International Task Force for Prevention Of Coronary Heart Disease

Coronary heart disease and stroke:
Risk factors and global risk

Slide Kit 5

PROCAM
(**Pro**spective **Ca**rdiovascular **M**ünster Heart Study)

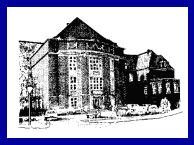
Diabetes mellitus

Diabetes mellitus as a risk factor for myocardial infarction

TABLE OF CONTENT

Slide 1:

PROCAM (Münster Heart Study): Mean values of age-standardized factors in middle aged men with and without diabetes



PROCAM (Münster Heart Study): Mean Values of Age-Standardized Factors for Male Participants Aged 40-65 Years, With and Without Diabetes Mellitus

Variable	non-diabetics (n = 4,430)	diabetics (n = 419)	p
Age (years)	49.0 (6.2)	51.2 (6.2)	<0.001
Cholesterol (mg/dl)	224.5 (41.1)	231.9 (48.4)	<0.003
HDL-Cholesterol (mg/dl)	45.4 (12.3)	43.0 (11.8)	<0.001
LDL-Cholesterol (mg/dl)*	149.1 (36.5)	150.7 (39.4)	n.s.
Cholesterol/HDL-Cholesterol ratio	5.3 (1.6)	5.8 (2.6)	<0.001
LDL-Cholesterol/HDL-Cholesterol	3.5 (1.2)	3.7 (1.3)	<0.02
Triglycerides (mg/dl)+	132.6	167.7	<0.001

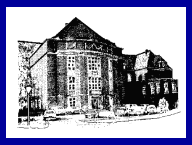
* n=4,292 in non-diabetics, n=389 in diabetics
\+ geometric mean
Values are mean and standard deviation (in brackets) unless otherwise indicated

Mean values of age-standardized factors in middle aged men with and without diabetes

This slide summarizes the mean levels of important coronary heart disease risk variables among diabetic and non-diabetic participants of the PROCAM heart study. As can be seen, total cholesterol, HDL cholesterol level, total cholesterol to HDL cholesterol ratio, LDL cholesterol / HDL cholesterol ratio and the triglyceride level were all significantly greater in diabetics than in non-diabetics. Note, however, that the LDL cholesterol level did not differ significantly between diabetic and non-diabetic middle aged men in PROCAM (see comment to slide 3).

Slide 2:

PROCAM (Münster Heart Study): Mean values of age-standardized risk factors in middle aged men with and without diabetes



PROCAM (Münster Heart Study): Mean Values of Age-Standardized Factors for Male Participants Aged 40-65 Years, With and Without Diabetes Mellitus

Variable	non-diabetics (n = 4,430)	diabetics (n = 419)	p
Age (years)	49.0 (6.2)	51.2 (6.2)	<0.001
Systolic blood pressure (mm Hg)	132.5 (18.8)	143.5 (21.0)	<0.001
Diastolic blood pressure (mm Hg)	86.4 (11.2)	90.1 (11.8)	<0.001
Body mass index (kg/m^2)	26.2 (3.0)	27.8 (3.4)	<0.001
Fibrinogen (mg/dl)*	261.5 (57.1)	265.0 (54.9)	n.s.

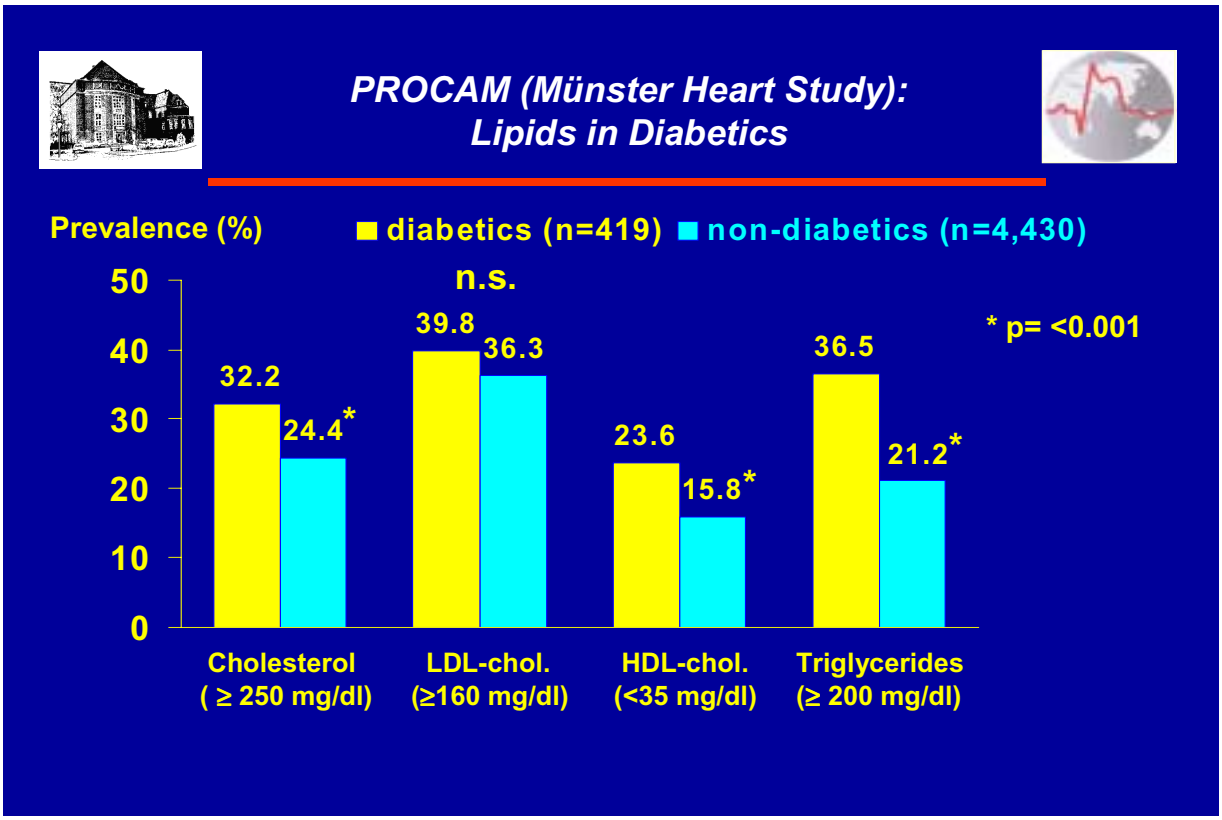
* n=2,569 in non-diabetics, n=211 in diabetics
Values are mean and standard deviation (in brackets)

Mean values of age-standardized risk factors in middle aged men with and without diabetes

This slide shows non-lipid related CHD risk factors among diabetic and non-diabetic middle aged men in PROCAM. Note, that the systolic and diastolic blood pressure, and body mass index were significantly greater in diabetics than in non-diabetics. The diabetics were also slightly older than the non-diabetics. There was no difference in fibrinogen level between diabetics and non-diabetics.

Slide 3:

PROCAM (Münster Heart Study): Lipid levels in diabetic and non-diabetic middle aged men in the PROCAM Heart Study

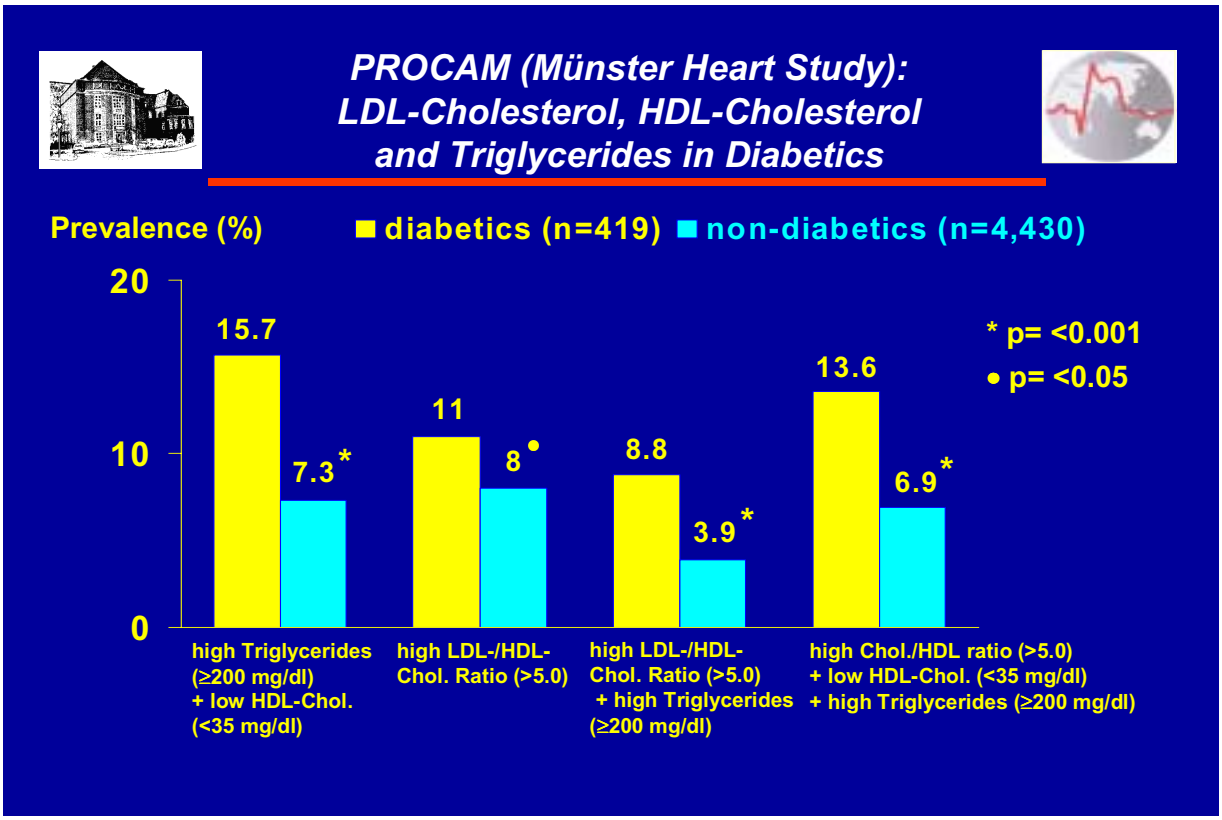


Lipid levels in diabetic and non-diabetic middle aged men in the PROCAM Heart Study

This slide shows the prevalence of hypercholesterolemia (>= 250 mg/dl), a high level of LDL cholesterol (>= 160 mg/dl), a low level of HDL cholesterol (< 35 mg/dl), or a high level of triglycerides (>200 mg/dl) among middle aged diabetic and non-diabetic men in the PROCAM Heart Study. It is clear from this data that hyperlipidemia is more prominent in diabetic subjects. This particularly relates to a high triglyceride and low HDL level. Hypercholesterolemia was also significantly more common in diabetics. Of note is the fact, however, that high levels of LDL cholesterol were not significantly more common in diabetic than in non-diabetic middle aged men in the PROCAM Heart Study.

Slide 4:

PROCAM (Münster Heart Study): The lipid triad in diabetic subjects

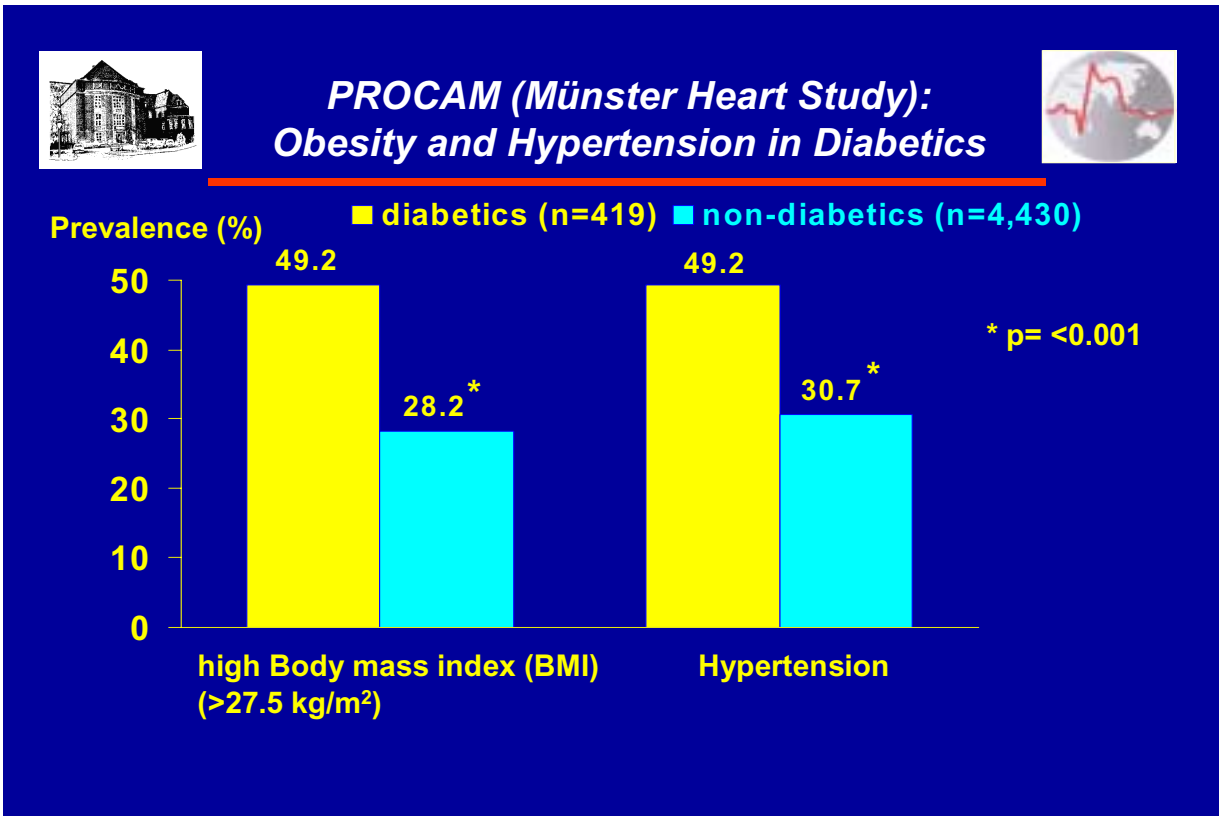


The lipid triad in diabetic subjects

The lipid triad refers to the combination of high LDL cholesterol, low HDL cholesterol and high triglyceride levels. As shown on the previous slide, low HDL cholesterol und high triglycerides are a particular feature of diabetes mellitus. This slide shows the prevalence of the combination of high triglycerides and low HDL cholesterol, of an LDL / HDL cholesterol ratio of >5, of an LDL / HDL cholesterol ratio >5 together with high triglycerides, and of a total cholesterol to HDL cholesterol ratio >5 together with a low HDL cholesterol and high triglycerides among diabetic and non-diabetic middle aged men in the PROCAM Heart Study. It is clear from this slide that all of these metabolic abnormalities are more common in diabetic than in non-diabetic men. This particularly applies to combinations which include HDl and triglycerides. The LDL / HDL cholesterol ratio by contrast was only slightly more prevalent in diabetics than in non-diabetics. This is in agreement with the small change in LDL observed in diabetic subjects as shown in slide 3.

Slide 5:

PROCAM (Münster Heart Study): Obesity and hypertension in diabetes

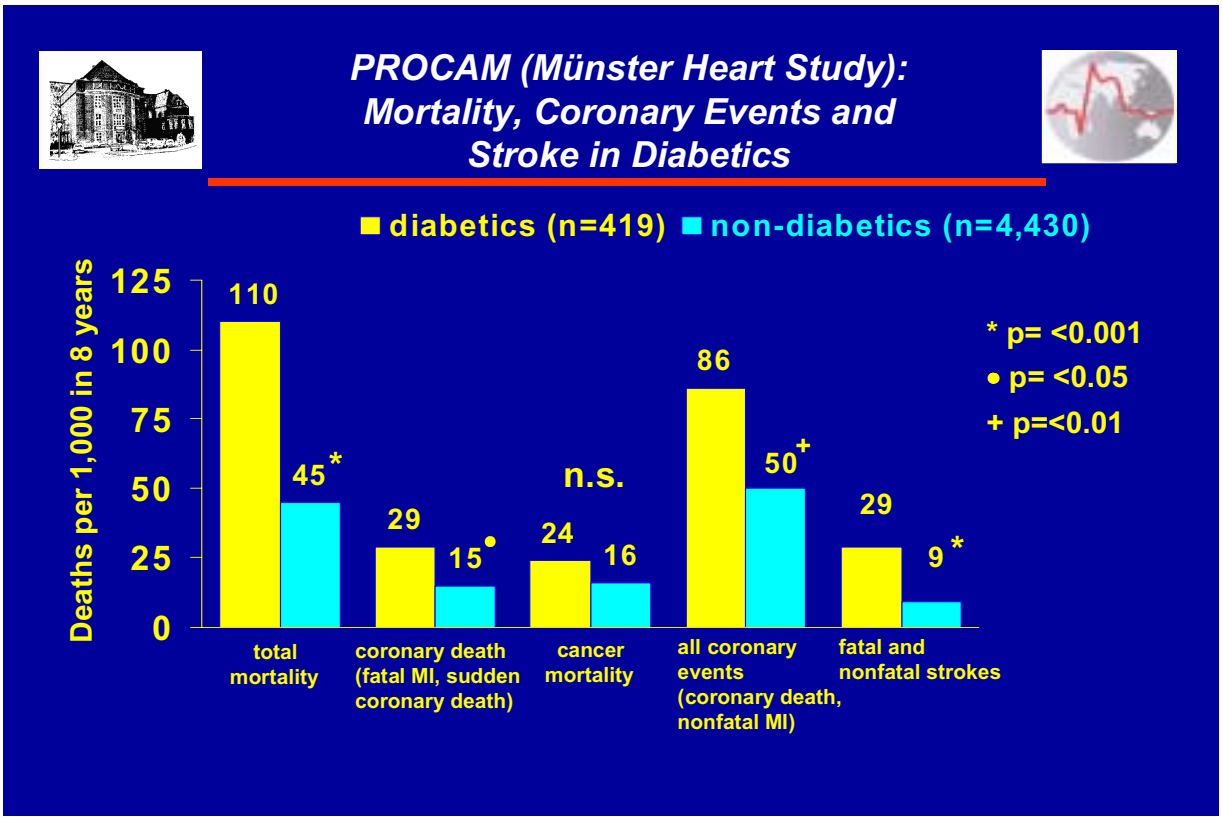


Obesity and hypertension in diabetes

One of the most important findings in the PROCAM Heart Study was the recognition of the central role of the metabolic syndrome in coronary risk. In fact, among survivors of myocardial infarction in PROCAM, this was the single most common lipid disturbance. The metabolic syndrome refers to a cluster of metabolic abnormalities comprising hyperinsulinemia, insulin resistance, and the lipid triad (high total cholesterol, low HDL cholesterol, high triglycerides), together with visceral or truncal obesity, and hypertension. This slide shows two important components of the metabolic syndrome, body mass index and hypertension, among diabetic and non-diabetic middle aged men in PROCAM. As might be expected, obesity (body mass index >27,5 kg/m^2) was twice as common in diabetics as in non-diabetics. Hypertension (systolic >=140 mmHg and / or diastolic >= 90 mmHg) was 60% more common in diabetics than in non-diabetics.

Slide 6:

PROCAM (Münster Heart Study): Mortality, coronary events and stroke in diabetics



Mortality, coronary events and stroke in diabetics

Together with smoking, diabetes mellitus is probably the strongest predictor of overall mortality. This is clear from the data from the PROCAM Heart Study presented on this slide. It can be seen that total mortality in diabetics was more than twice that of non-diabetics. This excess mortality in diabetes is explained largely by cardiovascular mortality. As is shown on this slide, coronary death was twice as common in diabetics than in non-diabetics and coronary events (coronary death + non-fatal myocardial infarction) was also almost twice as common in diabetics than in non-diabetics. Interestingly, stroke mortality was three times as common in diabetics as in non-diabetics. This latter finding has been reported in other studies but has received little attention to date. For completeness, cancer mortality is also shown on this slide. Mortality rates in cancer were similar in diabetics and non-diabetics.

Slide 7:

PROCAM (Münster Heart Study): Risk factors for type 2 diabetes mellitus in PROCAM

PROCAM (Münster Heart Study): Prevalence and Incidence of Diabetes Mellitus in 36 to 60 Years Old Men and Women Who Were Recruited by the PROCAM-Study and had Follow-Up Examinations Within 4 to 10 Years

Total population of 36 to 60 years old men with repeat examinations during 4 to 10 years follow-up	**3,951**
Excluded because of known diabetes mellitus	**76**
Excluded because of fasting glucose > 7 mmol/l	**123**
No Diabetes mellitus and included into the prospective study	***3,737***
Newly developed known diabetes	**31**
Newly developed but unknown diabetes mellitus detected by fasting glucose > 7 mmol/l	**169**
Sum of cases with newly developed diabetes mellitus (=cases)	***200***
No Diabetes mellitus during follow-up (=controls)	***3,537***

von Eckardstein, Schulte, Assmann; JCEM, in press 2000

Risk factors for type 2 diabetes mellitus in PROCAM

One of the most important characteristics of type 2 diabetes mellitus is the long latency period of impaired glucose tolerance which always precedes frank disease. This period of impaired glucose tolerance is characterized by a number of metabolic abnormalities such as mixed dyslipidemia and impaired glucose tolerance. In order to investigate these risk factors in more detail, a subgroup of middle-aged men was identified who had one examination at entry and a second follow-up examination 4 to 10 years later. This slide shows the characeteristics of this subgroup.

Slide 8:

PROCAM (Münster Heart Study): Risk factors for development of type 2 diabetes mellitus in PROCAM

PROCAM (Münster Heart Study): Mean Values of Age-Standardized Risk Factors for Male Participants, aged 36 to 65 Years, With (DM+) and Without (DM-) Development of Diabetes Mellitus Within 4 to 10 Years (mean 6.3 years) Follow-Up

	DM- (n=3,537)	DM+ (n=200)
Follow-up (month)	76.4 ± 15.0	78.8 ± 15.7*
Age (years)	46.7 ± 5.3	46.7 ± 5.3
BMI (kg/m²)	26.1 ± 2.9	27.9 ± 3.5**
Systolic blood pressure (mm Hg)	128.9 ± 16.8	135.9 ± 20.3**
Diastolic blood pressure (mm Hg)	84.5 ± 10.5	89.1 ± 12.4**
Glucose (mmol/l)	5.47 ± 0.51	6.07 ± 0.57**
Cholesterol (mmol/l)	5.84 ± 1.07	5.91 ± 1.09
Triglycerides (mmol/l)[1]	1.45	1.84**
HDL-cholesterol (mmol/l)	1.22 ± 0.31	1.13 ± 0.32**
LDL-cholesterol (mmol/l)	3.86 ± 0.95	3.84 ± 0.96
Uric acid (µmol/l)	342 ± 66	366 ± 78**

[1] geometric mean ; * p<0.05; ** p<0.001

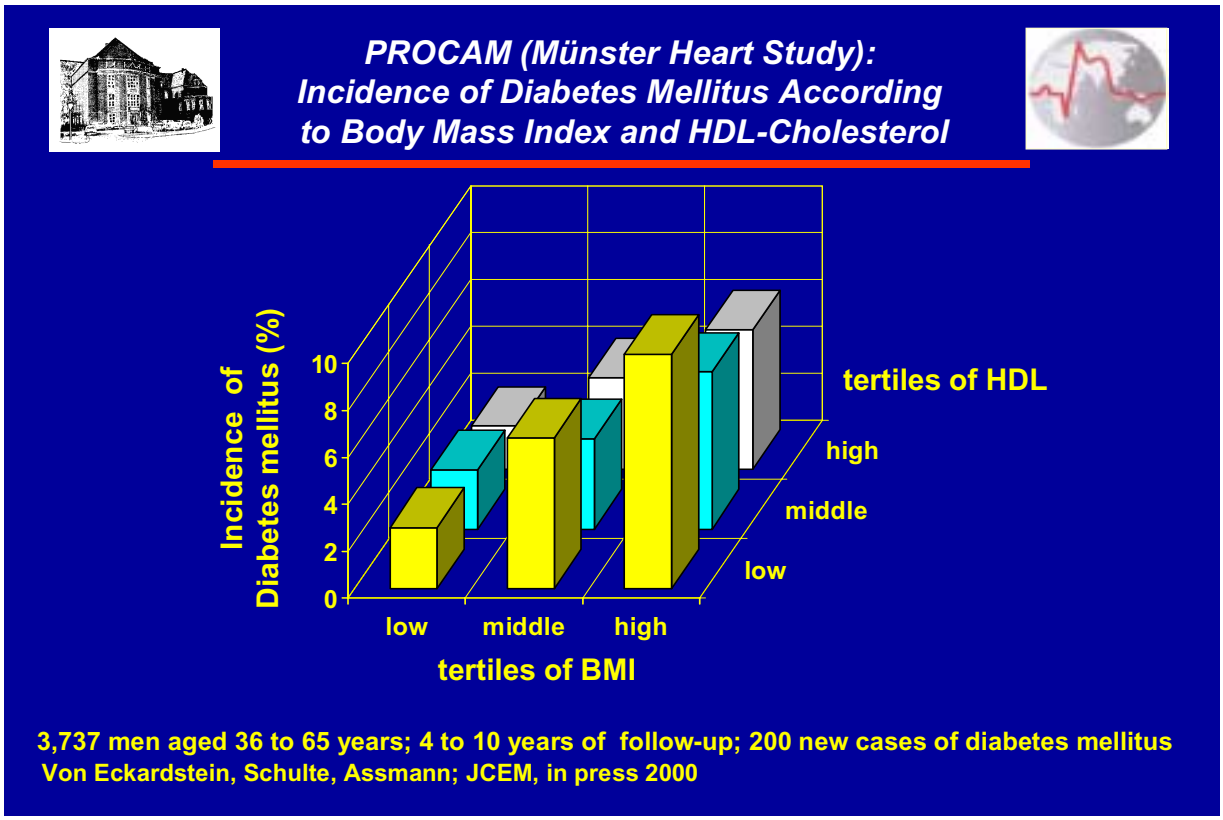
von Eckardstein, Schulte, Assmann; JCEM, in press 2000

Risk factors for development of type 2 diabetes mellitus in PROCAM

This slide shows the levels of risk factors in 200 middle aged PROCAM participants who developed type 2 diabetes mellitus and 3,537 middle-aged controls. In univariate analysis, the following factors were significantly elevated at baseline in those persons who went on to develop diabetes: blood pressure (systolic and diastolic), glucose, triglycerides, uric acid. HDL-cholesterol was significantly lower at baseline in those persons who later became diabetic.

Slide 9:

PROCAM (Münster Heart Study): Risk factors for development of type 2 diabetes mellitus in PROCAM; HDL and BMI

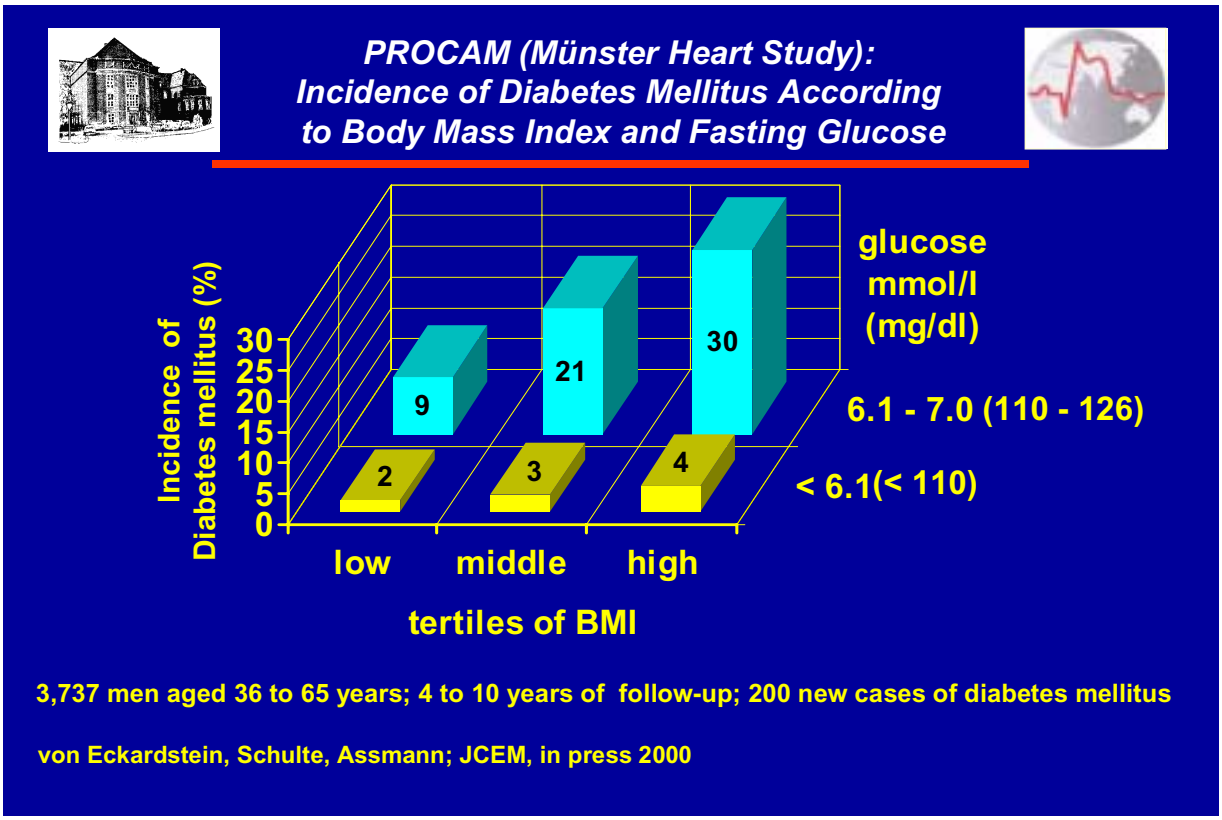


Risk factors for development of type 2 diabetes mellitus in PROCAM; HDL and BMI

This slide is an extension of the data shown in slide 8. It clearly demonstrates that there was a positive interaction between low HDL-cholesterol and overweight in terms of increase risk of developing diabetes mellitus.

Slide 10:

PROCAM (Münster Heart Study): Risk factors for development of type 2 diabetes mellitus in PROCAM



Risk factors for development of type 2 diabetes mellitus in PROCAM

Just as there is an interaction between body mass and HDL-cholesterol (slide 9), so is there also an interaction between body mass and blood glucose in prediction of risk of developing diabetes mellitus.

Slide 11+12:

PROCAM (Münster Heart Study): Development of type 2 diabetes mellitus in PROCAM; establishment of a multiple logistic function

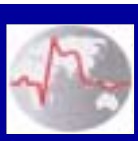
PROCAM (Münster Heart Study): Multiple Logistic Function (MLF) Analysis of Risk Factors for the Development of Diabetes Mellitus

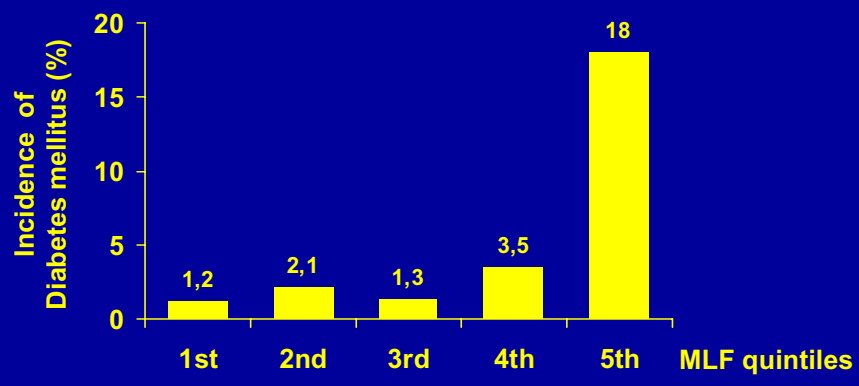
	Parameter Estimate	Standard Error	p (chi-square test)
Age (years)	0.0259	0.0150	0.0841
BMI (10 kg/m^2)	0.0105	0.0026	0.0001
Hypertension (yes=1/no=0)	0.1674	0.0699	0.0166
Glucose (mmol/l)	0.0064	0.0051	0.0000
Family history of diabetes mellitus (yes=1/no=0)	0.4187	0.1732	0.0156
Triglycerides (mmol/l)	2.3 x 10^{-6}	5.7 x 10^{-6}	0.6398
HDL-cholesterol (mmol/l)	42.8 x 10^{-3}	20 x 10^{-3}	0.0318
Uric acid (µmol/l)	0.0060	0.0073	0.8869

3,737 men aged 36 to 65 years; 4 to 10 years of follow-up;
200 new cases of diabetes mellitus

von Eckardstein, Schulte, Assmann; JCEM, in press 2000

PROCAM (Münster Heart Study): Incidence of Diabetes Mellitus According to Quintiles of Risk Estimated by MLF Analysis





Independent risk factors contributing to MLF are:
age, glucose, BMI, HDL-cholesterol, family history of diabetes mellitus, hypertension

3,737 men aged 36 to 65 years; 4 to 10 years of follow-up; 200 new cases of diabetes mellitus

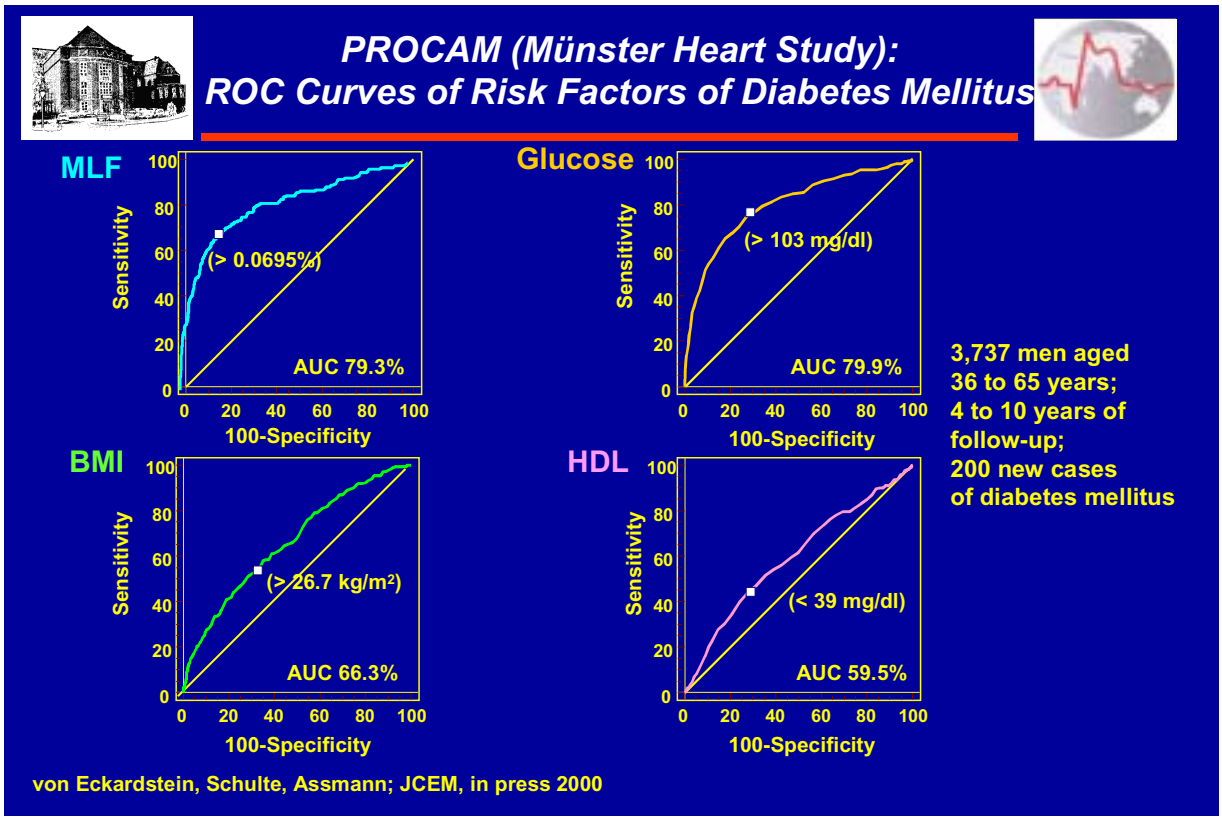
von Eckardstein, Schulte, Assmann; JCEM, in press 2000

Development of type 2 diabetes mellitus in PROCAM; establishment of a multiple logistic function

By means of regression analysis, those factors which independently contributed to risk of developing diabetes mellitus in the PROCAM population were identified and combined to generate a multiple logistic function with the parameters shown on slide 11. When divided into quintiles, this function provided a striking gradation of risk: while those persones in the bottom quintile had an incidence of diabetes in 4 to 10 years of follow-up of 1,2%, the risk in persons in the top quintile was no less than 18%.

Slide 13:

PROCAM (Münster Heart Study): Prediction of diabetes mellitus in PROCAM; performance of individual risk factors and a multiple logistic function



Prediction of diabetes mellitus in PROCAM; performance of individual risk factors and a multiple logistic function

The standard and most unbiased means of calculating the performance of a diagnostic test or risk function is by means of receiver-operated characteric (ROC) curve analysis. The more the ROC-curve deviates from the 45^0 diagonal (given in numeric terms by the area under the curve (AUC)), the better the test. This analysis clearly shows that both HDL-cholesterol (AUC 59,5%) and Body Mass Index (66,3%) alone are poor predictors of risk, since the ROC-curve barely deviates from the diagonal. Glucose is a better performer (AUC 79,9%), and performed slightly better than a multiple logistic function (79,3%).