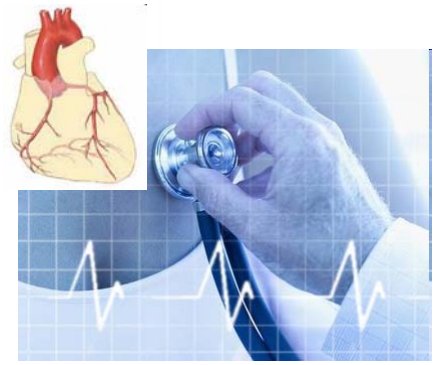
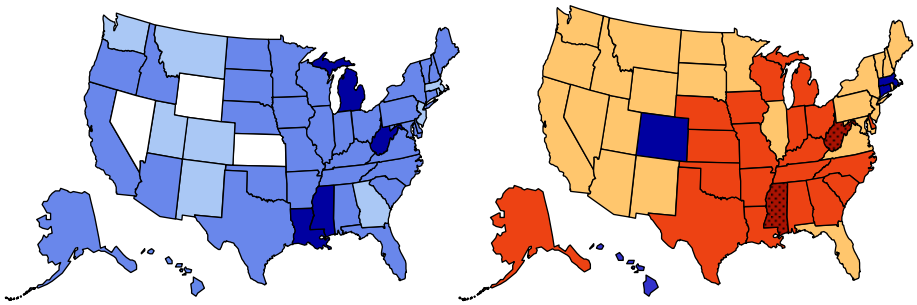
Bioactive compounds in food to prevent dyslipidemia and dyslipoproteinemia, a major cause for cardiovascular disease



A. Parlesak, DTU Systems Biology, CBS
J. Starke, DTU Mathematics
J. Eckhold, Hohenheim University, Stuttgart, Germany
K. Winkler, University Medical Center Freiburg, Germany
C. Schäfer, Robert-Bosch-Hospital Stuttgart, Germany

ØFN seminar, 9.3.2010

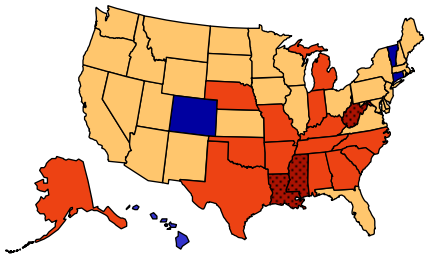
Obesity Trends Among U.S. Adults
1991 - 2006



source: http://www.cdc.gov/nccdphp/dnpa/obesity/trend/maps/index.htm

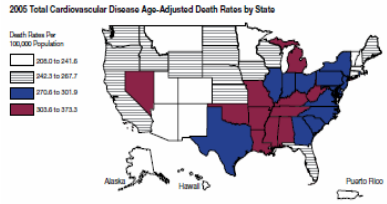
Overweight Prevalence and Cardiovascular Disease

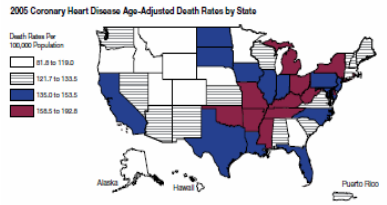
2005



Percentage of population having a BMI ≥ 30

15%–19% 20%–24% 25%–29% ≥30%

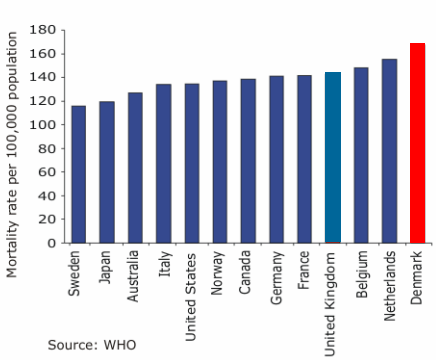




Source: CDC

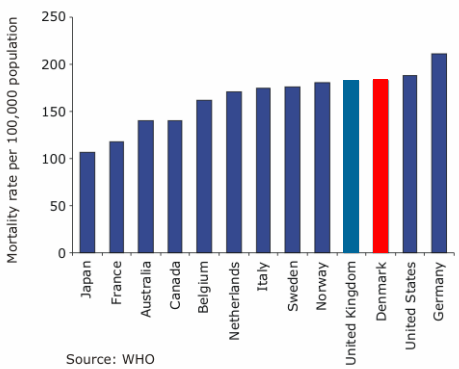
Mortality Rates for Cancer And Cardiovascular Disease

Cancer



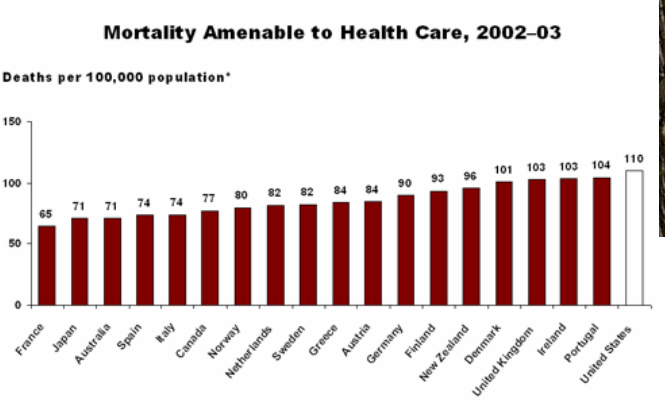
Source: WHO

Cardiovascular Disease

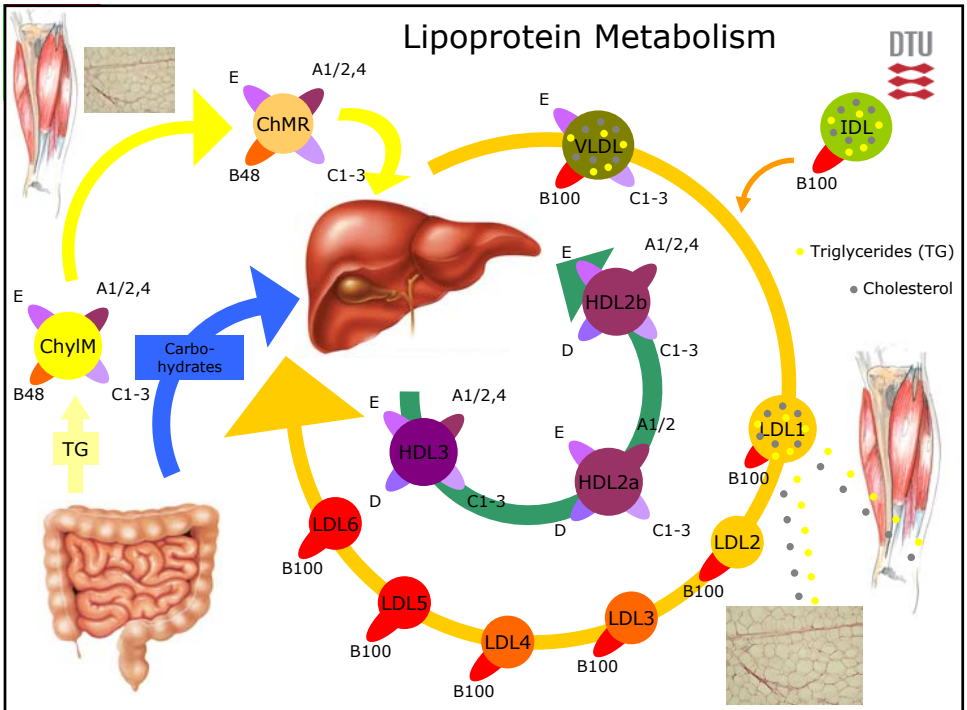


Source: WHO

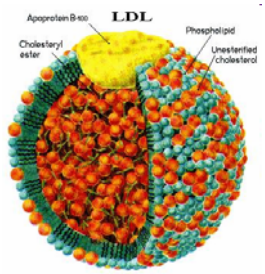
Preventable Mortality Rate



Lipoprotein Metabolism



Lipoproteins: Key Risk Factors of Atherosclerosis



- Concentration of lipoproteins: atherogenic (i.e. low density lipoprotein, LDL) and antiatherogenic (i.e. high density lipoprotein, HDL)
  -parameters: c(cholesterol)/triglycerides in LDL/HDL, ApoB, ApoA1/2
- Adhesion/activation of phagocytosing cells (monocytes), systemic sub-clinical inflammation
  -parameters: hsCRP
- Tendency towards clot formation
  -parameters: c(fibrinogen)
- Blood pressure

General Approach to Study Causes of Diseases

1. **Epidemiological survey**: identification of relevant factors
2. **Hypothesis-driven approach** of factor identification:
   - Hypothesis generation:
     Specific behavior enhances disease onset
   - Study conduction (i.e. intervention)
   - Acceptance or rejection of hypothesis

Disadvantages:

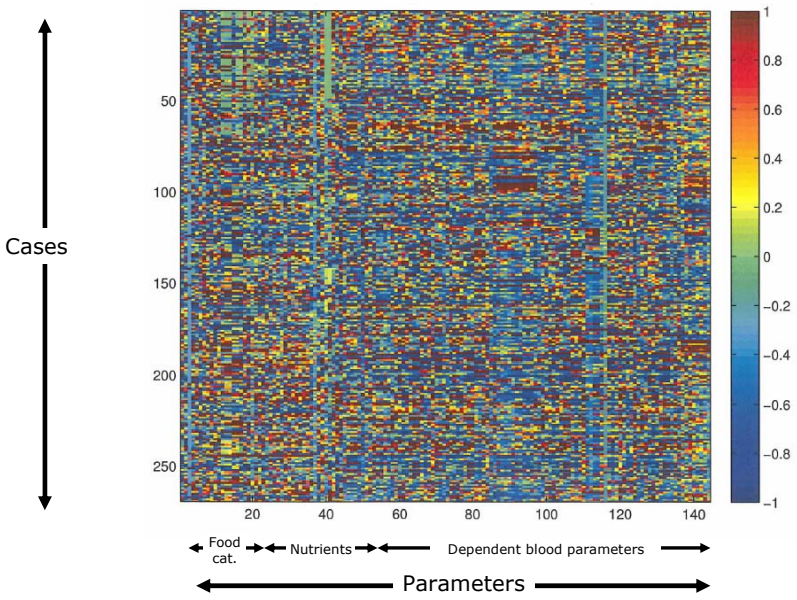
Fortuitous generation of hypotheses harboring the danger to
- *miss relevant factors*
- *neglecting synergistic/antagonistic effects*

***Goal**: Achieve systemic solutions that include comparability of impact of single factors*

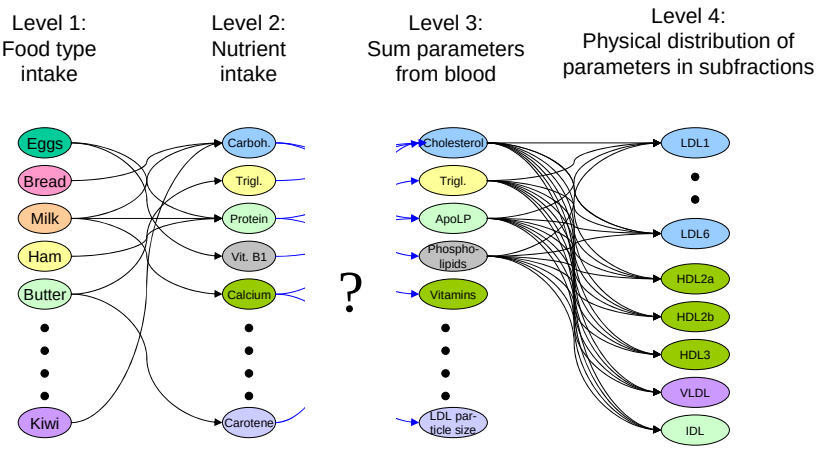
Which Nutritional/Life Style Factors Can Contribute to CVD Risk Reduction? – Study design

- **Aim:** PhD study to identify changes in risk factors of coronary vascular disease (CVD) due life style factors and consumption of nutrients
- **Type of study:** cross-sectional prospective study
- **Study participants:** 269 apparently healthy men, working, without diabetes or treatment of high blood pressure
- **Main Outcomes:** Distribution of cholesterol(-esters), apolipoproteins, and phospholipids in lipoprotein-subfractions (lipoproteome).

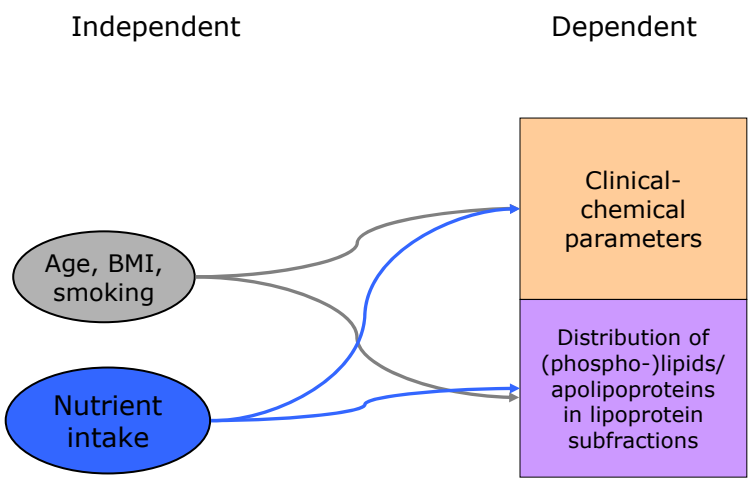
Standardized Color-Coded Visualization of Results



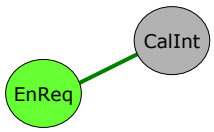
Evaluation Levels of Explorative Data Investigations



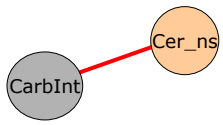
Grouping for Investigation of Interaction

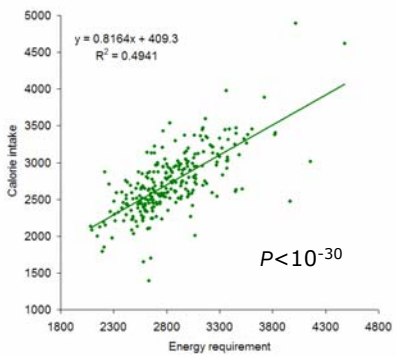


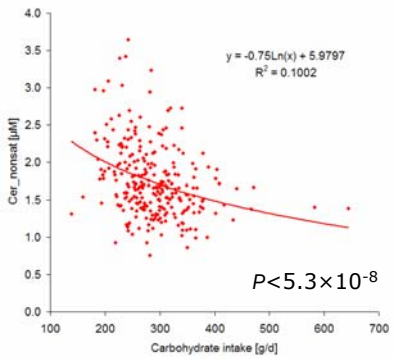
Visualization of Non-Parametric Correlations (Spearman's test)



- Nodes represent parameters
- Lines represent significant correlation
  - green: positive
  - red: negative
- Thickness of lines indicates significance level

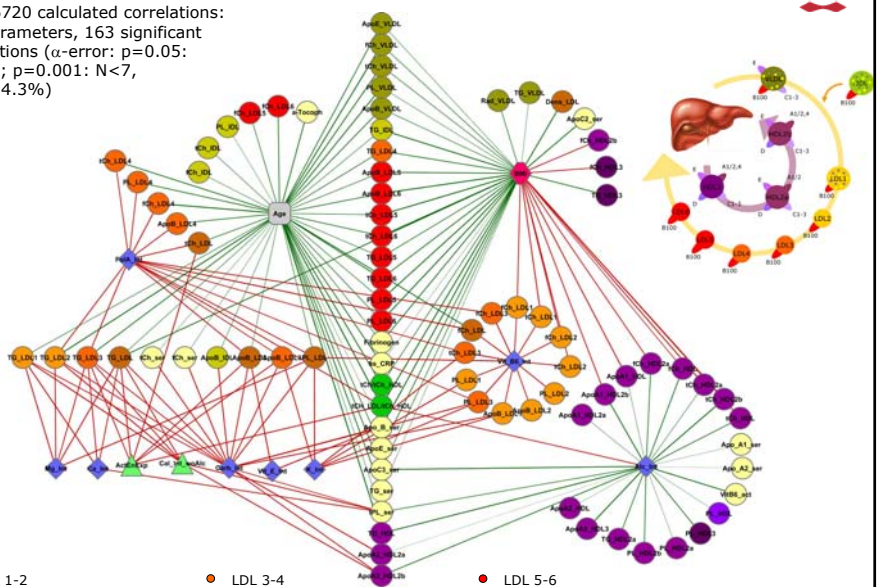






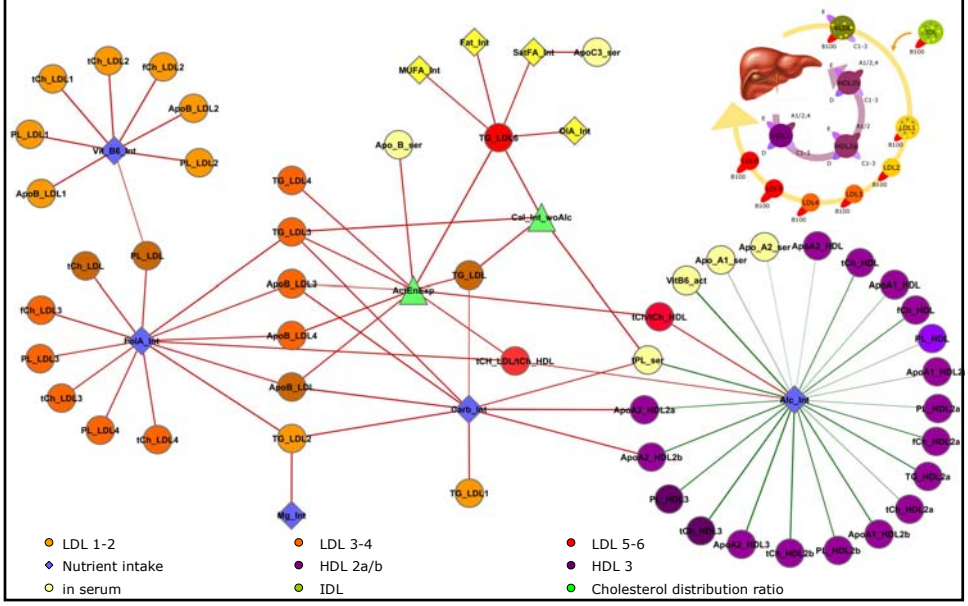
Correlations between Nutrient Intake and Lipoprotein Composition

From 6720 calculated correlations: 178 parameters, 163 significant correlations (α-error: p=0.05: N~336; p=0.001: N<7, FDR < 4.3%)

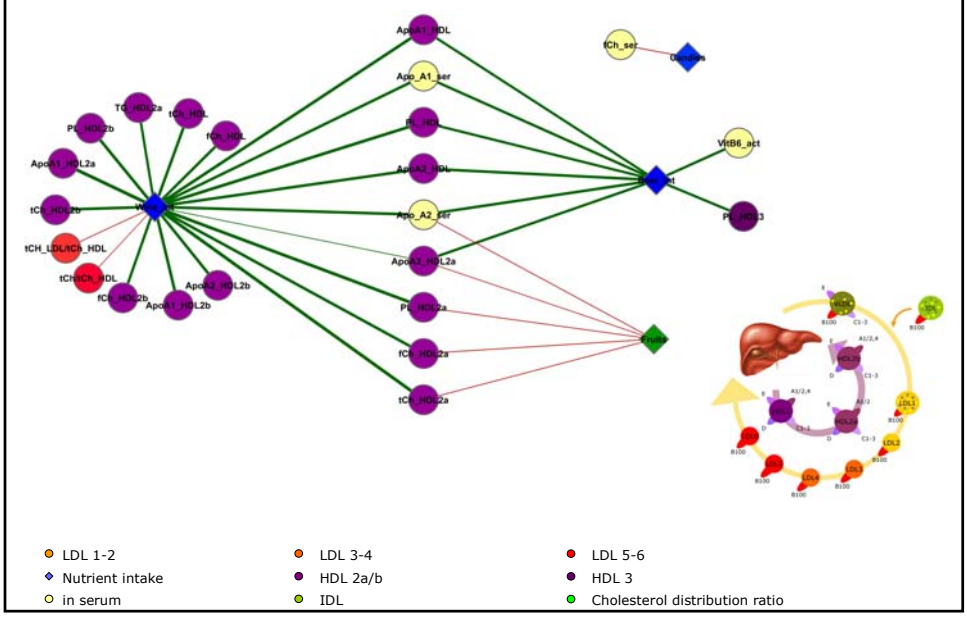


- LDL 1-2
- LDL 3-4
- LDL 5-6
- Nutrient intake
- HDL 2a/b
- HDL 3
- in serum
- IDL
- Cholesterol distribution ratio

Correlations between Nutrient Intake and Lipoprotein Composition, Adjusted for Age and BMI



Correlations between Food Category Intake and Lipoprotein Composition, Adjusted for Age and BMI



Significant Coefficients of General Linear Models for Cholesterol, TG, PL, ApoB, ApoA1/2 in LDL, LDL1, LDL3, LDL5, and HDL

c(BP) = a0 +a1*(Age) + a2*(BMI) + a3*(VitB6_Int) + a4*(FolA_Int) + a5*(Alc_Int) + a6*(Carb_Int) + a7*(ActEnExp)

BP, blood parameter: cholesterol, triglycerides, phospholipids, ApoB, Apo A1, ApoA2

P<0.05; P<0.01; **P<0.001**

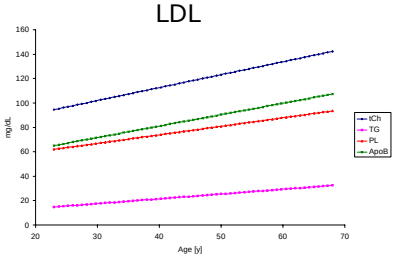
		tCh	TG	PL	ApoB	ApoA1	ApoA2
LDL	Age	**0.299**	**0.232**	**0.313**	**0.323**		
	BMI		0.211				
	VitB6_Int						
	FolA_Int			-0.162			
	Alc_Int				-0.119		
	Carb_Int						
	ActEnExp		-0.216				
HDL	Age		0.137				
	BMI	**-0.325**		**-0.235**		**-0.316**	
	VitB6_Int						
	FolA_Int						
	Alc_Int	**0.272**	**0.203**	**0.369**		**0.339**	**0.413**
	Carb_Int			-0.182		-0.186	
	ActEnExp	0.245		**0.255**		0.238	

		tCh	TG	PL	ApoB
LDL1	Age	0.145	0.210	0.165	0.155
	BMI	-0.200		-0.168	-0.155
	VitB6_Int	**-0.213**		-0.212	-0.216
	FolA_Int				
	Alc_Int				
	Carb_Int				
	ActEnExp				
LDL3	Age	0.143	0.164	0.156	0.162
	BMI				
	VitB6_Int				
	FolA_Int	-0.195		-0.209	-0.184
	Alc_Int				
	Carb_Int				
	ActEnExp				
LDL5	Age	**0.291**	**0.237**	**0.303**	**0.285**
	BMI	0.166	**0.266**	0.172	0.203
	VitB6_Int				
	FolA_Int				
	Alc_Int				
	Carb_Int				
	ActEnExp	-0.243	**-0.256**	-0.225	-0.258

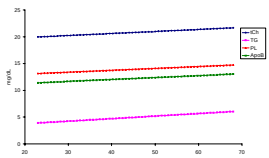
Average Aging Man, Low Alcohol Consumption

General Linear Models for Cholesterol, TG, PL, $ApoA_{1/2}$ in LDL, LDL1, LDL3, LDL5, and ApoB in HDL

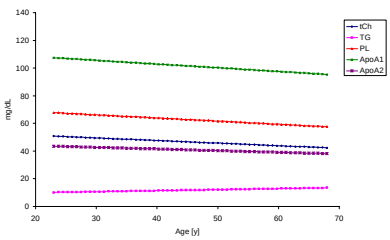
LDL



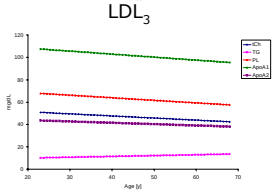
LDL_1



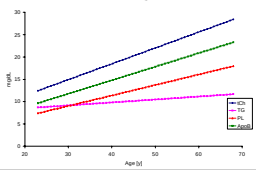
HDL



LDL_3



LDL_5

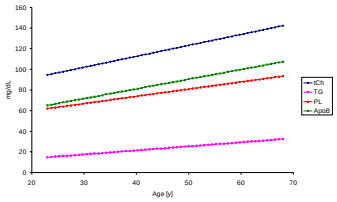


23	Age [y]	67
24	BMI [kg/m²]	27
2.0	VitB6_Int [mg/d]	1.9
135	FolA_Int [µg/d]	124
5	Alc_Int [g/d]	5
305	Carb_Int [g/d]	269
941	PhysAct [kcal/d]	877

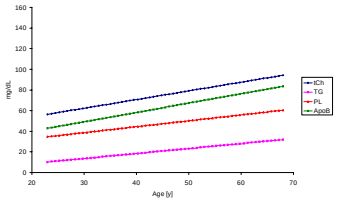
Average Aging Man,
Low Alcohol Consumption

Average Aging Man, Opt. Intake
of Folic Acid, Vit. B6, Alcohol

LDL

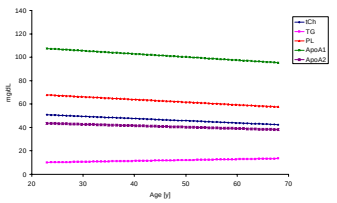


LDL

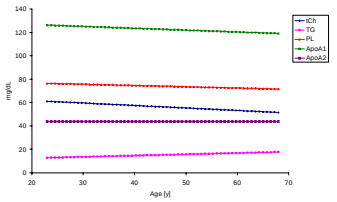


23	Age [y]	67
24	BMI [kg/m²]	27
2.5	VitB6_Int [mg/d]	4.0
400	FolA_Int [µg/d]	400
20	Alc_Int [g/d]	40
305	Carb_Int [g/d]	269
941	PhysAct [kcal/d]	877
0	%	100

HDL



HDL



The Framingham Heart Study

- **Original Cohort**
  1948: 5,209 men and women (30 - 62 years) from Framingham, Massachusetts: Every 2. year extensive physical examinations and lifestyle interviews related to CVD development.
- **Offspring Cohort**
  1971: 2. generation group - 5,124 of the original participants' adult children and their spouses - to participate in similar examinations
- **Generation III Cohort**
  since 2002: 3. Generation (the children of the Offspring Cohort) is currently being recruited and examined (also genetic factors)
  Goal: recruit and examine 3,500 grandchildren of the original cohort.

Further Progression of the Framingham Risk Score (FRS): CVD 10-Year Risk (β) Prediction Based on a Cox Model

$$\beta = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta i Xi - \sum_{i=1}^{p} \beta i \overline{Xi})}$$

$S_0(t)$: baseline survival at follow-up time t
Xi: log-transformed value of the *i*th risk factor
β_i: estimated regression coefficient (log hazard ratio)

p: number of risk factors
Xi: corresponding mean to Xi

Case: 61 year aged women, total cholesterol 180 mg/dL, HDL-cholesterol 47 mg/dL, (untreated) systolic blood pressure 124 mm Hg, smoker: yes, diabetes: no

$$\sum_{i=1}^{p} \beta_i X_i = 2.3289 * \log(61) + 1.2090 * \log(180) - 0.7083 * \log(47) + 2.7616 * \log(124) + 0.5287 * 1 + 0.6915 * 0 = 26.9653$$

$$\beta = 1 - 0.95012^{\exp(26.9653 - 26.1931)} = 0.1048 \approx 10.5\%$$

D'Agostino et al., Circulation 2008

Estimated 10-Year Risk Reduction for CVD (β) after Intervention Based on the Framingham Risk Score Cox Model

$$\beta = 1 - S_0(t)^{\exp(\sum_{i=1}^{p} \beta i Xi - \sum_{i=1}^{p} \beta i \overline{Xi})}$$

$S_0(t)$: baseline survival at follow-up time t
Xi: log-transformed value of the *i*th risk factor
β_i: estimated regression coefficient (log hazard ratio)

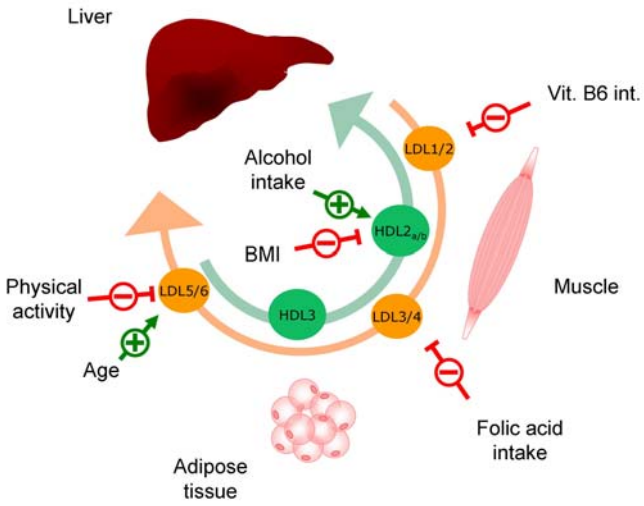
p: number of risk factors
Xi: corresponding mean to Xi

Case: 65 year aged man, total cholesterol 221 mg/dL (183), HDL-cholesterol 43 mg/dL (52), (untreated) systolic blood pressure 145 mm Hg, smoker: no/yes, diabetes: no

	Average aging man, low alcohol consumption	Average aging man, opt. intake of folic acid, vit. B6, and alcohol
Non-smoker:	β = 26.8 %	β = 18.9 %
Smoker:	β = 45.1 %	β = 33.3 %

D'Agostino et al., Circulation 2008

Summary



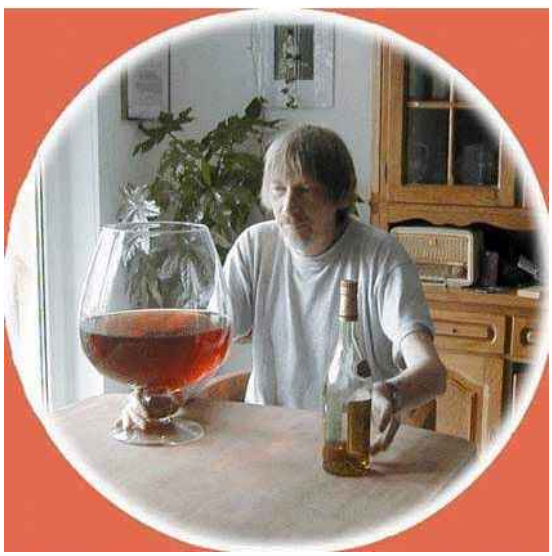
Conclusion I

- Most important key factors of **lipoproteome** modulation are **age**, **BMI**, **motion**, and the intake of **alcohol, carbohydrates, Vit. B6,** and **folic acid**.
- Each of these factors affects a different part of the lipoproteome: **ethanol** affects **HDL** composition only, **folic acid** impacts **LDL3/4**, **physical activity** changes **LDL5/6**, **Vit. B6** intake modifies **LDL1/2.**
- While **ethanol** and **vitamin B6** antagonize rather **BMI**-induced changes of the lipoproteome, **folic acid** antagonizes rather **age**-induced alterations.
- **Fat** and **cholesterol** intake has **barely any** effect on the composition of the **lipoproteome**.

Conclusion II

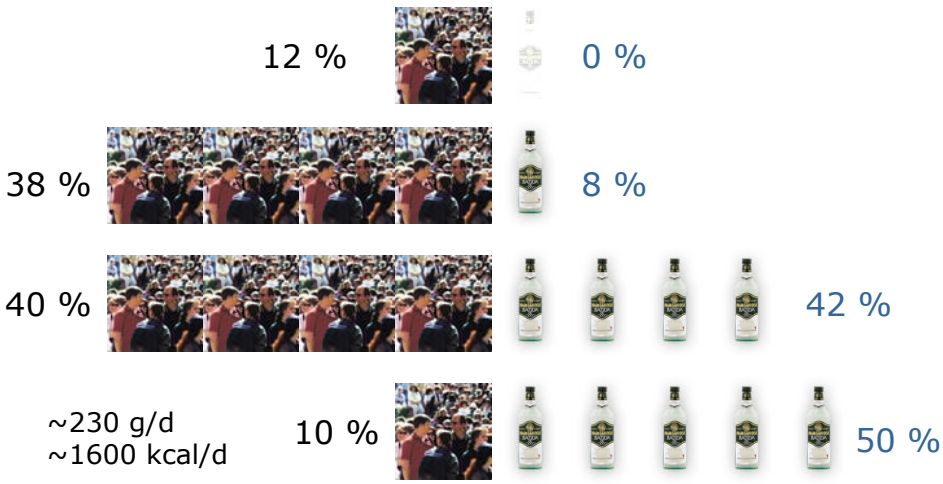
- Due to the "aging" of **lipoproteome** profile, **BMI** and nutritional factors (alcohol, vit. B6, and folic acid) can be seen to have "**pro-aging**" or "**anti-aging**" effects.
- **Wine** has the highest influence on the **lipoproteome** compared to other alcoholic beverages, much higher than any other food category, but **beer** contributes significantly to **vit. B6** supplementation.
- Due to their **different target lipoproteins**, the **highest intervention success** can be expected by **using synergistic effects of single factors** of life style and nutrition.

My Doctor said "Only 1 glass of alcohol a day". I can live with that.



Alkohol Consumption in Central Europe

- Percentage of population
- Percentage of alcohol consumption



Alcohol Abuse in Europe

- ~ 3-4% of all citizens in Western Europe are alcohol abusers that require treatment (2,000,000 Germans, 160,000 Danish citizens).
- **40.000 deaths/year** are caused by alcohol abuse.
- ~2.500 people/year die in **traffic accidents** with alcohol enrolled.
- 5-10% of employees: **alcohol dependent**
- Each 6. single case **dismissal**: due to alcohol abuse
- Each 4. **work accident**: consequence of alcohol abuse
- 2.500 babies are born with **alcoholic embryopathia** (fetal alcohol syndrome, FAS)

Deutsche Hauptstelle gegen die Suchtgefahren (ed.) Jahrbuch Sucht 2001