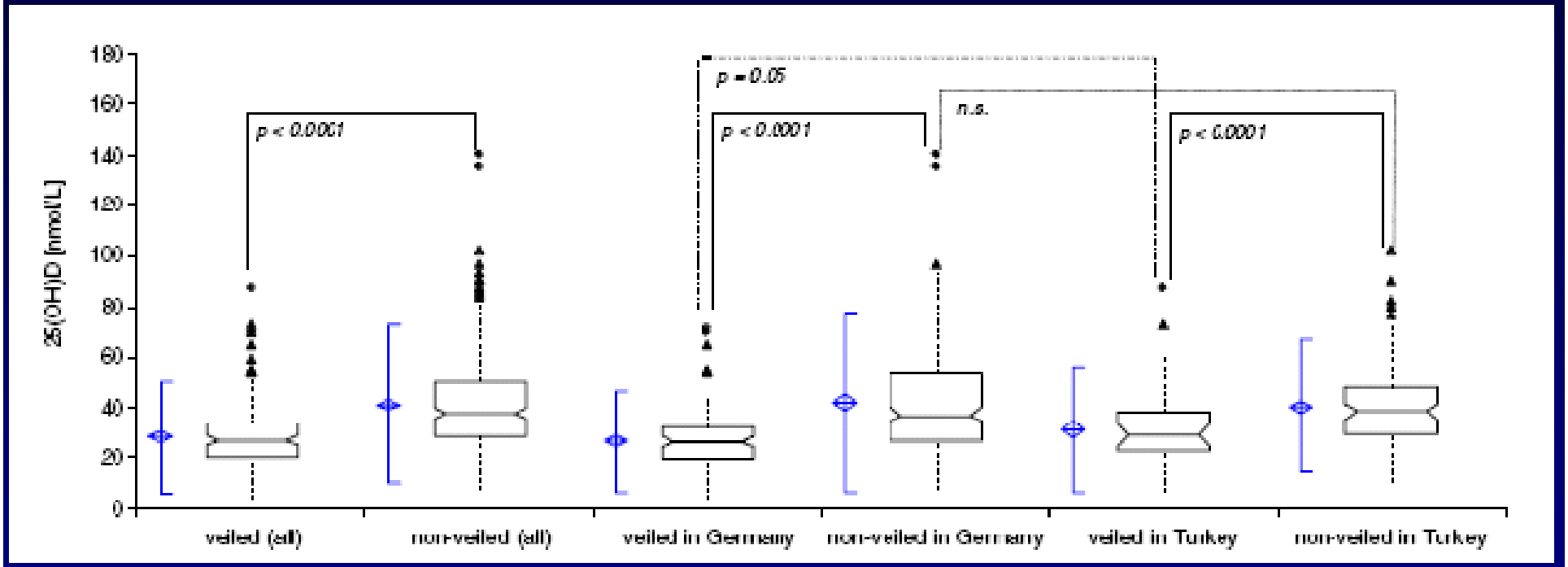
Treating the pathophysiology: Non-steroidal-antiinflammatory drugs?

Treating the deficiency: Vitamin D?

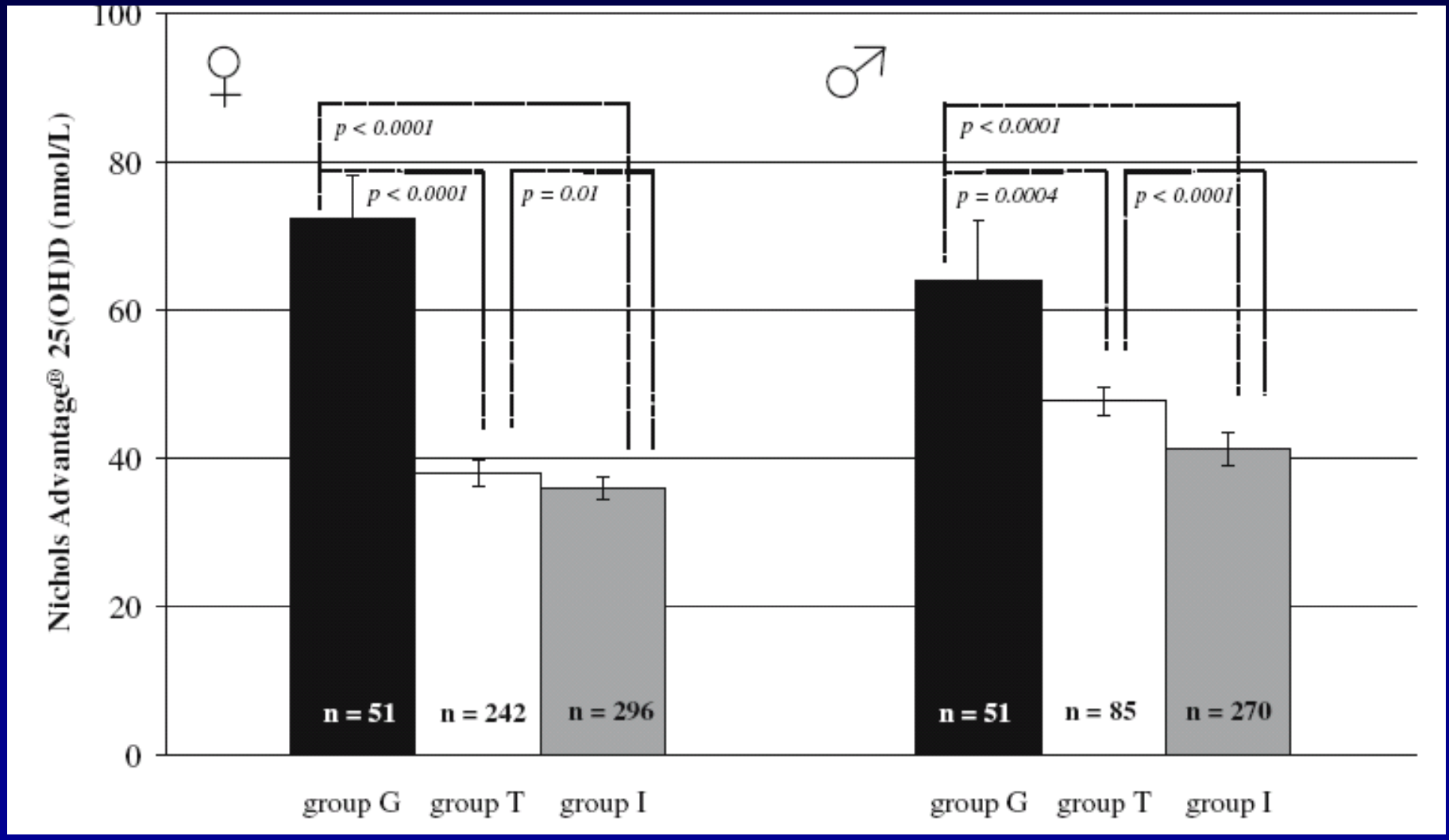
NSA may result in risk reduction without any impact on pathophysiology

Vitamin D compensates deficiency with impact on pathophysiology and physiology

Consequences of insufficient dermal vitamin D synthesis: Low Plasma levels – near deficiency!

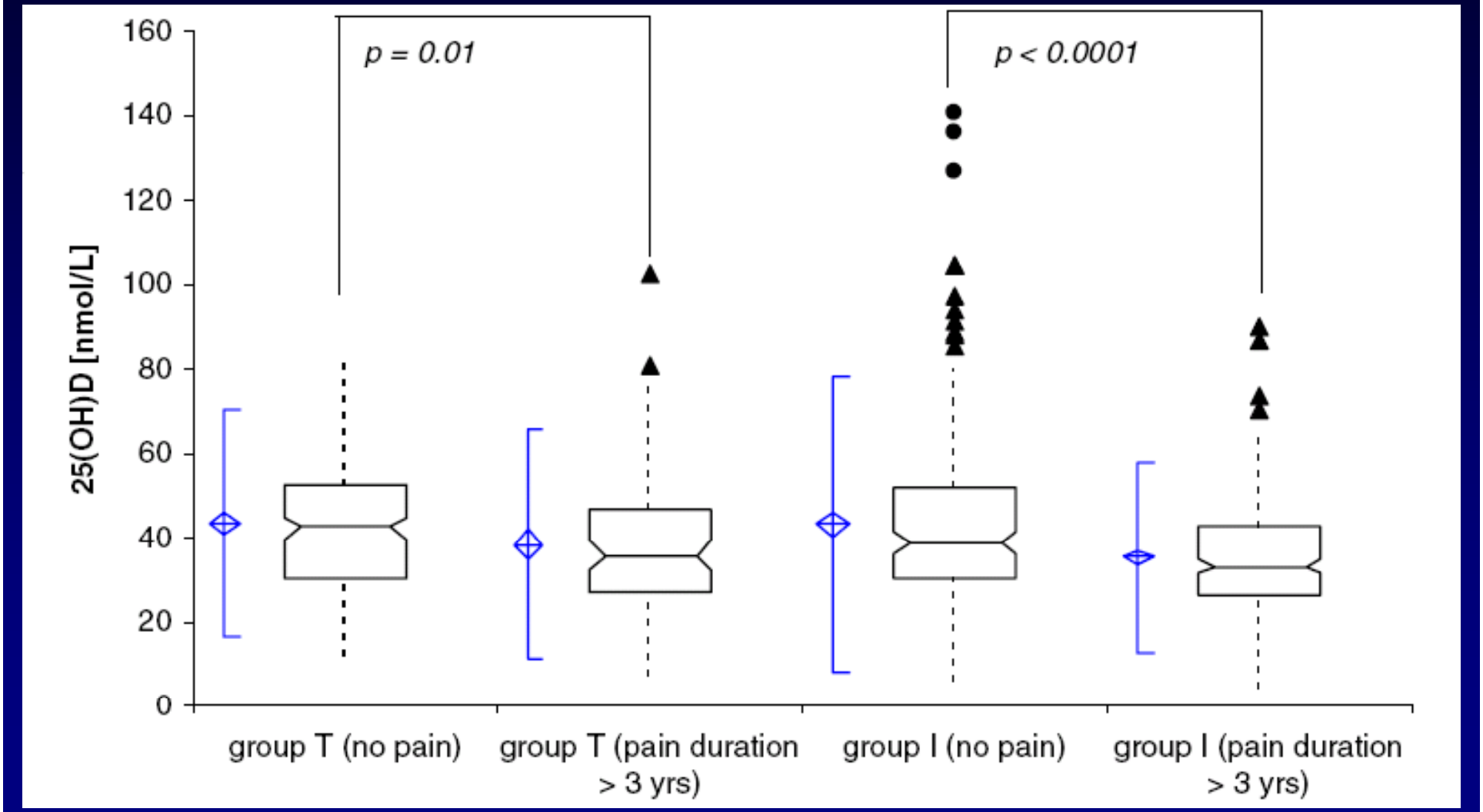


Vailed and non-vailed turkish women in Germany and Turkey (Erkal et al., 2006)



25(OH)D blood levels women from turkey and of immigrants (T, I) compared to german females (G) (Erkal et al., 2006)

Low plasma levels are correlated with chronic pain (Erkal et al., 2006)



Accordingly we treat nutrients like drugs: they need to have one specific target and measurable endpoint.

But we should not forget that nutrients have more than one target and are often closely linked together to other nutrients.

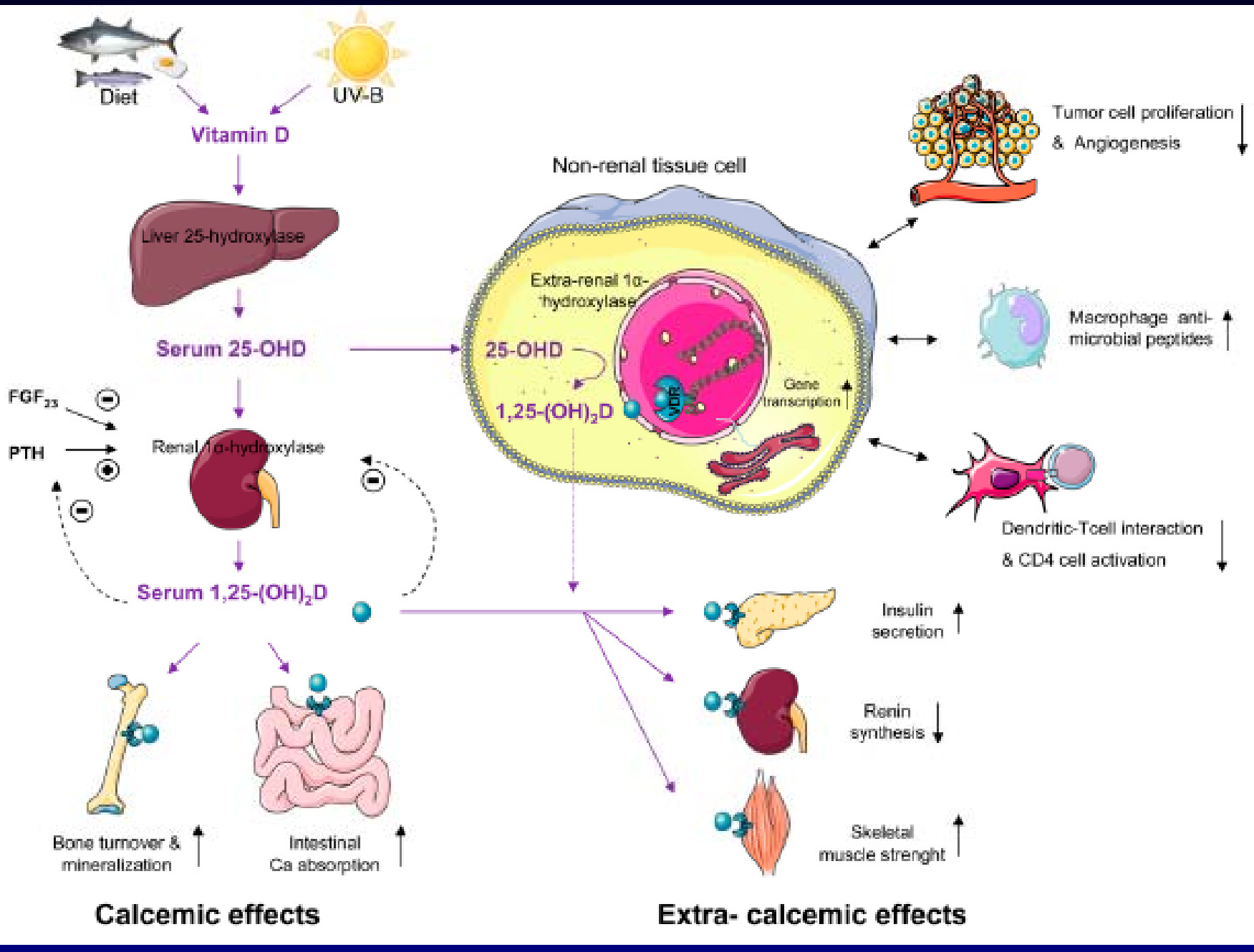

Diet
UV-B
Vitamin D
Liver 25-hydroxylase
Serum 25-OHD
FGF23
PTH
Renal 1α-hydroxylase
Serum 1,25-(OH)2D
Bone turnover & mineralization
Intestinal Ca absorption
Calcemic effects
Non-renal tissue cell
Extra-renal 1α-hydroxylase
25-OHD
1,25-(OH)2D
VDR
Gene transcription
Tumor cell proliferation & Angiogenesis
Macrophage anti-microbial peptides
Dendritic-Tcell interaction & CD4 cell activation
Insulin secretion
Renin synthesis
Skeletal muscle strenght
Extra- calcemic effects

Table 1 Effects of Vitamin D[33,35,43,45-47,49,52,56-58,60,65,68,72]

Bone	Decreases the risk of osteoporotic fractures
Falls	May retard sarcopenia and decreases the risk of falls
Pain	Decreases neuropathic pain in type 2 diabetes mellitus
Autoimmune disease	Decreases the risk of multiple sclerosis, rheumatoid arthritis, and type 1 diabetes mellitus
Cancer	Decreases the risk of colorectal cancer and leukemia
	Decreases the total cancer incidence and mortality
	Decreases digestive system cancer incidence and mortality
	Decreases the incidence of breast cancer
Heart disease	Decreases the risk of myocardial infarction
	Decreases vascular calcification
Mortality	Decreases total mortality
Cognitive function	Increases cognitive function
	Improves depression and seasonal affective disorder

Vitamin D has multiple functions in contrast to drugs.

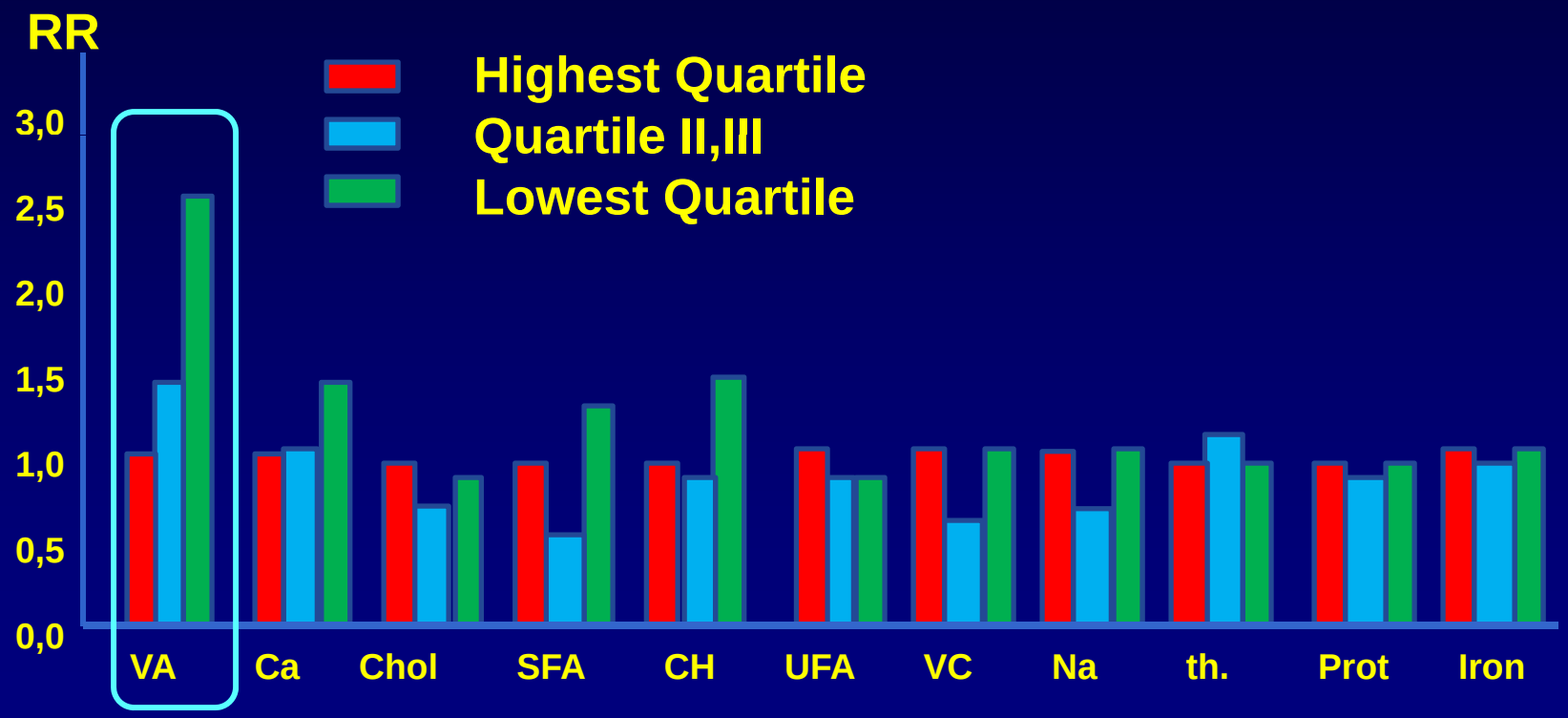
Table 1. Some of the Polyphenols that Induce NAG-1 Expression **(NSAID-activated gene 1)**

Compounds	Concentration (μM)	NAG-1	Reference
Resveratrol	10-100	UP	7
Capsaicin	10-100	UP	*
Curcumin	0.01-0.1	NO Change	*
ECCC	10-100	UP	6
ECG	50	UP	6
EGC	50	NO Change	6
EC	50	NO Change	6
Indol-3-carbinol	50	UP	8
DIM	10-100	UP	8
6-gingerol	10-100	UP	*
CAPE	1-50	UP	*
Genistein	10-100	UP	9

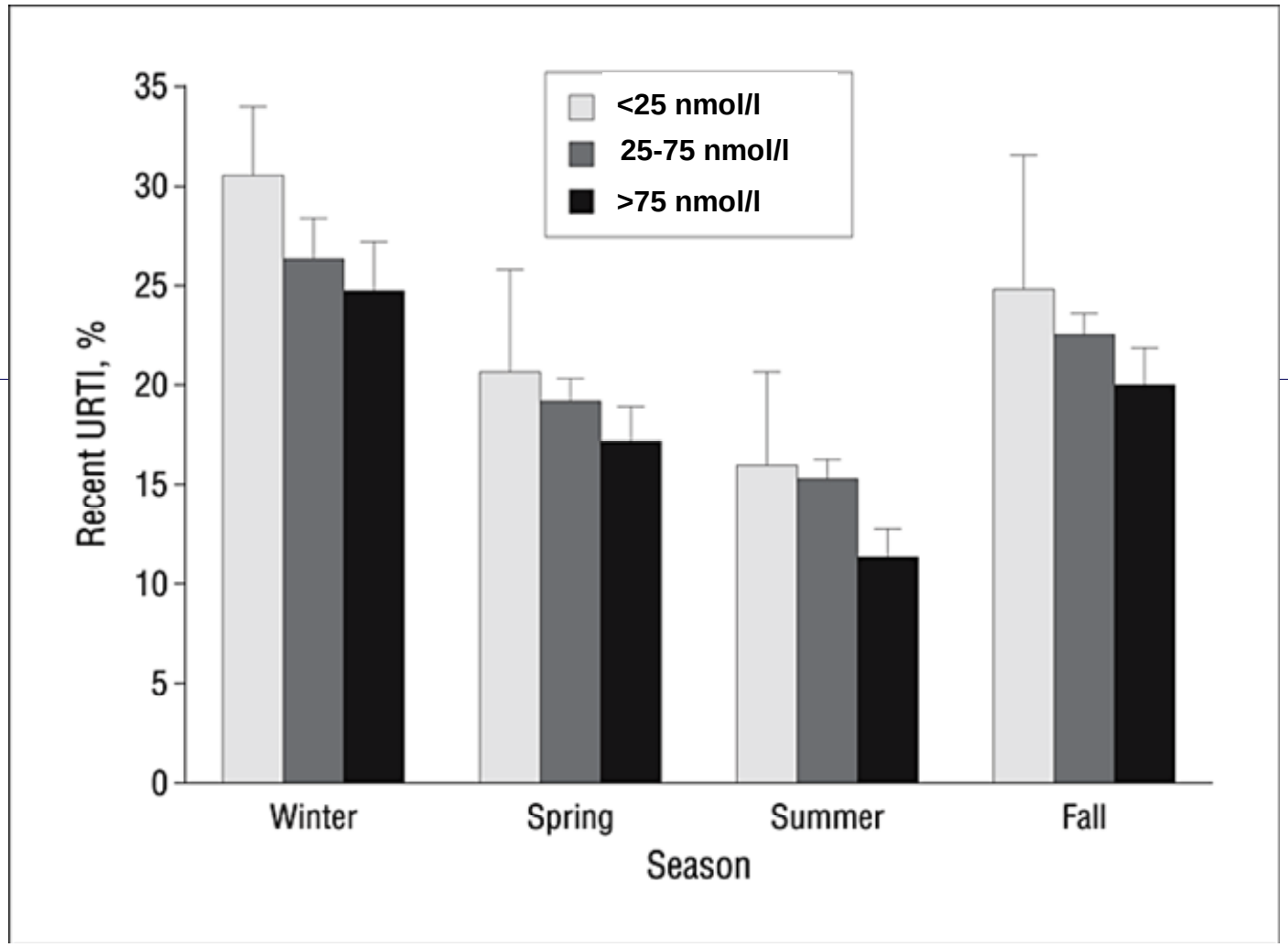
EGCG, (-)-epigallocatechin gallate; ECG, (-)-epicatechin gallate; EGC, (-)-epigallocatechin; and EC, (-)-epicatechin; DIM, 3,3'-diindolylmethane. Western blot analysis was performed to determine if the compounds induced NAG-1 expression.
*represents unpublished data.

Polyphenols act via up-regulation of NAG-1 as COX independant antiinflammatory action

Relative risk for bronchitis and single nutrients or biomarker in the NHANES study 1991



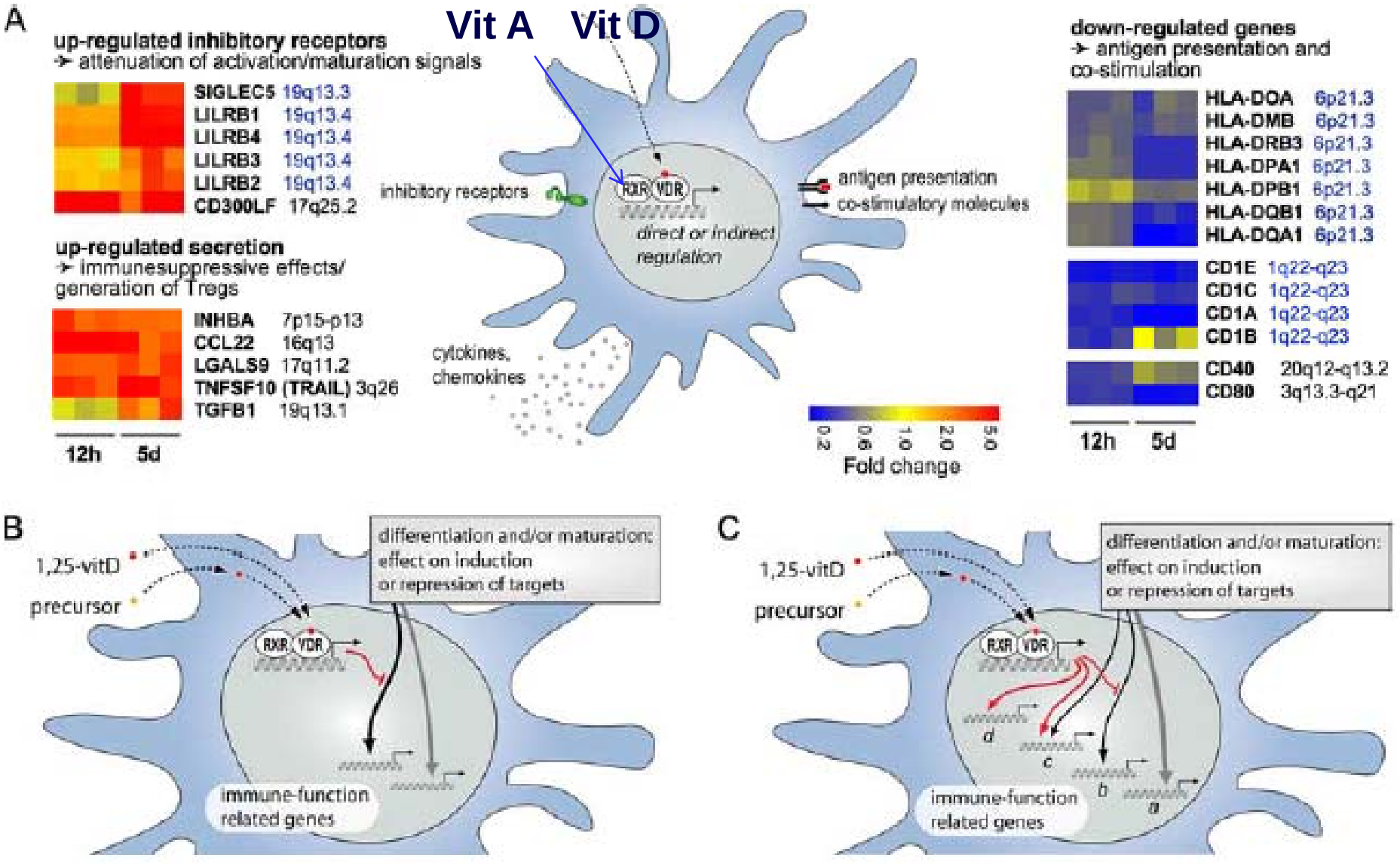
Participants with recent upper respiratory tract infection (URTI) stratified by serum 25-hydroxyvitamin D level and season



Ginde, A. A. et al. Arch Intern Med 2009;169:384-390.

ARCHIVES OF INTERNAL MEDICINE

Vitamin A and D regulate the immune function of dendritic cells. (Szeles et al. J Immunol. 2009)



Cod liver oil (containing vitamin A and D) significantly reduces respiratory tract infections in children (Canell et al., 2008; Linday et al., 2010)

Controversies between epidemiology and intervention studies:

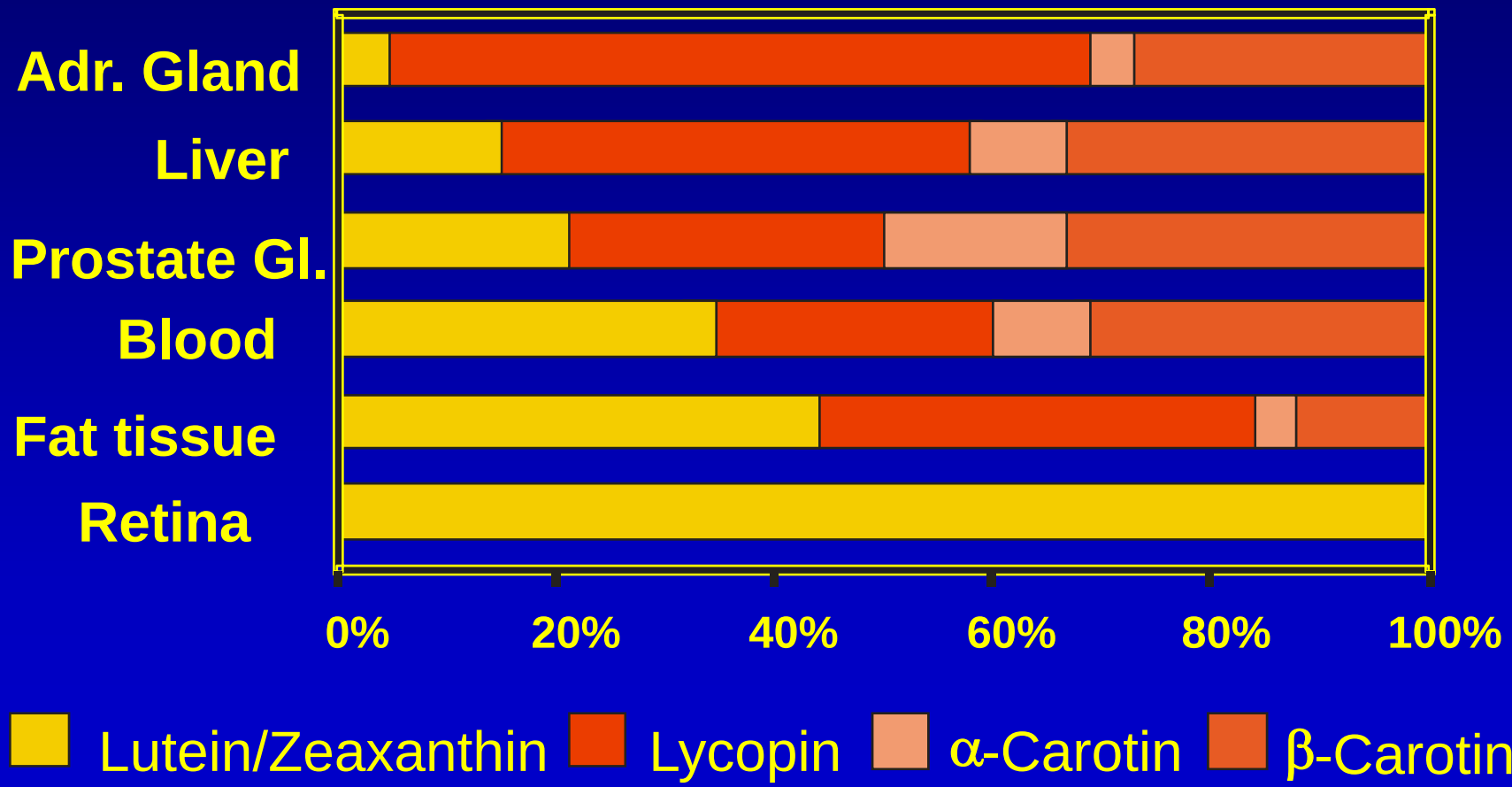
High dietary lycopene protects from prostate cancer

High dietary selenium decreases prostate cancer risk

Intervention studies are controversial

Why do we need carotenoids – are they esssentiel?

Different carotenoids occur preferably in:



Lycopine:

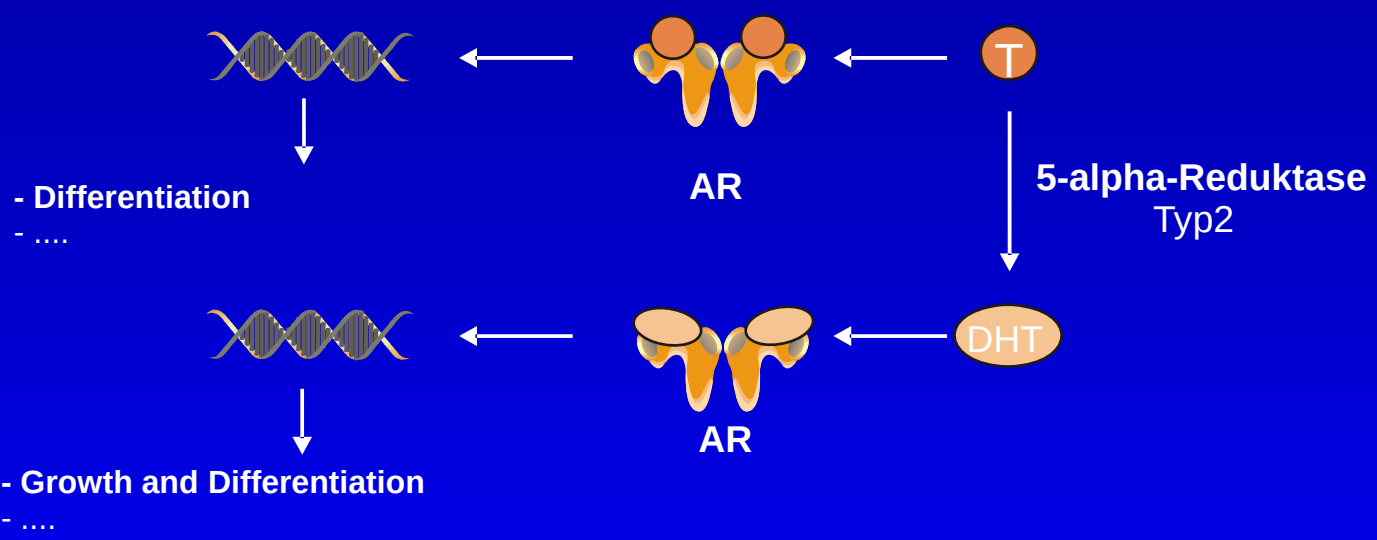
- reduces cellcycle
- reduces DNA damage
- increases phase II metabolism
- increases antioxidative defense

The „first“ hit which results in a pathophysiological condition leading finally to a disease must not be the event which is responsible for further progression.

The disease progression is embedded in a complex metabolism and genotype consequently if a nutrient is claimed to protect from the first hit it needs not necessarily be protective for the progression.

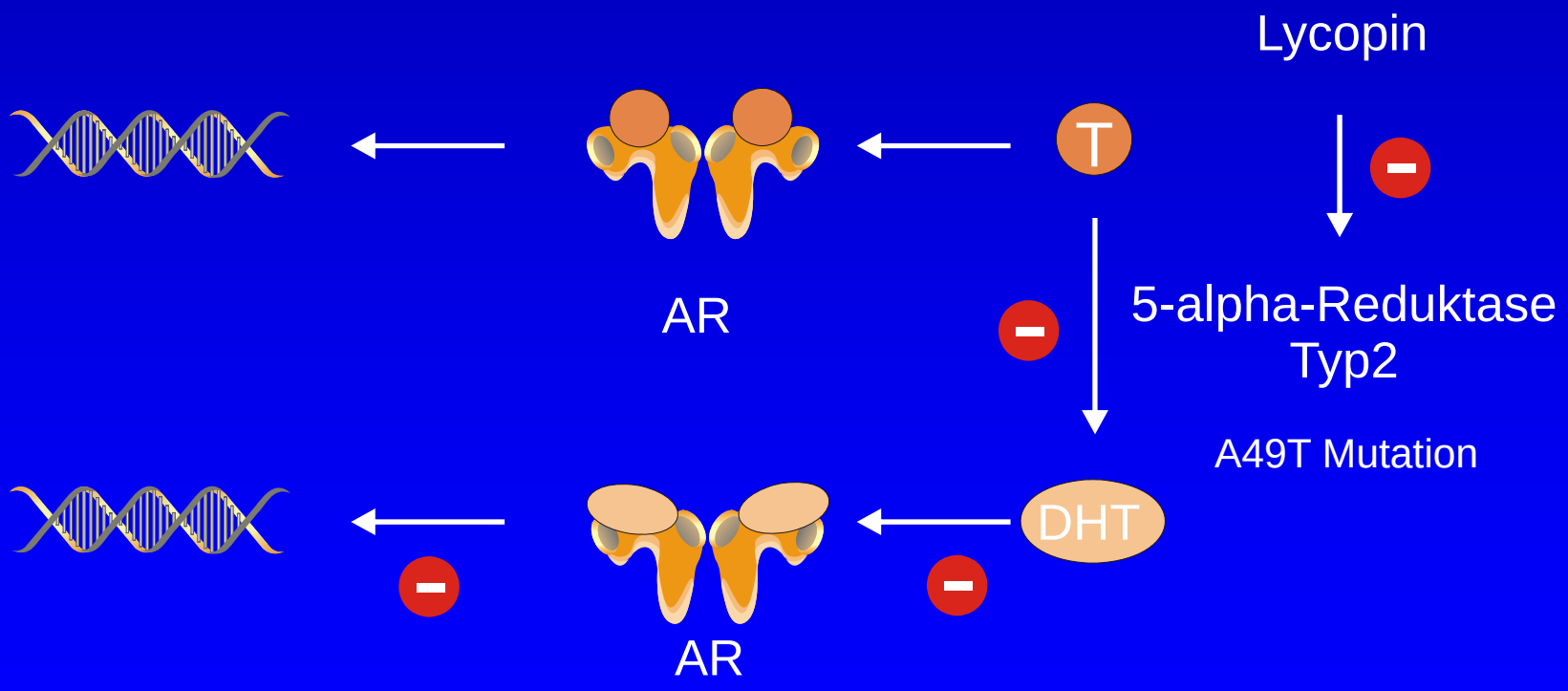
Understanding risk reduction must therefore combine the physiology of protection with the pathophysiology of the progression

First hit: Genes



- Young japanese men have a lower 5-a-reductase activity than young caucasians
- DHT : Testosterone ratio is greater in young caucasians than in japanese men
- BPH and prostate cancer are more frequent in caucasians

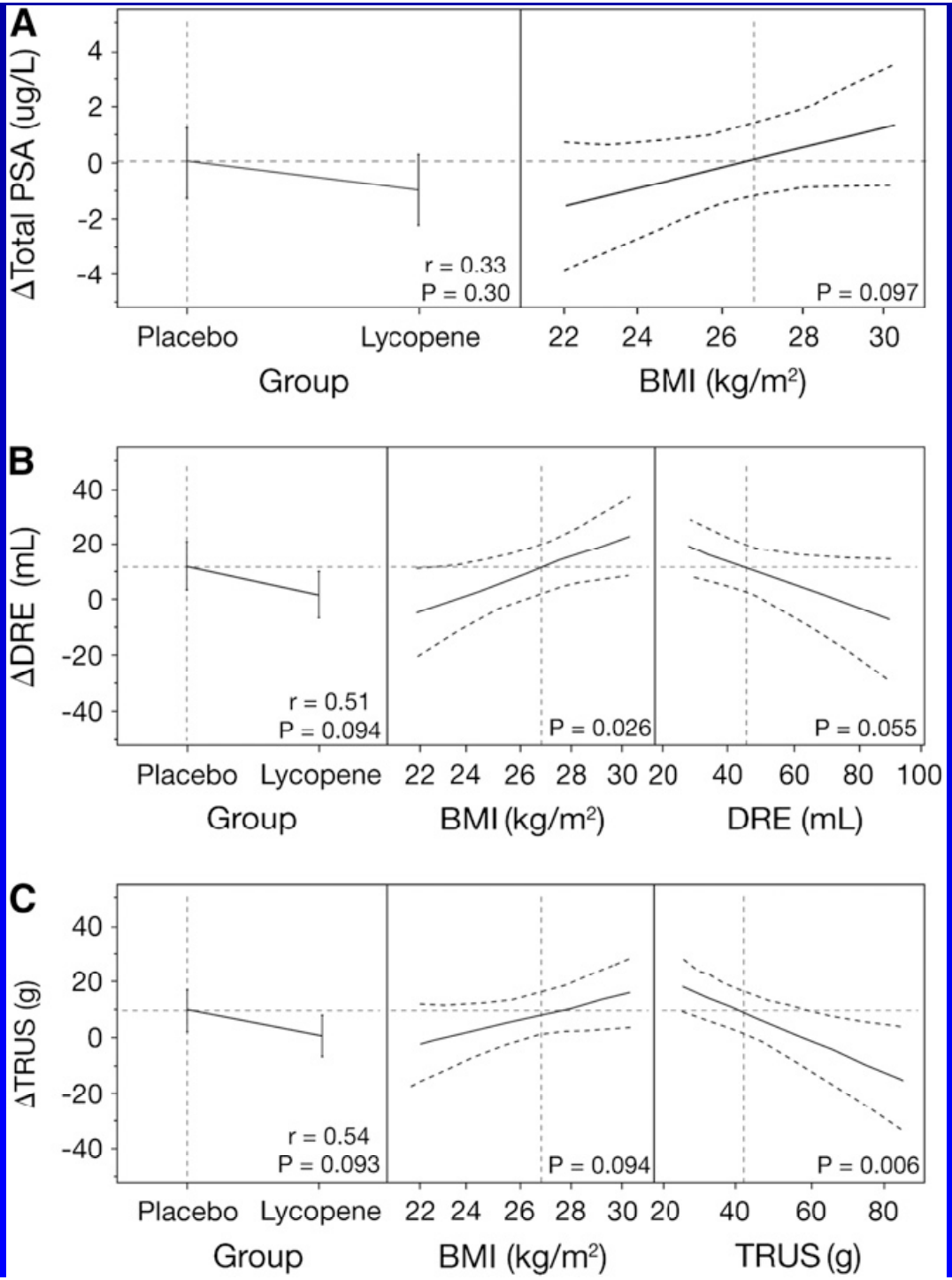
Men with an increased 5-a-reductase activity based on a mutation and subsequent higher rsik for BPH and prostate cancer may benefit from lycopene



Prevention: Lycopene reduces 5-aR-activity

Lycopene inhibits disease progression in patients with benign prostate hyperplasia. Schwarz S, Obermüller-Jevic UC, Hellmis E, Koch W, Jacobi G, Biesalski HK. J. Nutr. 2008

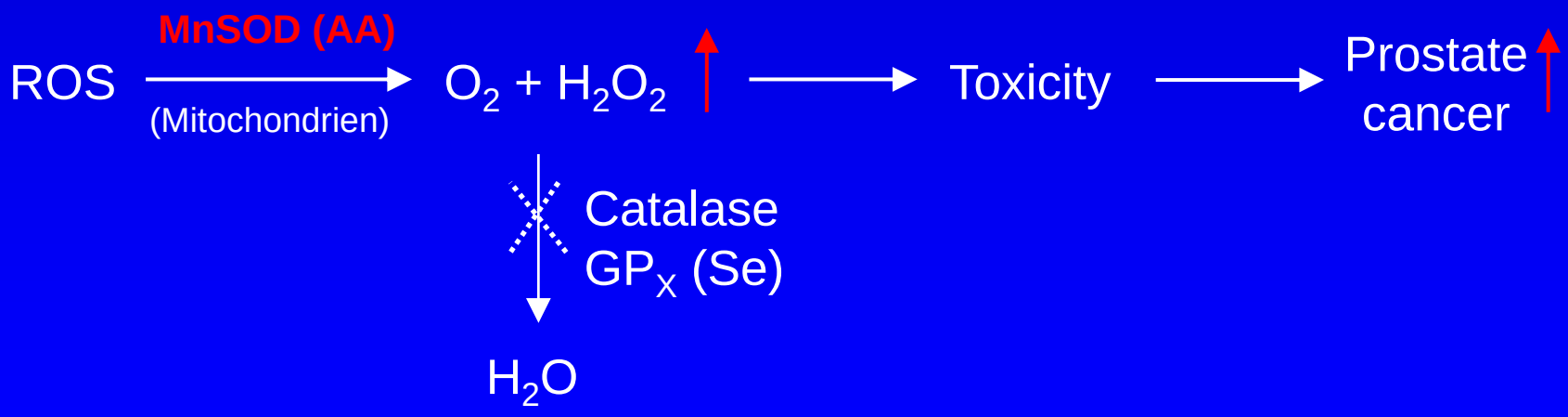
Whereas progression of prostate enlargement occurred in the placebo group as assessed by trans-rectal ultrasonography ($P < 0.05$) and digital rectal examination ($P < 0.01$), the prostate did not enlarge in the lycopene group. Symptoms of the disease, as assessed via the International Prostate Symptom Score questionnaire, were improved in both groups with a significantly greater effect in men taking lycopene supplements. In conclusion, lycopene inhibited progression of BPH.



Changes in total PSA, DRE and TRUS in BPH patients supplemented with lycopene or placebo for 6 month

Disease ProgressionMnSOD-Polymorphism and prostate cancer

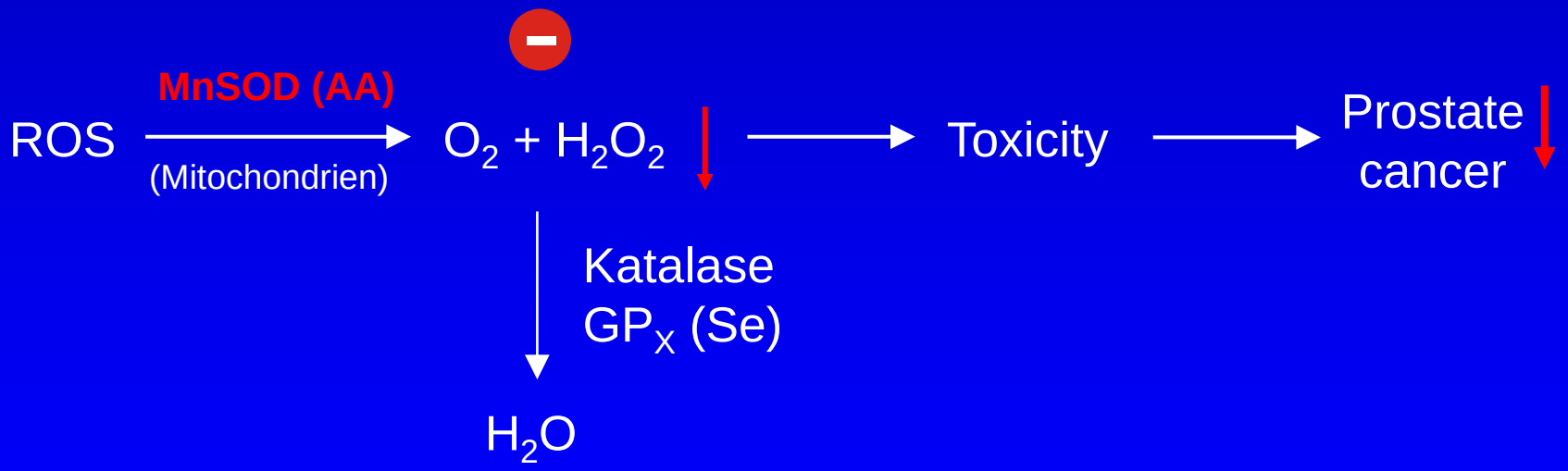
The MnSOD in the AA genotyp is overexpressed and should protect from cancer!
But: the AA genotype has an increased risk for prostate cancer
The AA genotype occurs in 12% of young japanese men and 45% of young caucasians



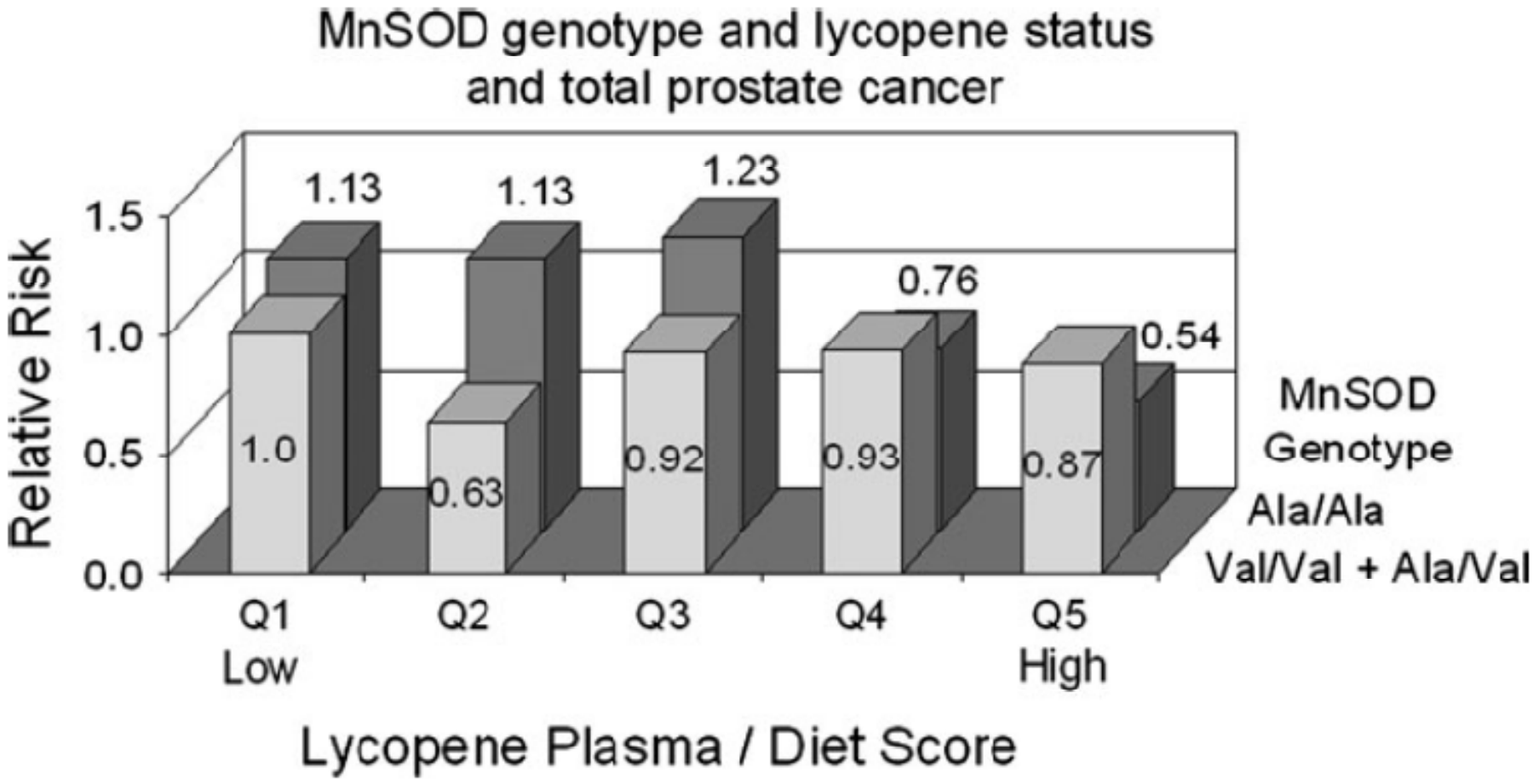
(Haojie et al.: MnSOD Polymorphism, Prediagnostic Antioxidant Status, and Risk of Clinical Significant Prostate Cancer. *Cancer Research 65(6): 2498-2504; 2005*)

Risk reduction in men with MnSOD polymorphism

Lycopin and Se



(Haojie et al.: MnSOD Polymorphism, Prediagnostic Antioxidant Status, and Risk of Clinical Significant Prostate Cancer. *Cancer Research 65(6): 2498-2504; 2005*)


MnSOD genotype and lycopene status
and total prostate cancer
Relative Risk
1.5
1.0
0.5
0.0
1.13
1.13
1.23
0.76
0.54
1.0
0.63
0.92
0.93
0.87
MnSOD
Genotype
Ala/Ala
Val/Val + Ala/Val
Q1
Low
Q2
Q3
Q4
Q5
High
Lycopene Plasma / Diet Score

Different types of claims—equal or different standard of evidence?

- We cannot realy separate physiology from pathophysiology because they are always linked together.
- To understand prevention and risk reduction we need to under stand the physiology and pathophysiology in selected and well defined groups
- Biomarker for physiology and pathophysiology should be combined