

Mikronährstoffe in der Medizin: Aktueller Potpourri

17. Juni 2023 - 9.00 bis 17.00 Uhr im Seehotel Waldstätterhof, 6440 Brunnen

## **Homocystein, B-Vitamine und Kognition**

Prof. Dr. Rima Obeid

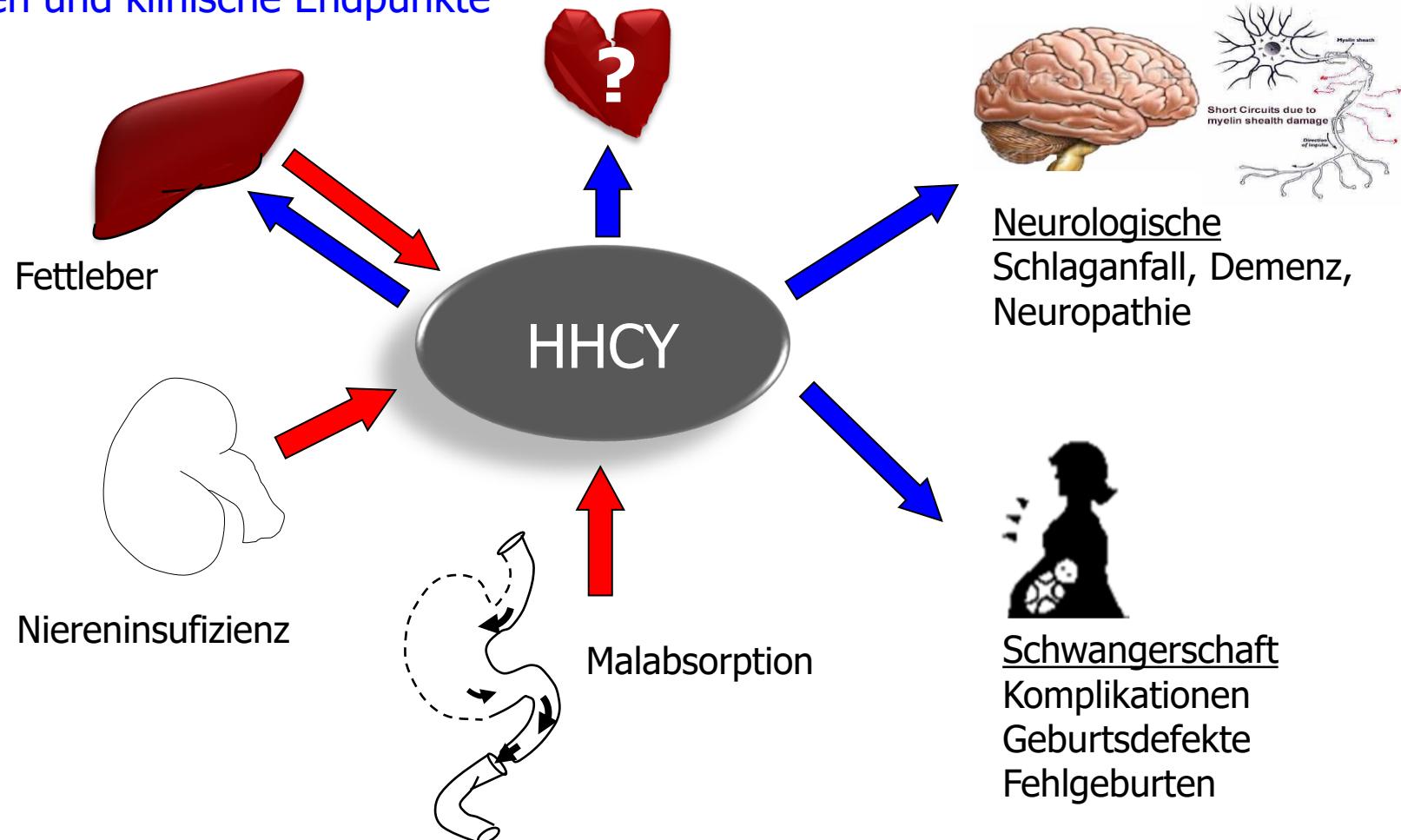


Universitätsklinikum des Saarlandes, Klinische Chemie und  
Laboratoriumsmedizin / Zentrallabor, Geb. 57, 66421 Homburg

# Interessenkonflikte

- Lebensmittelverband Deutschland e. V.
- Merck & Cie
- P & G Health Germany
- HiPP GmbH
- Worwag Pharma
- Balchem
- Bo Hjelt Foundation

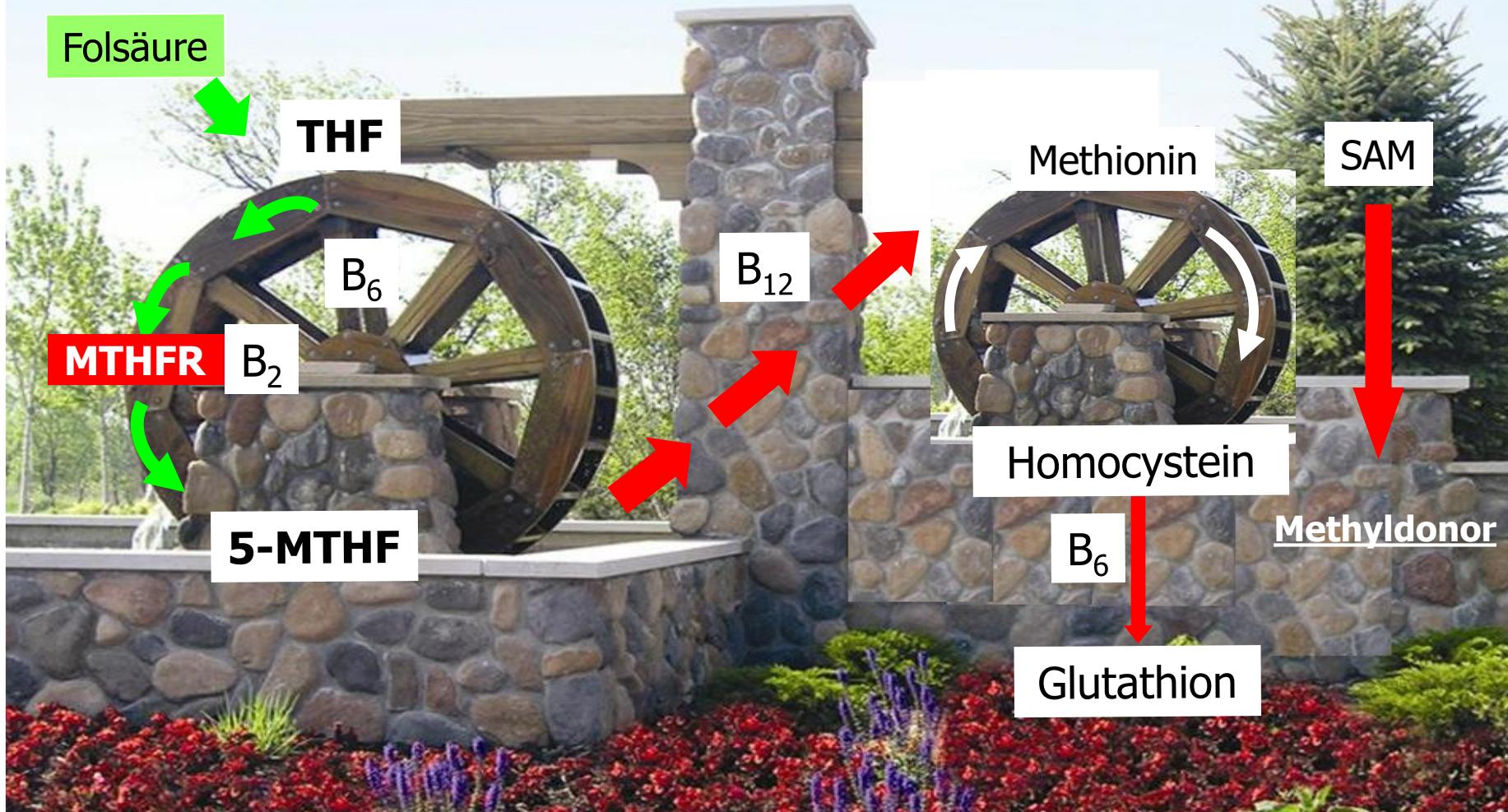
## Ursachen und klinische Endpunkte



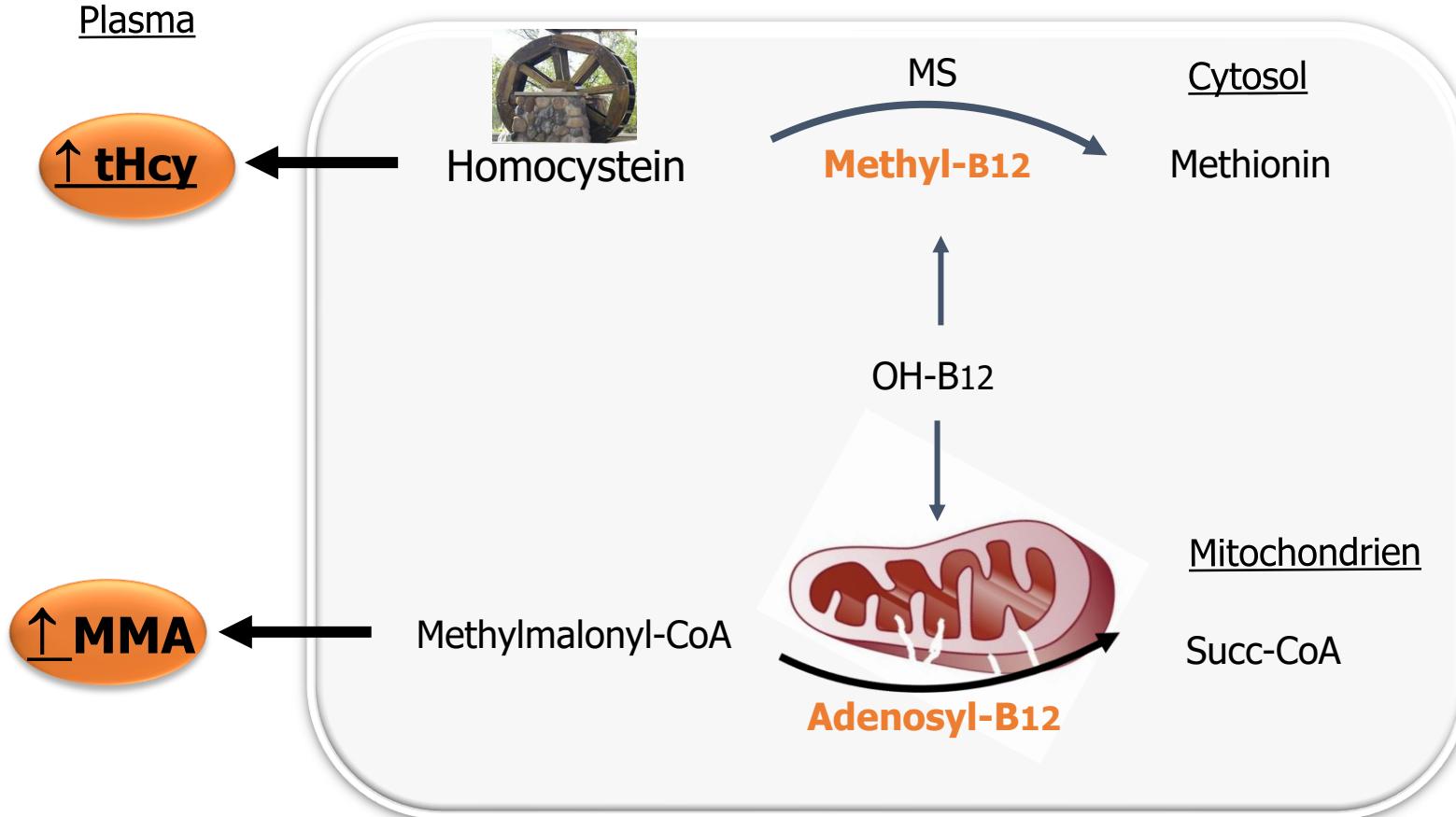
# **Homocystein: Risikofaktor oder Risikomarker?**

- B-Vitamine und Homocystein-Stoffwechsel
- B12-Mangel als Ursache für HCY (insbesondere bei Ältere Menschen)
- HCY als Risikofaktor für kognitive Dysfunktion: was spricht für Kausalität?
- Wann kann HCY-Senkung das Risiko reduzieren?

# Homocystein Stoffwechsel benötigt 4 B-Vitamine

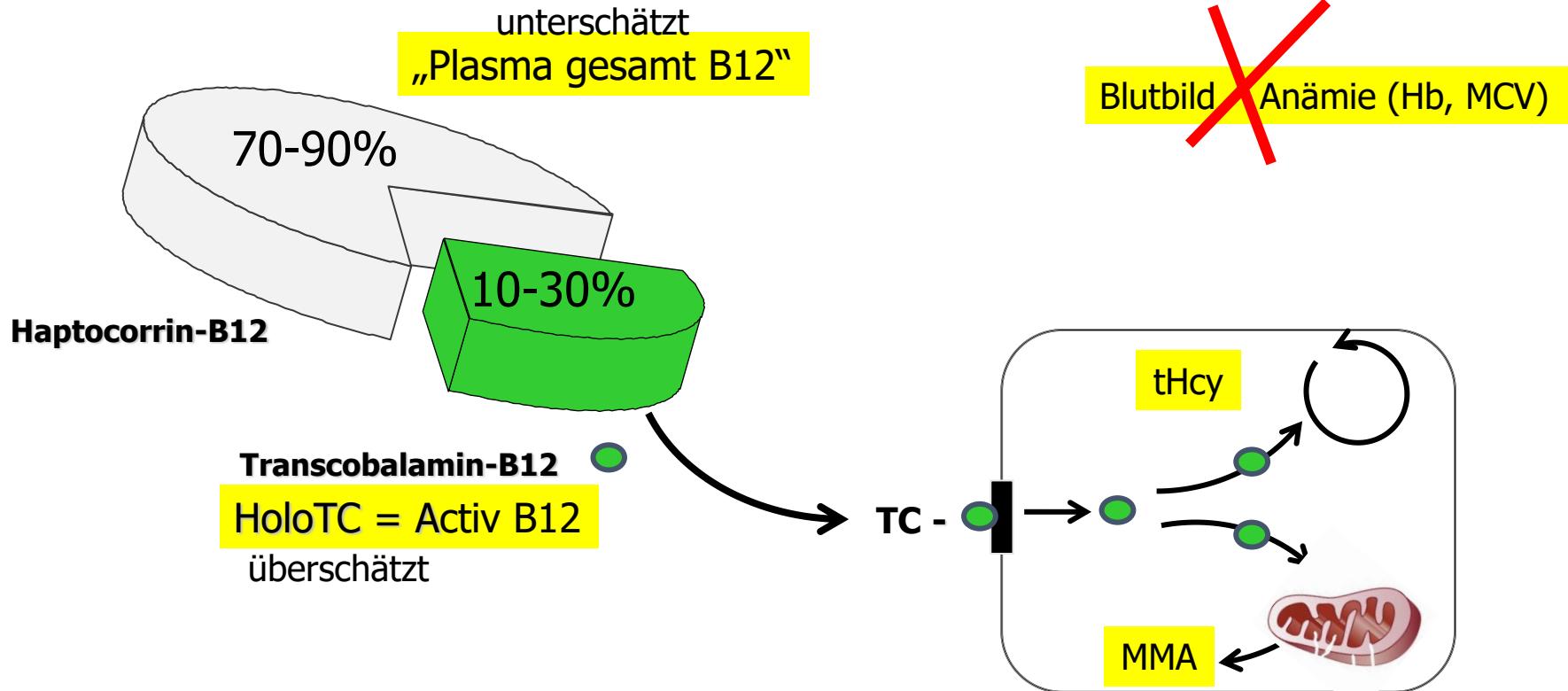


# Vitamin B12: ein Co-faktor für nur 2 Reaktionen



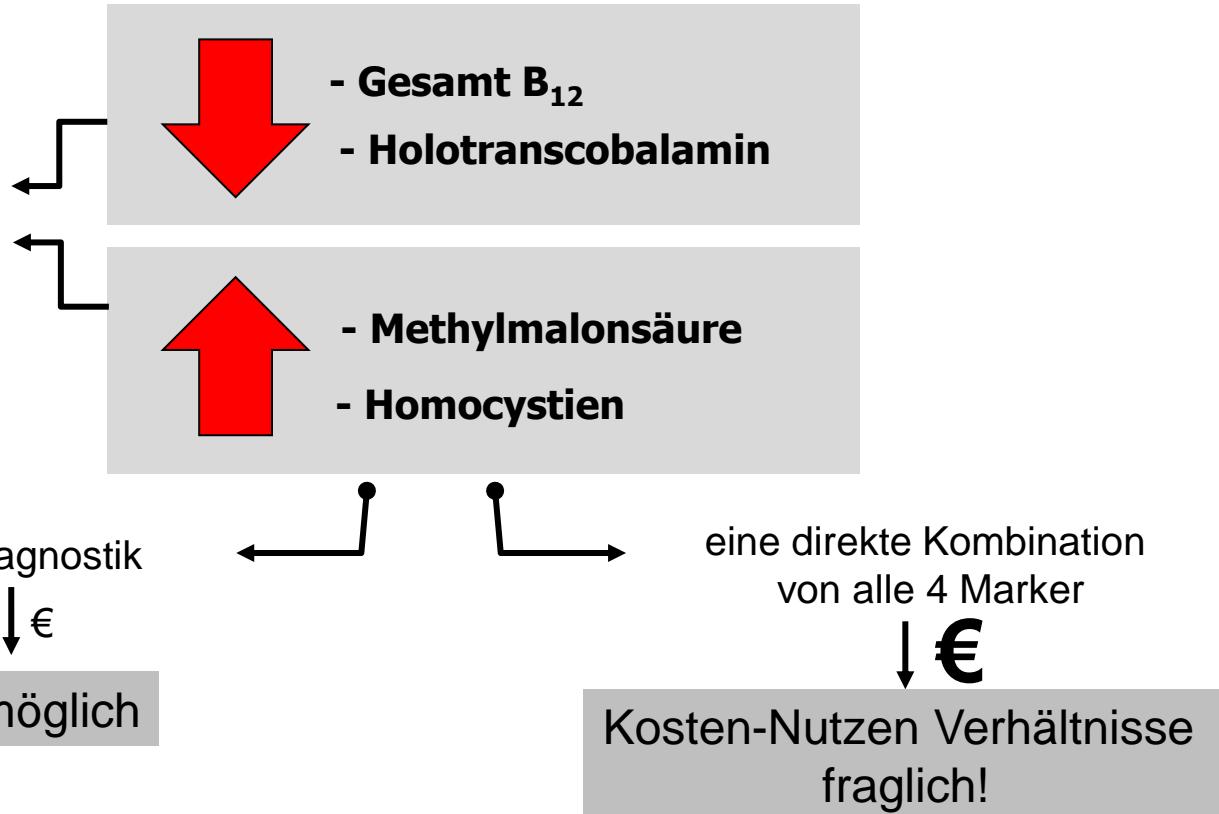
Limitation der Einzelmarker-Strategie ( $\downarrow$ Sensitivität &  $\downarrow$  Spezifität)

Der Mangel kann über- oder unterschätzt werden



# B<sub>12</sub> Marker

Einzel Marker  
nicht hilfreich!



## Erhöhte B<sub>12</sub>-Marker, die nicht auf B<sub>12</sub>-Status zurückzuführen



### HoloTC

Nieren-Patienten  
Diabetes



### Gesamt B<sub>12</sub>

Leber-Erkrankungen  
Nieren-Patienten  
Krebs  
Diabetes Komplikation



### Homocystien

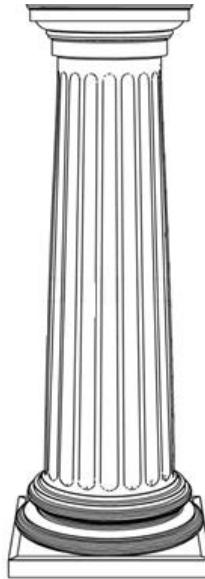
Nieren-Patienten  
Ältere Probanden  
Folat Mangel  
Pre-analytik



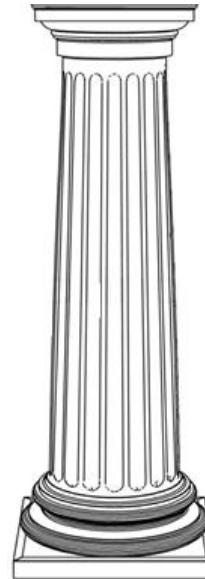
### Methylmalonsäure

Nieren-Patienten  
Ältere Probanden  
Darmbakterien

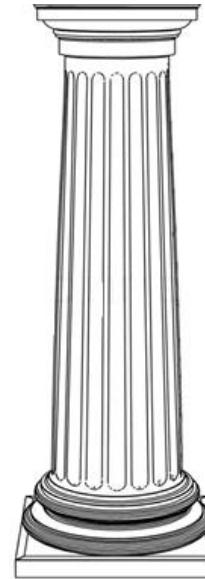
# Die Säulen der B12-Mangel Diagnostik



**Klinische Symptome**  
neurologische,  
neuropsychiatrische und  
hämatologische  
Komponente



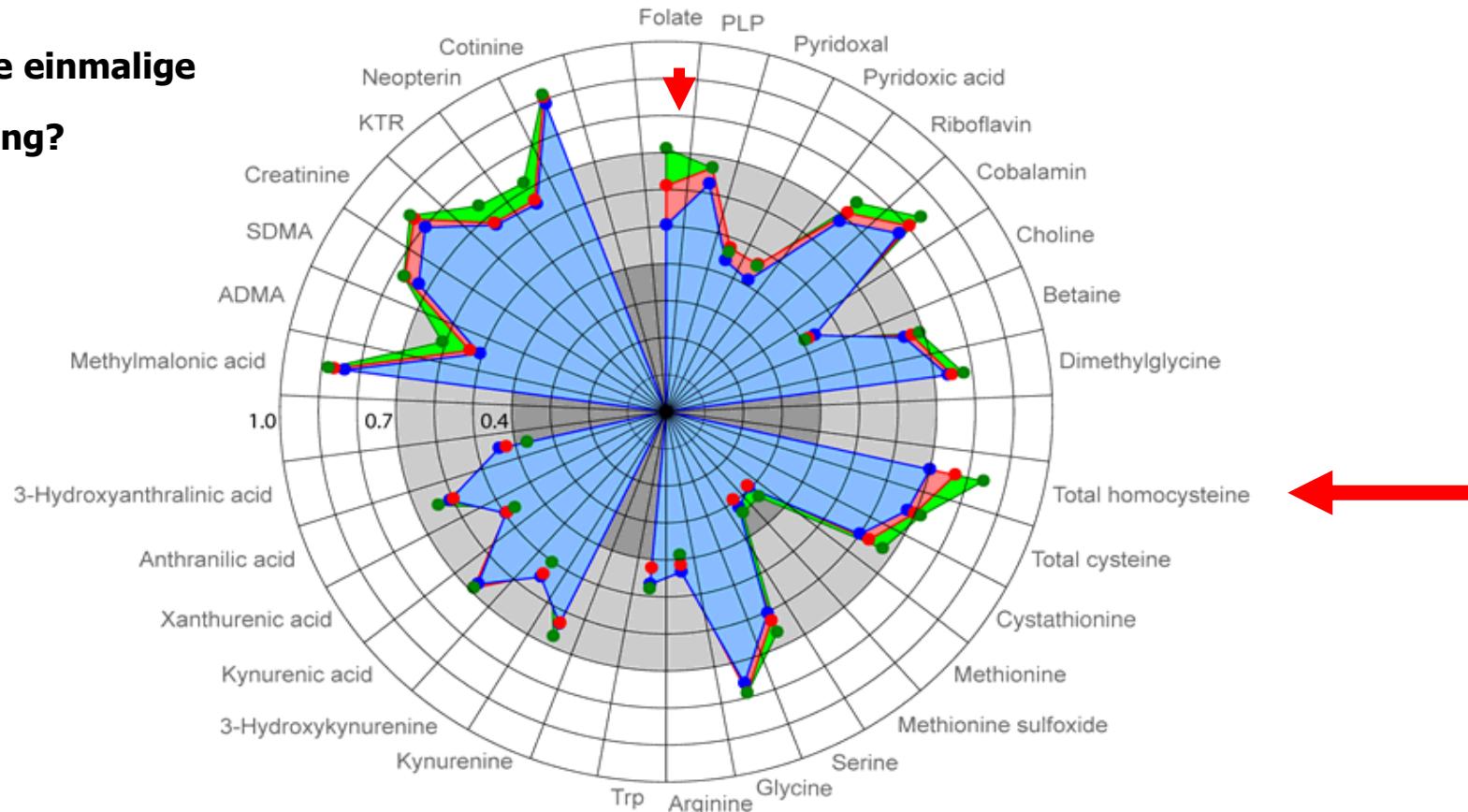
**Risikoprofil/Ursachen**  
Vegan/Ernährung  
Alter  
Perniziöse Anämie  
Gastritis  
Magen-bypass  
Metformin



**Biomarker**  
B12 oder  
holoTC  
*Plus*  
MMA oder  
tHcy

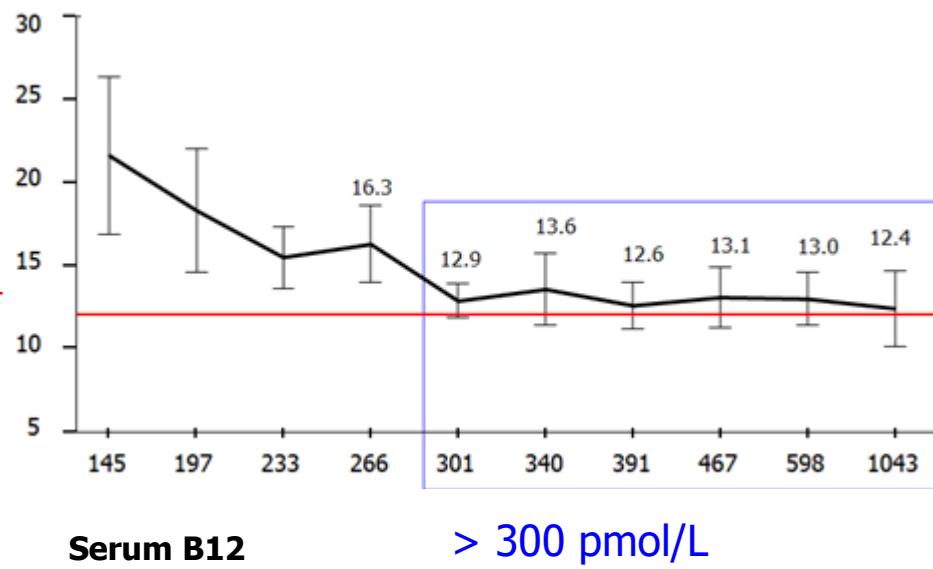
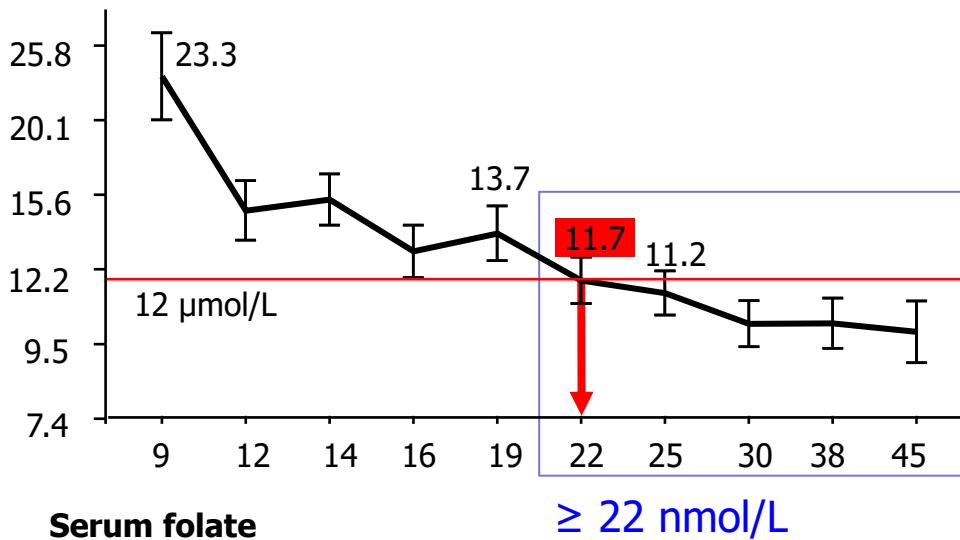
■ Baseline, 28 days, 1 year and 38 months ■ Baseline, 28 days and 1 year ■ Baseline and 28 days

## Genügt eine einmalige tHcy Messung?

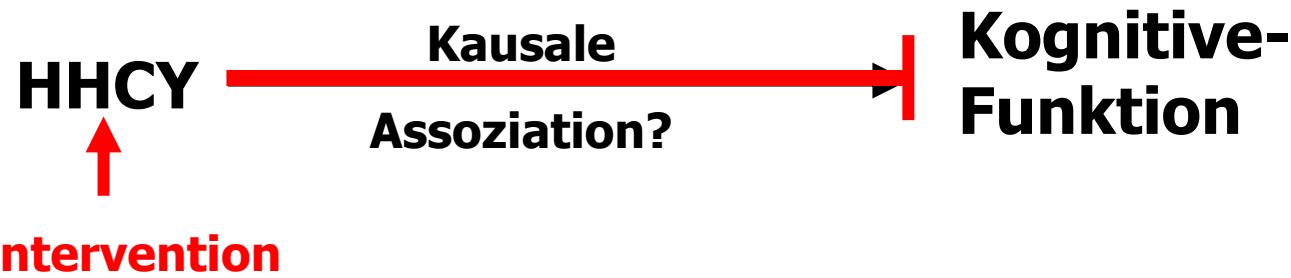


## HHCY; kein Bezug zu den Referenzintervallen für die B-Vitamine

### tHcy, $\mu\text{mol/L}$ (mean, 95% CI)

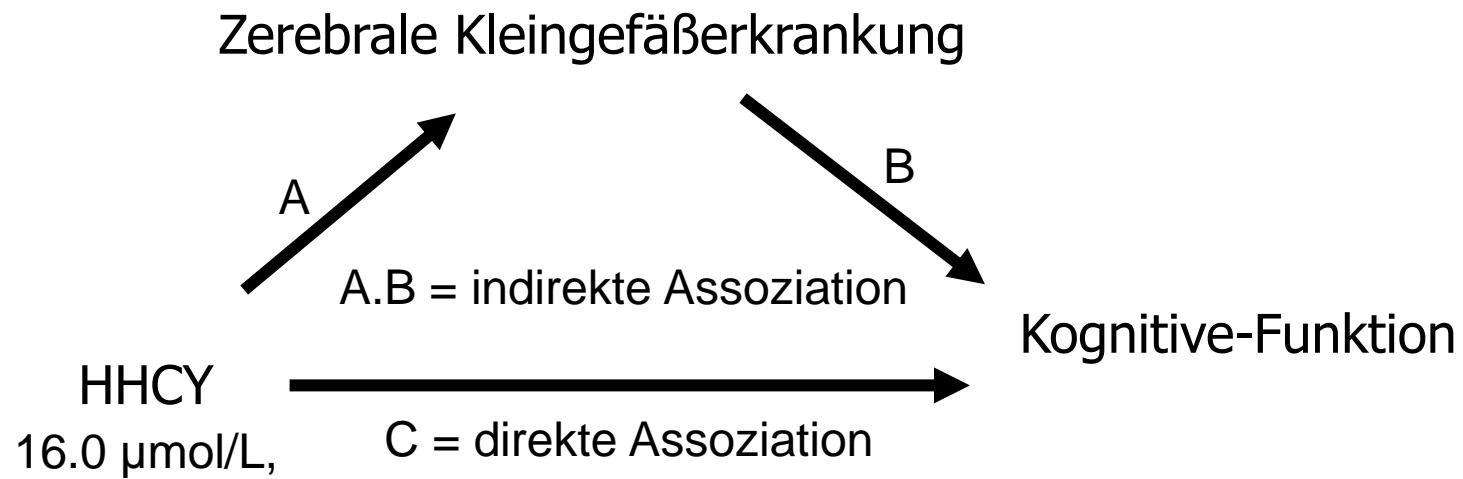


# Ist HCY ein Risikofaktor für Demenz?



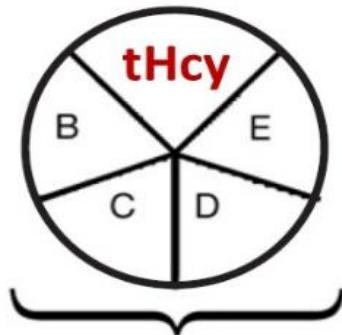
Kausalitätsmodelle

**Mediation effect  
(ab/c) = 23.6%**



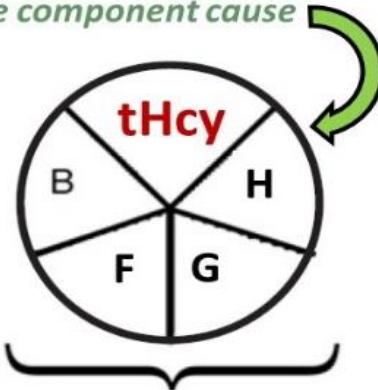
# (I) Rothman Kausalitätsmodell

*Sufficient cause I*



*Sufficient cause II*

*Single component cause*



One causal mechanism

Another causal mechanism

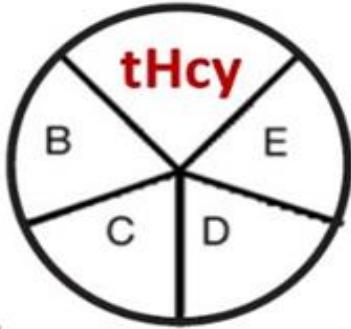
- B blood pressure
- C hypercholesterolemia
- D low education
- E smoking
- F ApoE4
- G low physical activity

Stroke

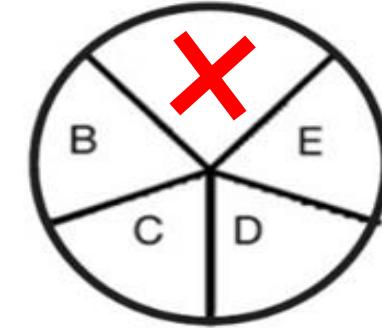
# (I) Rothman

Durch tHcy-Senkung werden andere Risikofaktoren deaktiviert!

*Sufficient cause I*



Wie wäre das Risiko  
wenn HHCY nicht wäre?



**B ApoE4**

**C hypercholesterolemia**

**D hypertension**

**E stroke**

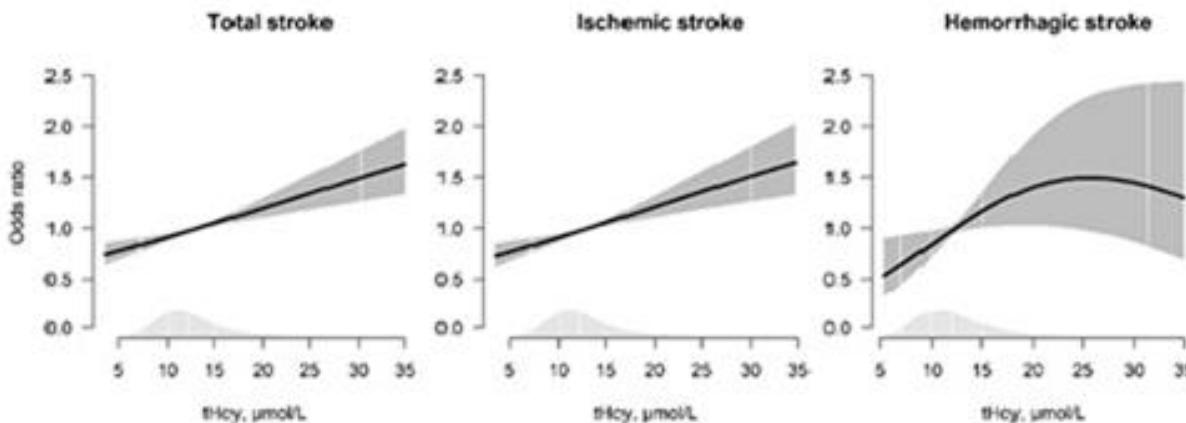
Die Prävalenz von anderen Risikofaktoren in der Zielpopulation ist entscheidend!

# Beobachtungsstudien

# Das Risiko für Gehirn Volumenverminderung (über 5 J): nach Plasma B12 und HoloTC zum Baseline

Tertiles of dependent variable	PBVL over 5 y			
	Simple model*		Adjusted model 2‡	
	OR (95% CI)	p Value	OR (95% CI)	p Value
<b>Vitamin B<sub>12</sub></b>				
>386 pmol/L	1.00 (reference)		1.00 (reference)	
308-386 pmol/L	2.89 (0.90-9.33)	0.076	4.39 (1.01-19.03)	0.048
<308 pmol/L	3.35 (1.02-11.00)	0.047	6.17 (1.25-30.47)	0.026
p Trend		0.053		0.028
<b>HoloTC</b>				
>78 pmol/L	1.00 (reference)		1.00 (reference)	
54-78 pmol/L	1.55 (0.50-4.86)	0.451	2.63 (0.63-10.92)	0.184
<54 pmol/L	2.61 (0.83-8.20)	0.100	5.99 (1.21-29.81)	0.029
p Trend		0.097		0.029

# tHcy and first stroke: significant dose-response association



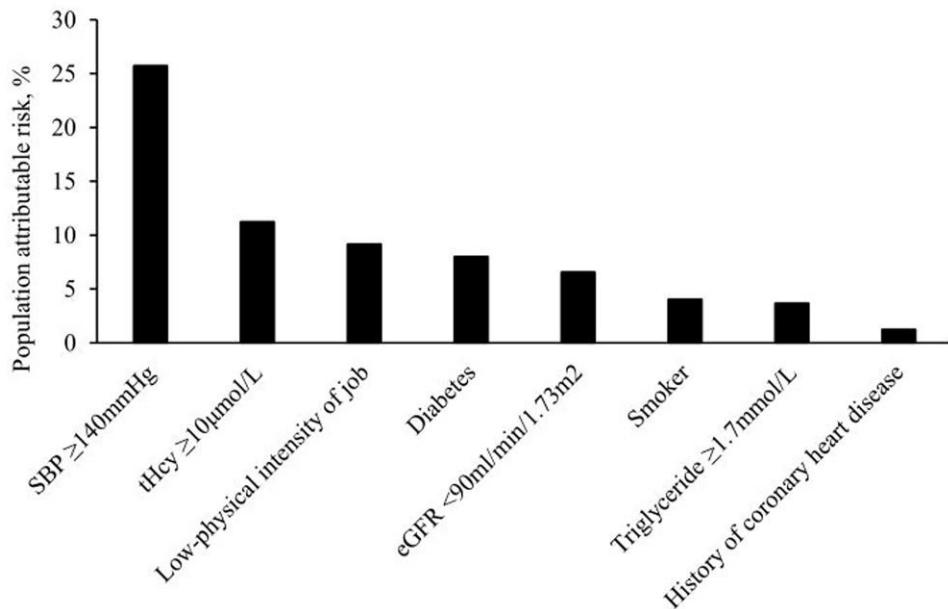
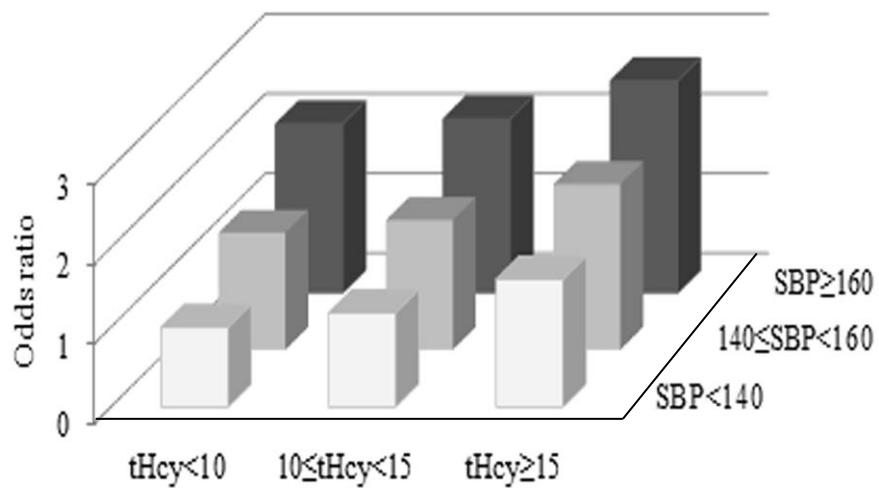
Nested case-control design, including 3,533 first stroke cases and 3,533 controls matched for age  $\pm 1$  years, sex, and residence

tHcy, $\mu\text{mol/L}$	Odds Ratio
< 10	OR = 1.00
10-15	1.11 (0.97, 1.26)
$\geq 15$	1.44 (1.22, 1.69)

Population attributable risk (PAR) for HHCY = 11%

Wie viele Fälle könnte man durch tHcy Senkung verhindern?

# Combined effects of blood hypertension and tHcy on the risk of first stroke



# HHCY & Demenz: die Assoziation aus Metaanalysen

<b>Metaanalyse (Beobachtungsstudien)</b>	<b>Relatives Risiko</b>
Van Dam, et al. 2009	RR: <b>2.5</b> (1.38-4.56)
Wald et al., 2011	OR: <b>1.50</b> (1.13-2.0)
Beydoun et al., 2014	RR: <b>1.93</b> (1.50-2.49)
Nie et al. 2014	RR: <b>1.53</b> (1.23-1.9)
Shen et al., 2015	RR: <b>1.77</b> (1.37-2.16)
Xu et al., 2015	RR: <b>1.15</b> (1.02-1.27)
Hu et al., 2016	OR TT vs. CC: <b>1.37</b> (1.15-1.63)

HHCY > 12 - 14 µmol/L

Studies overlap between the meta-analyses

# Risikoreduktion durch tHcy-Senkung? Erwartung

up to 27% of cases of dementia could be prevented by lowering tHcy

Metaanalyse	Relatives Risiko	PAR% (95%CI)
Van Dam, 2009	<b>2.50</b> (1.38-4.56)	<b>27.3 (7.5-47.1)</b>
Beydoun, 2014	<b>1.93</b> (1.50-2.49)	<b>18.9 (10.8-27.0)</b>
Nie, 2014	<b>1.53</b> (1.23-1.90)	<b>11.7 (3.8-19.6)</b>
Shen, 2015	<b>1.77</b> (1.37-2.16)	<b>16.1 (9.1-23.1)</b>
Xu, 2015	<b>1.15</b> (1.02-1.27)	<b>3.6 (0.69-6.51)</b>

PAR, Population Attributable Risk

Angenommen: Prävalenz von HHCY etwa 25% bei älteren Personen

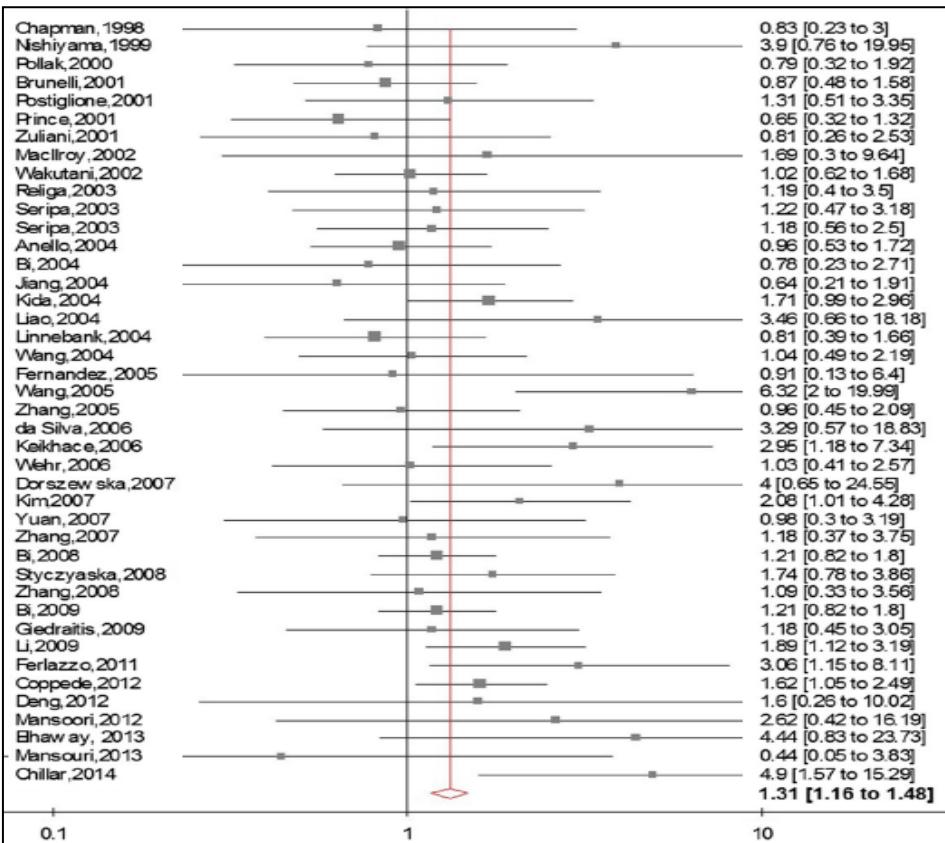
$$\text{PAR} = 100 * [P(\text{HHCY}) * (\text{RR}-1)] / 1 + [P(\text{HHCY}) * (\text{RR}-1)]$$

# Methylenetetrahydrofolate Reductase (MTHFR) C677T Polymorphism and Alzheimer Disease Risk: a Meta-Analysis

Mol Neurobiol (2017) 54:1173–1186

DOI 10.1007/s12035-016-9722-8

TT vs. CC



**OR = 1.31 (1.16–1.48)**

# Hyperhomocysteinemia: was ist normal?

Meta-analysis	Threshold
Van Dam, 2009	tHcy > 14.0, 15.0, or 15.6 µmol/L
Wald, 2011	For a 5 µmol/L increase in tHcy (i.e. 10.0 → 15.0 µmol/L)
Beydoun, 2014	Elevated tHcy (variety of cut-offs: 14.0, 15.0, 15.6, 14.6 and 12.6 µmol/L )
Nie, 2014	Elevated tHcy (variety of cut-offs: 15.8, 15.0, 14.0, 27.5, 15.4, 15.0, 13.4, 13.0, 14.3, 21.0, 15.1, 14.5, 17.0[?], 10.8 µmol/L)
Shen, 2015	Elevated tHcy (variety of cut-offs: 14.0, 12.0, 13.1, 13.3, 27.4, 15.0, 13.0, 15.0 µmol/L)
Xu, 2015	Elevated tHcy same as Shen et al.

**< 12 - 14 µmol/L**

## (II) Kausalität nach „Bradford Hill“ Kriterien

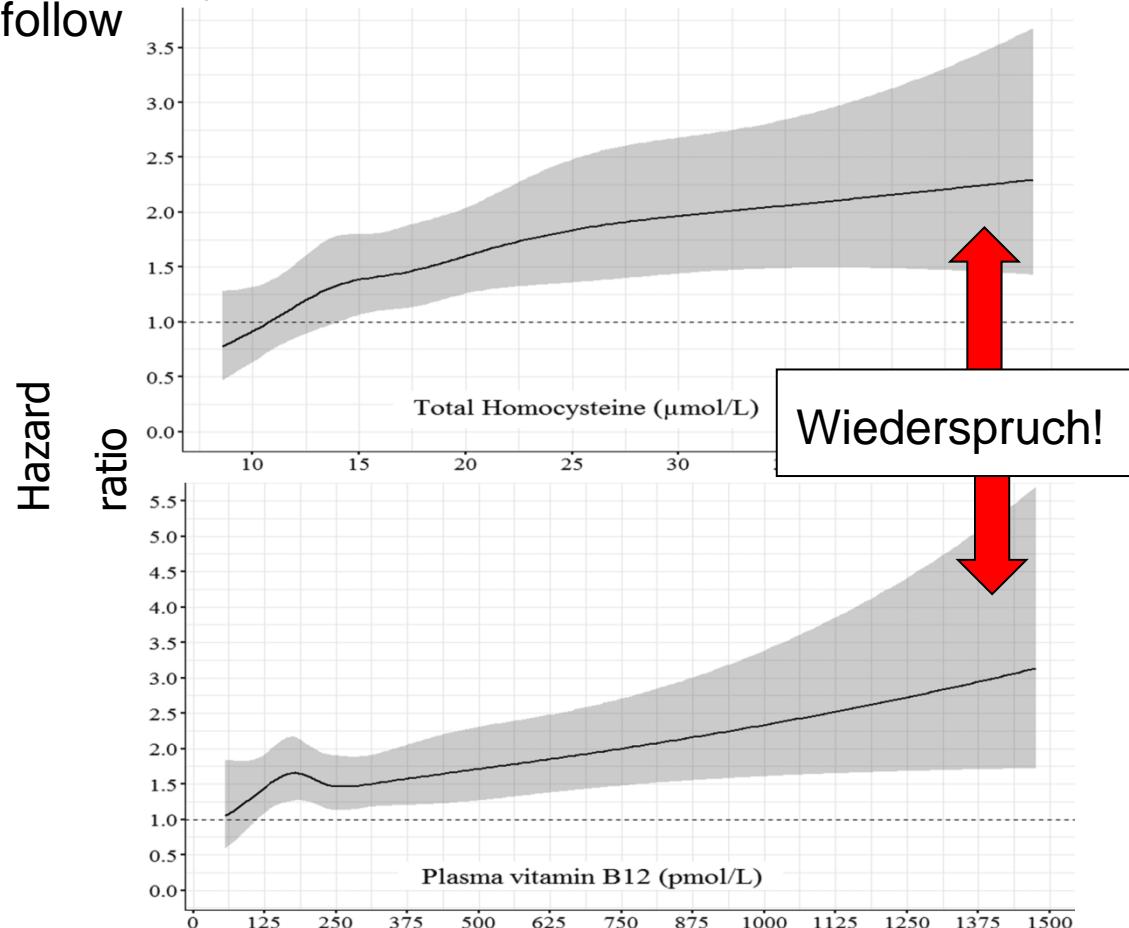
**HHCY** → **Demenz**

Strength of the association	RR (meta-analysis) = 1.93 (1.50-2.49)
Consistency	Most (not all studies)
Specificity	Not only for cognitive dysfunction
Temporality	HHCY precede cognitive decline
Dose-response	threshold > 12-14 µmol/L
Plausibility	Mechanisms (hypomethylation, oxidative stress, epigenetic, neurotransmitters, etc)
Coherence	new studies provide evidence supporting causality
Experimental evidence	some RCTs, though not all!
Analogy	MTHFR genotype associated with dementia

# Plasma tHcy and B12 in women & all-cause and cardiovascular mortality in the very old: The Newcastle 85+ Study (9-y follow



Kausalität Annahmen  
nicht möglich



# Prävention durch B-Vitamine: eine systematische Review und Meta-Analyse

## Subgroup analyses for the effects of B vitamin supplementation on the rate of cognitive decline.

### Population

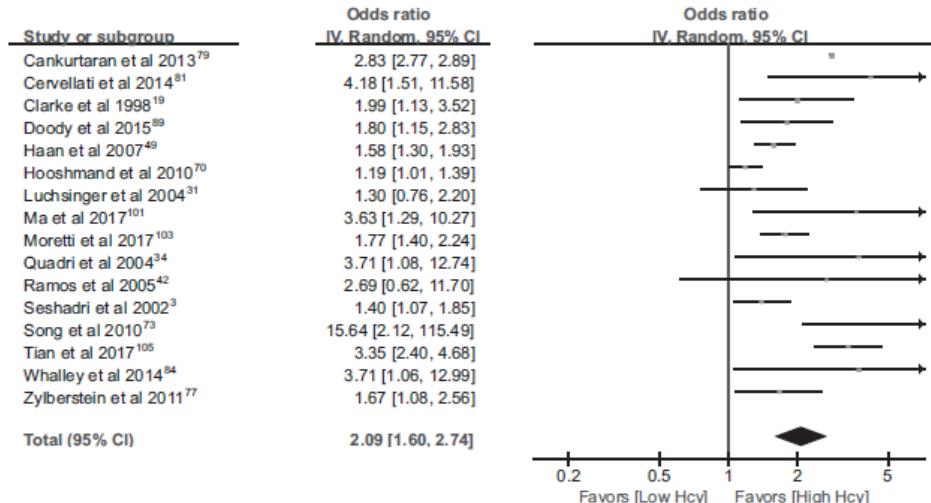
	MD	95% CI	P value	Study
The overall population	0.14	0.04 to 0.23	0.004	14
Intervention period, m				
>12	0.14	0.04 to 0.23	0.004	8
≤12	-0.01	-0.20 to 0.19	0.95	9
Baseline cognitive status				
Non-dementia	0.14	0.05 to 0.23	0.004	7
Dementia	0.14	-0.36 to 0.65	0.58	5
AD	0.29	-0.43 to 1.00	0.43	4
Baseline Hcy concentration, µmol/L				
>14	0.10	0.00 to 0.20	0.05	7
≤14	0.41	0.15 to 0.68	0.002	6
Folate fortification				
Yes	0.12	0.02 to 0.22	0.02	4
No	0.19	-0.01 to 0.40	0.07	10

Intervention länger als 12 Mo

kein Demenz zum baseline

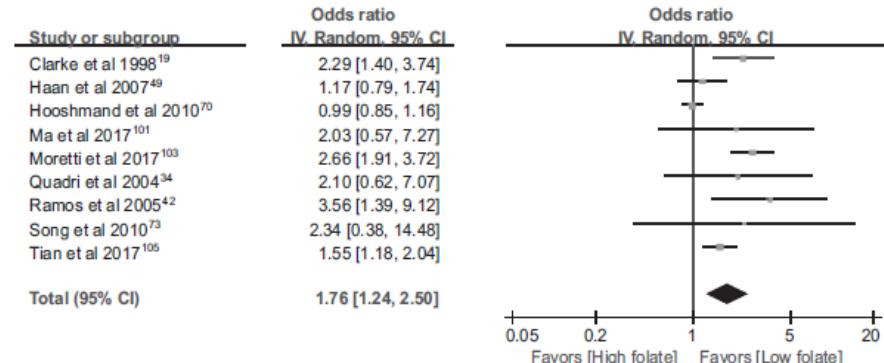
# Prävention durch B-Vitamine oder Vermeidung von HCY?

## Hcy and the risk of dementia



Heterogeneity:  $\tau^2 = 0.20$ ;  $\chi^2 = 208.87$ , df = 15 ( $P < 0.00001$ );  $I^2 = 93\%$

## Folate and the risk of dementia



Heterogeneity:  $\tau^2 = 0.18$ ;  $\chi^2 = 42.20$ , df = 8 ( $P < 0.00001$ );  $I^2 = 81\%$

## Interventionsstudien: B-Vitaminen zur Verlangsamung des kognitiven Leistungsabfalls bei älteren Menschen

Chang et al., Geriatr Nurs. 2023;51:143-9.

N = 23 trials

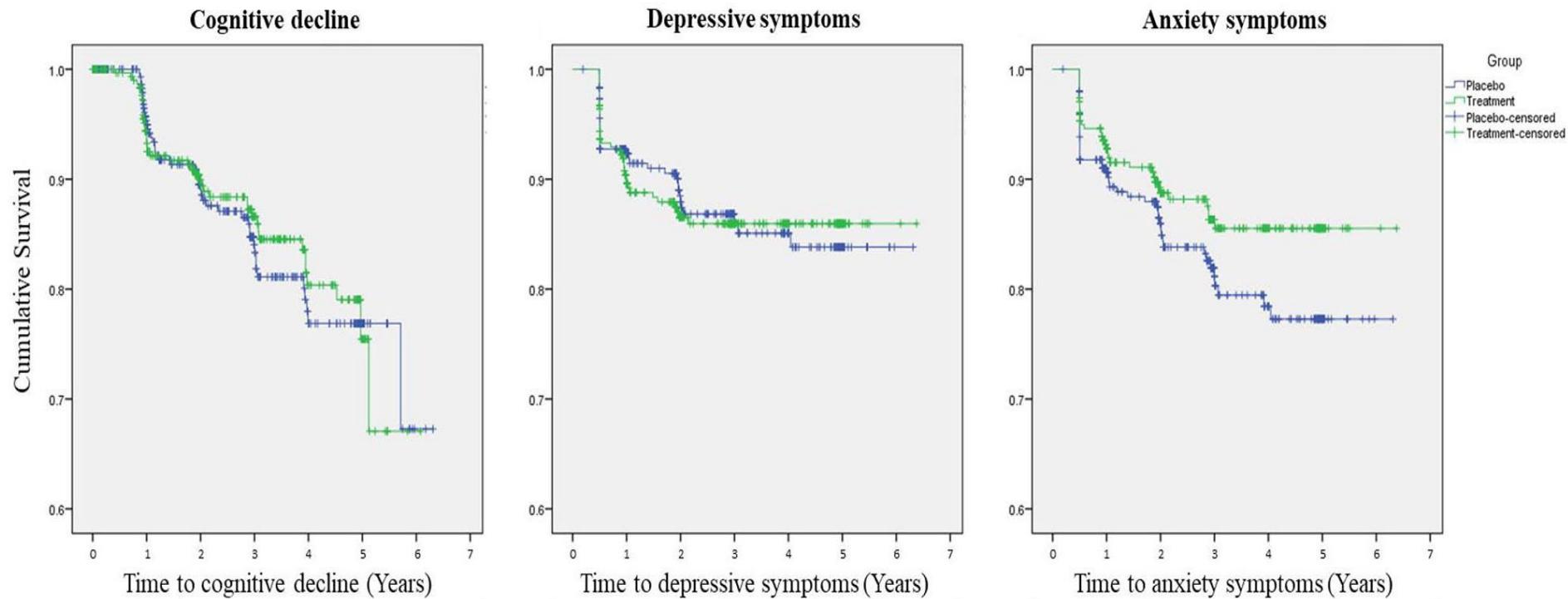
Homocysteine mean difference = -4.5; 95%CI:-5.4 to 3.6  $\mu\text{mol/L}$

The difference in the MMSE

The difference in Clinical Dementia Rating-sum of box (CDR-SOB) scores

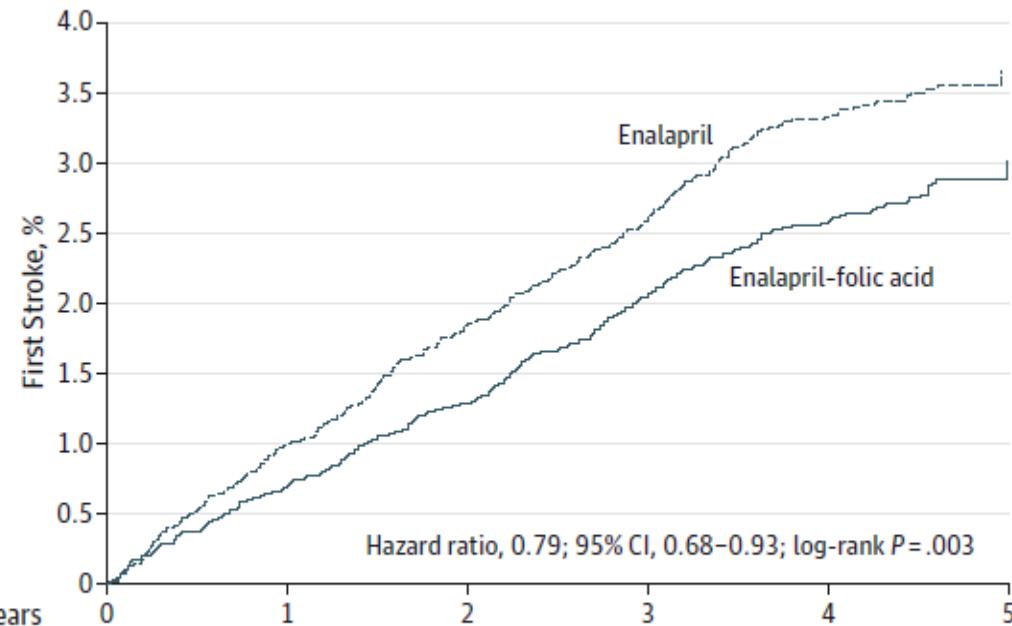
Were not significant between the vitamin and the comparator groups!

VITATOPS study- clinicaltrials.gov NCT00097669 – no effect of 25mg vitamin B6, 2mg Folic acid, and 0.5mg vitamin B12 or a placebo für 6 Mo bis 5 Jahre on cognitive edecline



# Primary Prevention of Stroke Among Hypertensive men; 800 µg/d Folic Acid

Kaplan-Meier Curves of Cumulative Hazards of First Stroke by Treatment Group



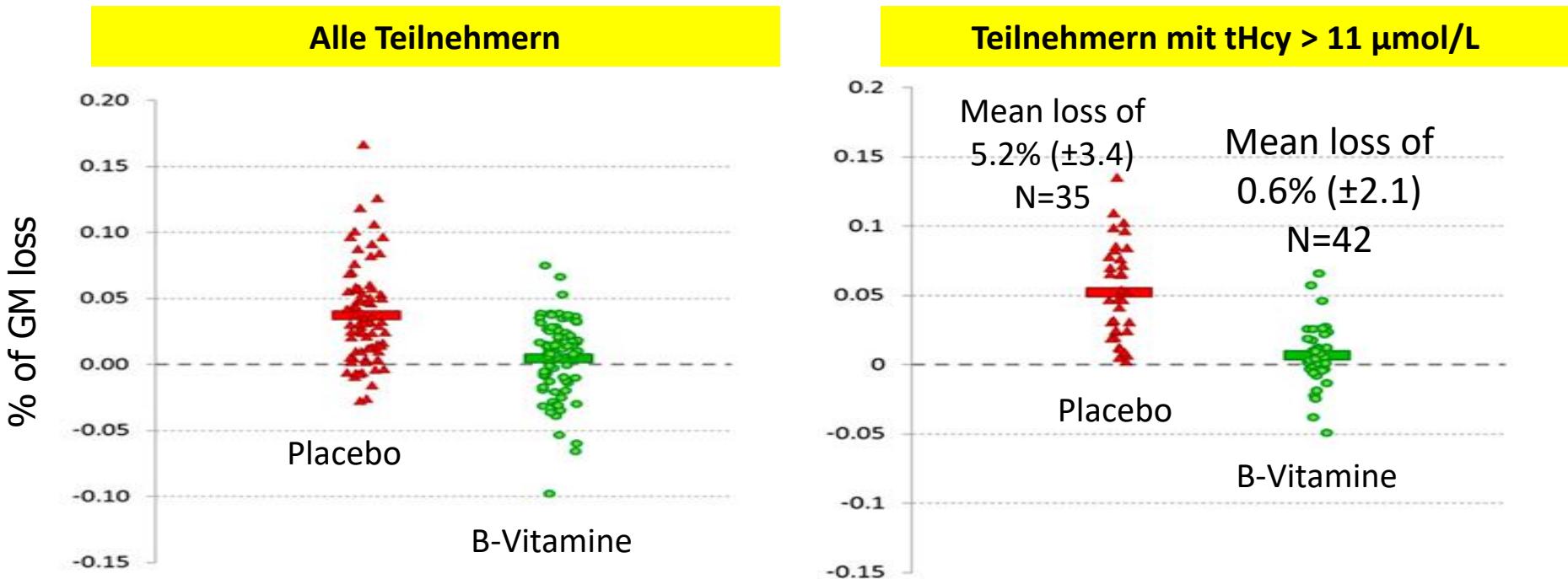
Population: Men with hypertension

Intervention:  
folic acid 0.8 mg/d + enalapril vs.  
enalapril

Median duration: 4.5 years

Outcome: Stroke

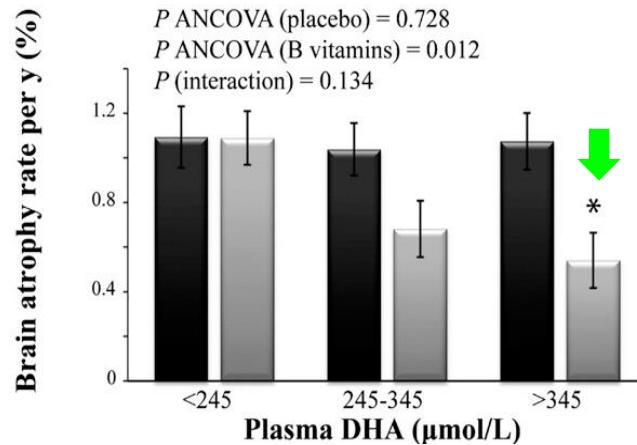
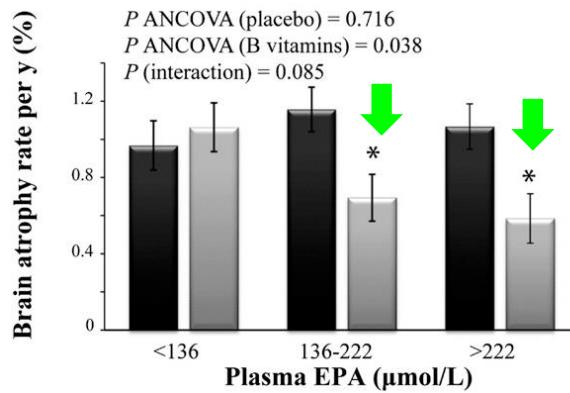
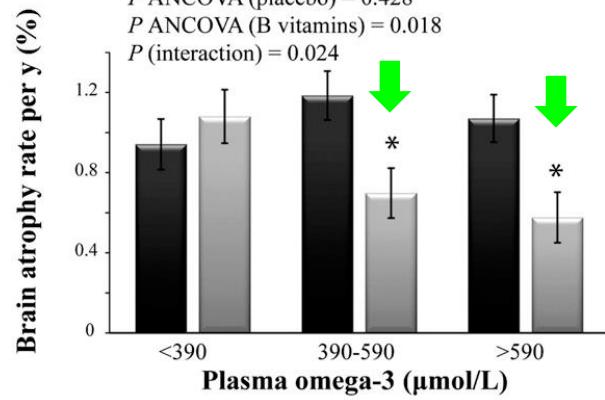
## Risikoreduktion nur wenn HCY zu Beginn der Studie erhöht war (VITACOG Trial)



Intervention: placebo vs. 0.8 mg FA, 0.5 mg B12, 20 mg B6/d; for 2 y. age  $\geq 70$  y. Outcome: % loss of **graue Substanz (MRT)**.

de Jager et al., Int J Geriatr Psychiatry 2012;27:592-600. Proc Natl Acad Sci U S A. 2013; 110: 9523–28.

# Higher Plasma DHA or Omega-3 was associated with better effect of the B-vitamins on brain atrophy rate



## Zusammenfassung: HCY-Senkung und das Demenzrisiko

Risikofaktor HHCY	HHCY oder B-Vitamin Mangel, muss vorhanden sein
Outcome	Verwendung von sensitive Testmethoden: individuelle kog. Leistungstests, Gehirnvolum, MRI
Ø Demenz zum Start	Demenz ist irreversibel ( <i>Prävention, Ø Therapie</i> )
Dauer der Intervention	> 18 Monate
Vitamin Dosierung und Kombination	<ul style="list-style-type: none"><li>• Diät Modifikation reicht nicht aus!</li><li>• Kombination von den B-vitamine Pharmakologische Dosierungen sind notwendig</li></ul>

B-Vitamine: Folat, B<sub>12</sub>, B<sub>6</sub>, B<sub>2</sub>

An aerial photograph of a large university campus nestled in a valley. The campus features numerous buildings of varying architectural styles, including modern glass-fronted structures and older stone buildings with red roofs. A network of roads and parking lots connects the buildings. The entire campus is completely surrounded by a dense, lush green forest, creating a serene and isolated atmosphere.

**Vielen Dank**