Diabetologia (1988) 31: 798-805

Diabetologia

Risk factors for Type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913

L.-O. Ohlson[1], B. Larsson[1], P. Björntorp[1], H. Eriksson[2], K. Svärdsudd[2], L. Welin[2], G. Tibblin[3] and L. Wilhelmsen[2]

[1] Gothenburg University, Section for Preventive Medicine, at the Department of Medicine I, Sahlgren's Hospital,
[2] Department of Medicine, Östra Hospital, Gothenburg, and [3] Department of Family Medicine, University of Uppsala, Sweden

Summary. This report presents data on antecedents of Type 2 (non-insulin-dependent) diabetes mellitus in a homogeneous sample of randomly selected 54-year-old men from an urban Swedish population with a diabetes incidence of 6.1% during 13.5 years of follow-up. The increased risk leading to diabetes for those in the top quintile compared to the lowest quintile of the distribution of statistically significant risk factors were: body mass index = 21.7, triglycerides = 13.5, waist-to-hip circumference ratio = 9.6, diastolic blood pressure = 6.7, uric acid = 5.8, glutamic pyruvic transaminase = 3.9, bilirubin = 3.2, blood glucose = 2.7, lactate = 2.4 and glutamic oxaloacetic transaminase = 2.0. Those with a positive family history of diabetes had 2.4-fold higher risk for developing diabetes than those without such a history. In a multivariate analysis glutamic pyruvic transaminase, blood glucose, body mass index, bilirubin, systolic blood pressure, uric acid and a family history of diabetes were all significantly associated with the development of diabetes. Our study demonstrates the great importance of adiposity and body fat distribution for the risk of diabetes. A number of established risk factors for coronary heart disease are risk factors for diabetes as well. Disturbed liver function and increased levels of lactate are early risk factors for diabetes - presumably indicators of the presence of impaired glucose tolerance and/or hyperinsulinaemia.

Key words: Prospective study, Type 2 (non-insulin-dependent) diabetes, risk factors, obesity, waist-to-hip ratio, liver metabolism, blood pressure, blood glucose, family history of diabetes, physical fitness.

According to the currently prevailing view, Type 2 (non-insulin-dependent) diabetes may develop as the consequence of the combined action of two factors. The first is an early onset of a peripheral insulin resistance, believed to result in a compensatory increase of insulin secretion. Secondly, this might eventually result in an insufficiency of insulin production in susceptible individuals [1]. In order to evaluate this concept further, information from prospective studies of non-selected groups is of particular value. Some attempts have previously been made to find risk factors for diabetes and to study the interaction between genetic and environmental factors. These studies have consistently shown that obesity, inheritance and blood glucose levels are predictors of diabetes while other factors are of less importance [2-4].

In a population study of middle-aged men in Gothenburg, Sweden, a large number of characteristics, both metabolic variables and lifestyle characteristics, were measured in 1967. This report presents the importance of these baseline data in 54-year-old men as predictors of either diabetes or 2-h blood glucose concentrations over a period of 13.5 years.

Subjects and methods

Study population

The study population comprised men living in Gothenburg, Sweden, who were born in 1913 and whose date of birth was divisible by three - that is, the third, sixth, ninth days, and so on, of each month. Of those men fulfilling the criteria, 855 (88%) agreed to be examined in 1963. The population, participants and nonparticipants, have been described in detail elsewhere [5, 6]. The 855 participants in 1963 were invited for re-examination in 1967 (aged 54 years), and 792 (94%) of those still alive accepted. As part of this re-examination, a large number of variables were measured and the results served as baseline values for the present analysis.

Excluded were 14 subjects with known diabetes, three subjects with fasting blood glucose ≥ 7.0 mmol/l, and nine subjects with missing data for blood glucose. The 766 remaining men who did not have diabetes comprised the population at risk from 1967.

Baseline data

Body weight was measured to the nearest 0.1 kg on a lever balance with the subjects wearing undershorts only.
Height was measured to the nearest 1 cm.
Body mass-index was calculated as weight/height (kg/m^2).

Waist-to-hip ratio was calculated as the ratio of waist circumference, measured to the nearest centimeter at the level of the umbilicus with the subject standing and breathing normally, and hip circumference, measured to the nearest centimeter at the level of the iliac crest (anterior superior iliac spine). This ratio was used as an index of abdominal adipose tissue distribution.

Blood pressure was measured on the right arm by the same observer, as casual blood pressure in the seated position after 5 min rest, using a mercury sphygmomanometer with a cuff size of 12 × 23 cm.

Six-hour postprandial blood glucose was determined from venous whole blood drawn from an antecubital vein in the afternoon [7].

Additional blood chemistry variables used in this analysis were serum oxaloacetic transaminase (GOT) and serum glutamic pyruvic transaminase (GPT) [8], serum bilirubin (Technicon Auto analyser), serum lactate (Assay kit, Boehringer-Mannheim, Mannheim, FRG), serum glycerol [9] and serum cholesterol [10]. From a previous examination of the same cohort four years earlier (i.e. in 1963), serum triglycerides [11] and serum uric acid [12] were added to the present analysis.

From an *exercise test, maximal systolic blood pressure, maximal heart rate and maximal oxygen uptake,* as an index of work capacity, were obtained [13, 14]. Exercise was performed for 6 min at each work load starting at 300 kpm/min and continuing at 600 kpm/min. After 4 min of rest in the supine position an electrocardiogram was recorded. It was then decided, according to predetermined criteria, whether the subjects should continue to the level of maximal exercise. The subjects exercised at an additional submaximal load, 900 kpm/min, if the heart rate was lower than 120 beats/min at 600 kpm/min. If during the previous work load of 600 kpm/min the heart rate was higher than 120 beats/min, this work load was again used for 2 min before the maximal work load was performed. Maximal oxygen uptake was predicted according to the formula proposed by Grimby et al. [14].

Stress. The subjects' experience of stress was assessed by a questionnaire and scored from 1 to 6, where 1 = never felt stress, 2 = experience of some period of stress, 3 = some period of stress during the last 5 years, 4 = several periods of stress during the last 5 years, 5 = permanent stress during the last year, 6 = permanent stress during the last 5 years. Stress was explained to the subjects as a state when you feel tense, are irritable, nervous, anxious or have problems with sleep on account of, for example, conditions at work or at home, etc.

Smoking habits were scored in 5 categories: 1 = non-smokers, 2 = ex-smokers, 3 = smokers of 1-14 g of tobacco daily, 4 = 15-25 g of tobacco daily, and 5 = 25 g of tobacco daily or more. One cigarette was considered to be equivalent to 1 g, 1 cheroot to 2 g and 1 cigar to 5 g. For pipe smokers, the average number of grams smoked daily was used.

Treatment for hypertension. Information on medical treatment for hypertension was obtained by a questionnaire.

Information about *alcohol consumption* was obtained by a questionnaire and the cohort was divided into two categories; those who had previous or current problems with alcohol or were drinking alcohol daily or several days a week (called "high alcohol consumption") and those who had no problems with alcohol and were drinking alcohol once a week or less.

Registration by the Temperance Board in Gothenburg of all alcoholic offences between 1920 and 1963 in the present cohort was obtained.

Physical activity at work was classified as sedentary, moderate or heavy. This information was obtained in 1963 (i.e. 4 years before baseline of the present analysis) from the participants by a questionnaire.

Information on a *family history of diabetes* (also data from 1963) among parents, brothers or sisters was obtained by a questionnaire.

Follow-up and endpoints

The analysis was based on 13.5 years of follow-up (1967-1980) of men aged 54 years at baseline. The men were followed by re-examination in 1973 and 1980. At the re-examination in 1980, 558 of all men who were still alive ($n = 629$, 88.7%), and who met our criteria of being at risk for diabetes agreed to be examined.

The criteria for development of diabetes were: (1) known clinical diabetes, information obtained by a questionnaire. ("Has a doctor ever told you that you have diabetes?"); (2) fasting venous blood glucose ≥ 7 mmol/l or a glucose value ≥ 10.0 mmol/l 2-h after an oral glucose load of 100 g, applying the WHO criteria [15]; or (3) development of diabetes during follow-up in subjects who, for some reason, were not re-examined in 1980. Ten such subjects were found by information from a questionnaire and from a fasting blood glucose value ≥ 7.0 mmol/l at the re-examination in 1973, by information from death certificates for those who died in 1967-80, and from hospital charts for those who were hospitalised in 1967-80.

In 1980, an oral glucose tolerance test of 100 g, instead of 75 g, as recommended by the WHO [15], was performed in order not to change the methodology in our study. Possible consequences of this difference in glucose challenge have been discussed previously [16].

When using "diabetes - non-diabetes" as endpoints this study was strictly prospective and the diabetic patients identified among the non-participants at follow-up ($n = 10$) were added to the number of diabetic patients found among the participants ($n = 37$). These men with diabetes were then compared with the non-diabetic group ($n = 719$). When the "2-h blood glucose concentration" was used as the predictive variable, (except for the diabetic patients), only those who participated *both* at baseline *and* at follow-up were included in this second analysis. Using this combined prospective and retrospective method, the study sample comprised 47 subjects with diabetes, 75 subjects with impaired glucose tolerance and 430 subjects with a normal glucose tolerance.

Statistical analysis

In the univariate analysis, Pitman's permutation test was used for all tests of association [17]. When relative risks were analysed, continuous variables were divided into quintiles and relative risks were calculated by comparing the top quintile with the lowest quintile. The aetiologic fraction (excess risk of diabetes or population-attributable risk of diabetes) was calculated as the number of subjects with an excess risk of diabetes in the upper four quintiles of baseline characteristics divided by the number of diabetic patients in the whole sample. This is one way of estimating the importance of various risk factors in the population. Testing for interaction between possible risk factors for diabetes, the logistic regression technique was used and an interaction term was added to each testing step. The logistic regression model was also used in the bivariate analysis (taking obesity into account). The stepwise logistic regression model was used to find independent risk factors associated with diabetes. We also used a multiple linear regression model to find independent risk factors for 2-h blood glucose concentration measured at follow-up in 1980 as an alternative indicator of diabetes status.

Life table curves were constructed by the Kaplan-Meier method [18]. A p-value of less than 0.05 was considered as statistically significant. All tests were two-tailed.

Results

Univariate association with risk factors

Among the 766 men at risk for diabetes 47 men (6.1%) who became diabetic were identified during 13.5 years of follow-up. Potential risk factors for diabetes are presented in Table 1. Compared to the non-diabetic subjects, those who became diabetic were significantly more obese at baseline as indicated by body mass index ($p < 0.001$), had a more pronounced central adipose

Table 1. Means and standard deviations (SD) of baseline characteristics by diabetic status and degree of glucose tolerance at follow-up

	Diabetic status at follow-up					Glucose tolerance at follow-up				
	Non-diabetic subjects ($n=719$)		Diabetic patients ($n=47$)		Non-diabetic subjects versus diabetic patients p	Impaired glucose tolerance ($n=75$)		Normal glucose tolerance ($n=430$)		Diabetic--impaired glucose tolerance -normal glucose tolerance
Baseline characteristics	Mean	(SD)	Mean	(SD)		Mean	(SD)	Mean	(SD)	p
Body mass index (kg/m^2)	24.8	(3.1)	27.4	(2.9)	<0.001	25.7	(3.1)	24.7	(2.8)	<0.001
Waist-to-hip ratio	0.924	(0.053)	0.961	(0.046)	<0.001	0.937	(0.047)	0.920	(0.053)	<0.001
Systolic blood pressure (mm Hg)	142.8	(21.1)	154.3	(18.6)	<0.001	154.7	(22.6)	139.6	(17.6)	<0.001
Diastolic blood pressure (mm Hg)	90.2	(12.4)	96.6	(13.2)	<0.001	95.3	(13.9)	88.2	(11.8)	0.001
Blood glucose (mmol/l)	3.6	(0.6)	4.1	(1.3)	<0.001	3.7	(0.7)	3.6	(0.6)	<0.001
Uric acid (μmol/l)	312	(63)	355	(64)	<0.001	331	(56)	304	(60)	<0.001
Cholesterol (mmol/l)	7.0	(1.2)	7.1	(0.9)	NS	6.8	(1.2)	6.9	(1.2)	NS
Triglycerides (mmol/l)	1.2	(0.7)	1.7	(1.9)	0.005	1.2	(0.4)	1.2	(0.7)	0.006
Glutamic oxaloacetic transaminase (U/l)	25.8	(9.6)	30.0	(15.7)	0.024	25.3	(7.5)	25.5	(7.5)	0.015
Glutamic pyruvic transaminase (U/l)	25.8	(13.2)	39.3	(29.9)	<0.001	25.5	(10.3)	25.3	(12.4)	<0.001
Bilirubin (μmol/l)	8.0	(3.9)	10.2	(6.6)	0.009	8.3	(6.6)	7.8	(0.6)	0.005
Lactate at rest (mmol/l)	0.82	(0.28)	0.95	(0.34)	0.008	0.76	(0.26)	0.79	(0.24)	0.003
Lactate during exercise (mmol/l)	5.92	(1.87)	5.93	(1.85)	NS	5.73	(1.96)	6.07	(1.76)	NS
Glycerol (mmol/l)	1.22	(1.04)	1.33	(1.31)	NS	1.12	(0.61)	1.25	(1.17)	NS
Max systolic blood pressure (mm Hg)	210.8	(24.1)	223.2	(23.6)	=0.001	213.3	(25.4)	210.3	(22.9)	0.003
Max heart rate (beats/min)	171.6	(12.8)	170.0	(14.1)	NS	172.0	(11.3)	172.6	(12.6)	NS
Max oxygen uptake (l/min)	2.32	(0.30)	2.35	(0.30)	NS	2.28	(0.28)	2.34	(0.29)	NS
Stress (1-6)	2.7	(1.8)	3.2	(1.7)	NS	2.6	(1.8)	2.7	(1.7)	NS
Smoking habits (1-5)	2.7	(1.2)	2.4	(1.1)	NS	2.5	(1.1)	2.5	(1.2)	NS
Treatment for hypertension (%)	5.6		8.5		NS	11.1		3.5		0.030
High alcohol consumption (%)	20.0		26.5		NS	21.3		21.0		NS
Registration by Temperance Board (%)	21.2		16.3		NS	9.3		16.9		NS
High physical activity at work (%)	32.9		20.8		NS	28.4		31.9		NS
Family history of diabetes (%)	12.0		24.5		<0.001	13.3		12.1		0.046

tissue distribution according to the waist-to-hip ratio ($p<0.001$), and had elevated systolic and diastolic blood pressures ($p<0.001$), although no significant differences was seen in treatment for hypertension.

Those becoming diabetic also had significantly increased levels of blood glucose ($p<0.001$), uric acid ($p<0.001$), triglycerides ($p<0.005$), glutamic oxaloacetic transaminase ($p=0.024$), glutamic pyruvic transaminase ($p<0.001$), bilirubin ($p=0.009$) and lactate at rest ($p=0.008$). No differences were found for cholesterol, lactate during exercise or glycerol.

Those becoming diabetic had significantly higher maximal systolic blood pressure. No differences were seen in maximal heart rate, or maximal oxygen uptake.

Among lifestyle characteristics, a non-significant trend towards experience of more stress was found among those who subsequently become diabetic ($p=0.060$). There were no differences in smoking habits, self-reported alcohol consumption, registration by the Temperance Board or physical activity at work.

Finally, those becoming diabetic had a 2-fold higher family history of diabetes (24.5% vs 12.0%, $p<0.001$). A positive family history of diabetes was reported by 98 men (12.8%) at entry. Using a life table presentation, the difference in risk of diabetes between those with and without a family history of diabetes (11.8% vs 5.0%, $p<0.001$) over 13.5 years is illustrated in Figure 1.

The cohort was divided according to degree of glucose tolerance into three groups (diabetic, impaired glucose tolerance and normal subjects), as presented in Table 1. When testing for trends with glycaemia no major differences were found comparing the non-diabetic/diabetic model, except for a significant excess of treatment for hypertension with glycaemia ($p=0.030$).

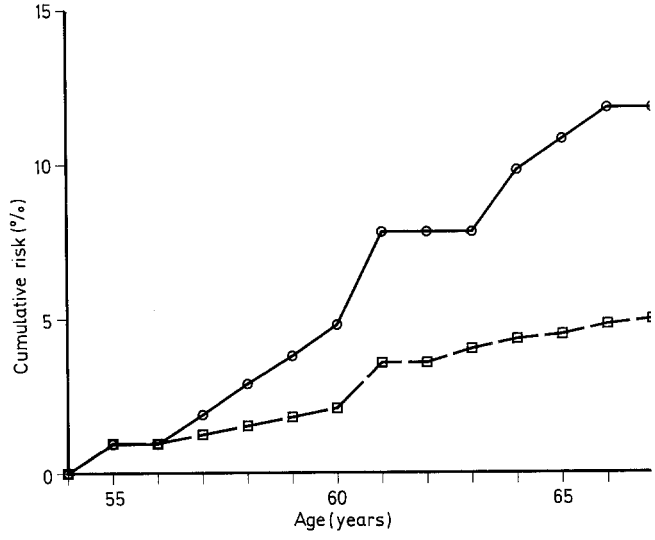

Fig. 1. Cumulative risk of developing diabetes mellitus from the age of 54 to the age of 67 for men with (○) and without (□) a family history of diabetes

Table 2 presents the 13.5-year incidence rate (%) of diabetes by quintiles of the distribution of those baseline characteristics that were significantly associ-

Table 2. Incidence of diabetes mellitus (%) by quintiles of the distribution of baseline characteristics

	Quintiles					Relative risk (RR) V/I	95% Confidence interval of RR	Aetiologic fraction[a]
	I	II	III	IV	V			
Body mass index	0.7	2.6	7.2	6.1	15.2	21.7	(4.3-80.0)	0.89
Triglycerides	0.6	4.8	9.0	8.8	8.1	13.5	(2.3-46.1)	0.90
Waist-to-hip ratio	1.3	3.2	8.3	6.7	12.5	9.6	(2.4-29.8)	0.79
Diastolic blood pressure	1.6	6.3	6.5	7.1	10.9	6.8	(2.4-22.2)	0.76
Systolic blood pressure	1.7	2.4	7.1	9.3	11.4	6.7	(2.4-22.5)	0.74
Uric acid	2.4	4.5	2.5	7.0	13.9	5.8	(2.2-16.0)	0.60
Glutamic pyruvic transaminase	2.9	2.9	5.2	10.0	11.4	3.9	(1.4-11.1)	0.36
Bilirubin	4.7	3.9	4.8	10.8	15.1	3.2	(1.5- 8.2)	0.40
Max systolic blood pressure	4.2	2.8	3.0	6.9	12.6	3.0	(1.2- 8.1)	0.29
Blood glucose	3.7	4.3	6.6	8.2	10.0	2.7	(1.1- 7.0)	0.44
Lactate at rest	4.7	5.0	4.3	6.9	11.3	2.4	(1.0- 5.9)	0.27
Glutamic oxaloacetic transaminase	4.3	4.5	7.6	4.4	8.6	2.0	(0.8- 5.1)	0.27

[a] Aetiologic fraction (excess risk or population-attributable risk) was calculated as described in the text (Statistical analysis)

Table 3. Matrix of correlation coefficients (Pearson) between baseline characteristics

	1	2	3	4	5	6	7	8	9	10	11	12	13
1. Body mass index	1.0	0.60	0.20	0.28	0.13	0.30	0.08	0.03	0.05	0.07	0.48	0.19	0.29
2. Waist-to-hip ratio		1.0	0.14	0.24	0.17	0.18	0.02	0.06	0.06	0.06	0.18	0.22	0.18
3. Systolic blood pressure			1.0	0.66	0.10	0.13	−0.03	0.06	0.06	0.03	−0.01	0.11	0.18
4. Diastolic blood pressure				1.0	0.08	0.16	0.03	0.03	0.11	0.03	0.06	0.15	0.19
5. Glutamic oxaloacetic transaminase					1.0	0.57	0.03	0.06	0.10	−0.01	−0.01	0.01	0.06
6. Glutamic pyruvic transaminase						1.0	0.02	0.02	0.10	−0.01	0.03	0.03	0.17
7. Bilirubin							1.0	0.03	0.02	−0.01	0.05	0.06	0.02
8. Blood glucose								1.0	0.15	−0.01	−0.09	0.06	−0.03
9. Lactate at rest									1.0	−0.03	−0.04	0.05	0.03
10. Family history of diabetes										1.0	0.03	−0.02	0.02
11. Maximal oxygen uptake											1.0	−0.01	0.14
12. Triglycerides												1.0	0.15
13. Uric acid													1.0

$r >= 0.07 = p < 0.05$

ated with becoming diabetic. The highest relative risk was found for body mass index (21.7), followed by triglycerides (13.5), waist-to-hip ratio (9.6), diastolic blood pressure (6.8), systolic blood pressure (6.7), uric acid (5.8) and glutamic pyruvic transaminase (3.9). The excess risk (aetiologic fraction) attributable to the various significant risk factors ranged from 90% for triglycerides and 89% for body mass index to 27% for lactate at rest and glutamic oxaloacetic transaminase (Table 2).

Family history of diabetes and baseline characteristics

Men with a positive family history of diabetes at baseline tended to have a higher body mass index than those without a family history of diabetes (25.5 vs 24.9, $p = 0.053$). No other differences in baseline characteristics were found.

We also tested for interaction between family history of diabetes and baseline characteristics. The only significant finding was a weak negative interaction with fasting blood glucose ($p = 0.039$).

Bivariate analysis

Most potential risk factors for diabetes were weakly intercorrelated in the univariate analysis (Table 3). Many of these variables are associated with obesity. Body mass index was, therefore, adjusted for in a bivariate analysis, using the logistic regression model. The association between diabetes and systolic blood pressure ($p = 0.003$) and diastolic blood pressure ($p = 0.049$) remained significant, as did the association between diabetes and blood glucose ($p > 0.001$), uric acid ($p = 0.001$), glutamic pyruvic transaminase ($p = 0.003$), bilirubin ($p = 0.017$), lactate at rest ($p = 0.018$) and a family history of diabetes ($p = 0.030$).

Maximal oxygen uptake, as an index of physical fitness, did not predict later diabetes in the univariate

Table 4. Stepwise multiple logistic regression model predicting diabetes over 13.5 years. The variables that met the 0.05 significance level for entry are listed in the order they entered the model. (Waist-to-hip ratio, lactate at rest and triglycerides were rejected)

Variables	Regression coefficient	p
Glutamic pyruvic transaminase	0.03	0.003
Blood glucose	0.04	<0.001
Body mass index	0.12	0.030
Bilirubin	1.31	0.003
Systolic blood pressure	0.02	0.029
Uric acid	0.004	0.033
Family history of diabetes	0.87	0.043

Table 5. Stepwise multiple linear regression analysis predicting 2-h blood glucose concentration 13.5 years later. The variables that met the 0.15 significance level for entry are listed in the order they entered the model. (Triglycerides and glutamic pyruvic transaminase were rejected.)

Variables	Regression coefficient	p
Body mass index	0.09	0.124
Systolic blood pressure	0.02	0.002
Bilirubin	1.62	0.004
Lactate at rest	1.01	0.058
Uric acid	0.01	0.026
Waist-to-hip ratio	6.6	0.035
Blood glucose	0.02	0.129
Family history of diabetes	0.65	0.130

analysis. A strong correlation between maximal oxygen uptake and body mass index existed ($r=0.48$, $p<0.001$). No association between maximal oxygen uptake and future diabetes was, however, found, even when accounting for body mass index as a possible negative confounding factor.

Stepwise multiple logistic regression analysis

To ascertain which of the baseline characteristics, being associated with diabetes in univariate analysis, were also independent predictors of diabetes, a stepwise multiple logistic regression analysis was performed (Table 4). The characteristics are listed in the order they entered the model.

Glutamic pyruvic transaminase, blood glucose, body mass index, bilirubin, systolic blood pressure, uric acid and a family history of diabetes were all significantly associated with the development of diabetes, while waist-to-hip ratio, lactate at rest and triglycerides lost significance in this multivariate analysis.

In order to uncover factors which are so strongly associated with blood glucose that they would be non-significant if run together, the analysis was repeated excluding blood glucose from the model. Family history of diabetes then lost its significance, but no other differences in the logistic model appeared.

Stepwise multiple linear regression analysis

To analyse which of the baseline characteristics, being associated with 2-h blood glucose concentration in univariate analysis, were also independent predictors of glucose level, a stepwise multiple linear regression analysis was performed (Table 5). The characteristics are listed in the order they entered the model.

Systolic blood pressure, bilirubin, uric acid, and waist-to-hip ratio were each significantly associated with 2-h blood glucose concentration while body mass index, lactate at rest, blood glucose, a family history of diabetes, triglycerides and glutamic pyruvic transaminase lost significance in this multivariate analysis.

Discussion

Since no glucose tolerance test was performed at baseline some of the subjects at risk for diabetes might already have impaired glucose tolerance at that point. Some of the risk factors for diabetes in the present analysis, especially the metabolic variables, could therefore be indicators of impaired glucose tolerance and/or hyperinsulinaemia.

As previously reported [19], obesity and central distribution of adipose tissue, as indicated by the waist-to-hip ratio, contributed strongly in the multivariate analyses to both the incidence of diabetes and to the prediction of later degree of glucose tolerance. Obesity is an important risk factor in most, but not all, prospective population studies [20–26]. In the Bedford Study [27], obesity seemed to have a "late diabetogenic effect". In the Israel Study of Glucose Intolerance, Obesity and Hypertension [28], obesity at entry (but not at follow-up) was associated with development of diabetes. In contrast, in the population of Nauru, obesity was a significant predictor of later diabetes only in women [29], and in the Whitehall Study no association between obesity and worsening to diabetes was found [30]. However, in the two British studies [27, 30] only subjects with an impaired glucose tolerance were followed prospectively, and this subgroup is often already obese compared to normal subjects, as also indicated by our own cross-sectional findings [16]. Once impaired glucose tolerance starts to deteriorate the worsening to diabetes might be less dependent on risk factors.

Systolic blood pressure was independently associated with the incidence of diabetes in our study, confirming previous results as recently reviewed [31, 32]. However, in the Framingham study, systolic blood pressure was important from a univariate standpoint only among women and lost significance in the multivariate analysis [21].

Treatment for hypertension was associated with glycaemia in the univariate analysis although not sig-

nificantly in the non-diabetic/diabetic model. Diuretics were used in almost all cases of hypertension medication and diuretics have been reported to be associated with later diabetes, especially is women [33, 34]. In another analysis of the study cohort (1973–1980) the association between hypertension medication and worsening to diabetes was not confirmed. Factors other than diuretics per se might therefore also be involved in the mechanism behind the hypertension-diabetes association, as will be discussed below.

Blood glucose was a strong predictor of diabetes, confirming previous reports [3, 4]. Uric acid, discussed as a precursor of diabetes in only a few studies [25, 35], was a predictor of later diabetes and degree of glucose tolerance, confirming our cross-sectional findings [16]. This association has been proposed to be explained by re-routing of glucose metabolism to the pentose shunt from the glycolytic pathway [36] and production of alloxan-like derivatives of uric acid, toxic to beta cells [4] as well as being a marker of a genetic and/or environmental susceptibility to diabetes [35].

In agreement with the Framingham Study [21], total cholesterol did not predict diabetes in our study. Serum triglyceride concentration showed a univariate association with diabetes, although it lost significance when obesity was considered.

Glutamic pyruvic transaminase and bilirubin were important predictors of diabetes in the logistic regression model. The relationship with glutamic pyruvic transaminase is in agreement with our cross-sectional data [16]. This association has apparently not been described previously in a longitudinal study. In the Paris Prospective Study [26], abnormal volume of the liver, "as a (rough) clinical sign of chronic alcoholism" was associated with later diabetes. Alcohol consumption might be of importance and we found a non-significant trend towards more alcohol consumption among those subsequently becoming diabetic. An association between alcohol consumption and glucose tolerance is suggested by previous studies, but the relationship remains unclear [37, 38].

The liver is also involved in the lactate homeostasis and baseline levels of lactate at rest showed a significant correlation with diabetes in the univariate analysis but lost its significance in the multivariate case. In a Finnish study, blood lactate showed a close correlation with liver histology and function in Type 2 diabetic patients undergoing liver biopsy [39]. Elevated levels of blood lactate have previously been described in unaffected co-twins of Type 2 diabetic patients in a cross-sectional study [40]. Based on cross-sectional findings it has been speculated that lactate might play an important role in the development of hyperglycaemia in patients with Type 2 diabetes. Lactate could act as a substrate for hepatic glucose production [41]. Our longitudinal prospective findings indicate that an elevated lactate level is an early predictor of glucose impairment.

Physical inactivity is commonly supposed to be associated with an increased risk of diabetes but previous reports are few and contradictory [42, 43]. Maximal oxygen uptake, as an index of work capacity, did not discriminate those who subsequently became diabetic in our study. Maximal oxygen uptake was strongly correlated with body mass index. We therefore also accounted for this factor in a bivariate analysis; but still found no association between diabetes and maximal oxygen uptake. However, there are cross-sectional data showing that maximal oxygen uptake is decreased in normoglycaemic, non-obese, middle-aged men with a familial aggregation of Type 2 diabetes independently of physical activity [44], indicating a possible common genetic factor for both physical fitness and susceptibility to diabetes.

Experience of stress showed a trend, although not significant ($p = 0.060$), towards higher scores among those becoming diabetic. Stress has been discussed as one of the factors involved in the development of Type 2 diabetes [2], possibly due to release of diabetogenic hormones. Another possibility is that stress might induce an increased lipolysis via enhanced sympathetic nervous system activity and induce decreased glucose tolerance by the peripheral effects of non-esterified fatty acids [19]. However, blood glycerol, an indicator of lipolysis, did not show any association with future diabetes.

A family history of diabetes was twice as common among those becoming diabetic than among the non-diabetic subjects. Twin studies have also revealed the importance of inheritance, with a concordance of 90% for Type 2 diabetes [45]. Previous reports have also shown a strong association between incidence of diabetes and parental diabetes, even when adjusting for obesity [22]. It was, therefore, surprising not to find any significant differences in baseline characteristics when dividing the cohort according to a family history of diabetes. The weak negative interaction found between a family history of diabetes and fasting blood glucose might be explained by a trend towards a higher body mass index ($p = 0.053$) among those with a positive family history.

Several early metabolic events, preceding non-insulin-dependent diabetes in obese animal models [46], seem to be recognisable at the initial examination of the men becoming diabetic during the observation period in this study. These men were somewhat obese, they had disturbed liver function, (perhaps as a sign of liver steatosis), high serum lactate levels at rest, (corresponding to increased liver production in the rat models), and elevated blood glucose, (perhaps due to elevated hepatic gluconeogenesis).

Many of the variables predicting future diabetes in our study are also known to be risk factors for cardiovascular disease. According to our data, it therefore seems possible that both diabetes and cardiovascular disease have common antecedents. That is, some fac-

tor or cluster of factors may induce both diabetes and cardiovascular disease, as discussed by Jarrett [47] and also indicated by our cross-sectional data [16]. Elevated blood pressure, found both in those becoming diabetic and among those with impaired glucose tolerance at follow-up, is a principal predictor of cardiovascular disease. It has been suggested that hypertension is due to hyperinsulinaemia and insulin resistance found not only in the early glucose intolerant state but also in non-obese normoglycaemic subjects with hypertension [48, 49].

In conclusion, three main groups of risk factors for Type 2 diabetes have been identified: (1) factors involving fundamental biology, i.e. a family history of diabetes; (2) factors involving biochemical and physiological mechanisms that may also be influenced by environmental factors, i.e. blood pressure, blood glucose, glutamic pyruvic transminase, bilirubin, uric acid and lactate at rest and (3) factors involving the social environment and lifestyle, i.e. obesity. Other factors like smoking habits, alcohol consumption, physical fitness and experience of stress did not predict diabetes. Compared to biochemical and physiological variables measurements of lifestyle factors used in this study provide "soft data". Negative results, therefore, are far from supporting lack of importance.

Acknowledgements. This study was supported by grants from the Swedish Medical Research Council (B 86-27X-06276-05). The King Gustav V and Queen Victoria's Foundation, the Swedish National Association against Heart and Chest Disease, the Gothenburg Medical Association, the Swedish Diabetes Association, Hoechst Diabetes Foundation, Sweden and Gothenburg University.

References

1. DeFronzo RA, Ferrannini E, Koivisto V (1983) New consepts in the pathogenesis and treatment of noninsulin-dependent diabetes mellitus. Am J Med 74 [Suppl 1A] 52-81
2. Zimmet P (1982) Type 2 (non-insulin-dependent) diabetes - an epidemiological overview. Diabetologia 22: 399-411
3. Everhart J, Knowler WC, Bennet PH (1985) Incidence and risk factors for non-insulin-dependent diabetes. Diabetes in America. Diabetes Data Compiled 1984. National Diabetes Data Group IV: 1-35 NIH Publication No 85-14668
4. Orchard TJ, Dorman JS, LaPorte RE, Ferrell RE, Drash AL (1986) Host and environmental interactions in diabetes mellitus. J Chron Dis 39: 979-999
5. Tibblin G (1967) High blood pressure in men aged 50 - A population study of men born in 1913. Acta Med Scand [Suppl] 479
6. Tibblin G (1965) A population study of 50-year-old men. An analysis of the non-participation group. Acta Med Scand 178: 453-459
7. Levin K, Linde S (1962) Determination of glucose in blood, cerebrospinal fluid and urine with a new glucose oxidase reagent. Svenska Laekartidn 59: 3016-3026
8. Karmen A, Wroblewski F, LaDue JS (1955) Transaminase activity in human blood. J Clin Invest 34: 126
9. Laurell G, Tibbling G (1966) An enzymatic fluorimetric micromethod for the determination of glycerol. Clin Chim Acta 13: 317-323
10. Cramer K, Isaksson B (1959) An evaluation of the Theorell method for the determination of total serum cholesterol. Scand J Clin Lab Invest 11: 213-216
11. Carlsson LA, Wadström LB (1959) Determination of glycerides in blood serum. Clin Chim Acta 4: 197
12. Praetorius E (1949) An enzymatic method for the determination of uric acid by ultraviolet spectrophyotometry. Scand J Clin Lab Invest 1: 222
13. Grimby G, Bjure J, Aurell M, Ekström-Jodal B, Tibblin G, Wilhelmsen L (1972) Work capacity and physiologic responses to work. Am J Cardiol 30: 37-42
14. Grimby G, Wilhelmsen L, Ekström-Jodal B, Aurell M, Bjure J, Tibblin G (1970) Aerobic power and related factors in a population study of men aged 54. Scand J Clin Lab Invest 26: 287-294
15. WHO Expert Committee on Diabetes Mellitus (1980) Second Report. WHO Tech Rep Ser No 646
16. Ohlson L-O, Larsson B, Eriksson H, Svärdsudd K, Welin L, Tibblin G (1987) Diabetes mellitus in Swedish middle-aged men. The study of men born in 1913 and 1923. Diabetologia 30: 386-393
17. Bradley JV (1968) Distribution-free statistical tests. Prentice-Hall, London, pp 68-86
18. Kaplan EL, Meier P (1958) Nonparametric estimation from incomplete observations. J Am Stat Assoc 53: 457-481
19. Ohlson L-O, Larsson B, Svärdsudd K, Welin L, Eriksson H, Wilhelmsen L, Björntorp P, Tibblin G (1985) The influence of body fat distribution on the incidence of diabetes mellitus. 13.5 years of follow-up of the participants in The Study of Men Born in 1913. Diabetes 34: 1055-1058
20. Westlund K, Nicolaysen R (1972) Ten-year mortality and morbidity related to serum cholesterol. Scand J Clin Lab Invest 30 [Suppl 127]: 1-24
21. Wilson PW, McGee L, Kannel WB (1981) Obesity, very low density lipoproteins, and glucose intolerance over fourteen years. The Framingham Study. Am J Epidemiol 114: 697-704
22. Knowler WC, Pettitt DJ, Savage PJ, Bennett PH (1981) Diabetes incidence in Pima Indians: contributions of obesity and parental diabetes. Am J Epidemiol 113: 144-156
23. Butler WJ, Ostrander Jr LD, Carman WJ, Lamphiear DE (1982) Diabetes mellitus in Tecumseh, Michigan. Prevalence, incidence and associated conditions. Am J Epidemiol 116: 971-980
24. O'Sullivan JB, Mahan CM (1965) Blood sugar levels, glycosuria, and body weight related to development of diabetes mellitus. The Oxford Epidemiological Study 17 years later. JAMA 194: 117-122
25. Medalie JH, Herman JB, Goldbourt U, Papier CM (1978) Variations in incidence of diabetes among 10.000 adult Israeli males and the factors related to their development. Adv Metab Disord 9: 93-110
26. Papoz L, Eschwege E, Warnet I-M, Richard J-L, Claude J-R (1982) Incidence and risk factors of diabetes in the Paris Prospective Study (G.R.E.A.). In: Eschwege E (ed) Advances in diabetes epidemiology, INSERM Symp No 22. Elsevier, Amsterdam, pp 113-122
27. Keen H, Jarrett RJ, McCartney (1982) The ten-year follow-up of the Bedford Survey (1962-1972): glucose tolerance and diabetes. Diabetologia 22: 73-78
28. Modan M, Karasik A, Halkin H, Fuchs Z, Lusky A, Shitrit A, Modan B (1986) Effect of past and concurrent body mass index on prevalence of glucose intolerance and Type 2 (non-insulin-dependent) diabetes and on insulin response. The Israeli study of glucose intolerance, obesity and hypertension. Diabetologia 29: 82-89
29. Balkau B, King H, Zimmet P, Raper LR (1985) Factors associated with the development of diabetes in the Micronesian population of Nauru. Am J Epidemiol 122: 594-605
30. Jarrett RJ, Keen H, McCartney P (1984) The Whitehall Study: ten year follow-up report on men with impaired glucose tolerance with reference to worsening to diabetes and predictors of death. Diab Med 1: 279-283

31. Drury PL (1983) Diabetes and arterial hypertension. Diabetologia 24: 1-9
32. Fuller JH (1985) Epidemiology of hypertension associated with diabetes mellitus. Hypertension 7 [Suppl II]: 3-7
33. Bengtsson C, Blohme G, Lapidus L, Lindqvist O, Lundgren H, Nyström E, Petersen K, Sigurdsson JA (1984) Do antihypertensive drugs precipitate diabetes. Br Med J 289: 1495-1497
34. Wilson PWF, Anderson KM, Kannel WB (1986) Epidemiology of diabetes mellitus in the elderly. Am J Med 80 [Suppl 5A]: 3-9
35. Mohan V, Snehalatha C, Jayashree R, Ramachandran A, Viswanathan M, Kameswaran L, Rocic B, Breyer D, Skrabalo Z (1984) Serum uric acid concentrations in offspring of conjugal parents. Metabolism 33: 869-871
36. Herman JB, Goldbourt U (1982) Uric acid and diabetes: observations in a population study. Lancet II: 240-243
37. Nikkilä EA, Taskinen M-R (1975) Ethanol-induced alterations of glucose tolerance, postglucose hypoglycemia, and insulin secretion in normal, obese, and diabetic subjects. Diabetes 24: 933-943
38. Trell E, Kristensson H, Peterson B, Fex G, Henningsen NC, Berntorp K, Hood B (1981) Two-hour glucose and insulin response after a standardized oral glucose load in relation to serum gamma-glutamyl transferase and alcohol consumption. Acta Diabetol Lat 18: 311-317
39. Salmela PI, Sotaniemi EA, Pelkonen RO, Arranto AJ (1983) Blood lactate, hepatic histology and microsomal enzye activity in non-insulin-dependent diabetics. Diabete Metab 9: 100-105
40. Barnett AH, Spiliopoulos AJ, Pyke DA, Stubbs WA, Burrin J, Alberti KGMM (1981) Metabolic studies in unaffected co-twins of non-insulin-dependent diabetics. Br Med J 282: 1656-1658
41. Reaven GM, Holenbeck C, Jeng C-Y, Wu MS, Chen Y-II (1988) Measurement of plasma glucose, free fatty acid, lactate and insulin for 24 h in patients with NIDDM. Diabetes 37: 1020-1024
42. Jarrett RJ, Shipley MJ, Hunt R (1986) Physical activity, glucose tolerance and diabetes mellitus: the Whitehall Study. Diab Med 3: 549-551
43. King H, Zimmet P, Raper LR, Balkau B (1984) Risk factors for diabetes in three Pacific populations. Am J Epidemiol 119: 346-409
44. Berntorp K, Lindgärde F (1985) Impaired physical fitness and insulin secretion in normoglycaemic subjects with familial aggregation of Type 2 diabetes mellitus. Diabetes Res 2: 151-156
45. Barnett AH, Eff C, Leslie RDG, Pyke DA (1981) Diabetes in identical twins. A study of 200 pairs. Diabetologia 20: 87-93
46. Jeanrenaud B, Halimi S, van de Werve G (1985) Neuroendocrine disorders seen as triggers of the triad: obesity-insulinresistance - abnormal glucose tolerance. In diabetes and Metabolism Reviews Vol 1. Wiley & Sons, New York, pp 261-291
47. Jarrett RJ (1984) Type 2 (non-insulin-dependent) diabetes mellitus and coronary heart disease - chicken, egg or neither? Diabetologia 26: 99-102
48. Editorial (Landsberg L) (1987) Insulin and hypertension: lessons from obesity. N Engl J Med 317: 378-379
49. Ferrannini E, Buzzigoli G, Bonadonna R, Giorico MA, Oleggini M, Graziadei L, Pedrinelli R, Brandi L, Bevilacqua S (1987) Insulin resistence in essential hypertension. N Engl J Med 317: 350-357

Received: 10 March 1988
and in revised form: 6 September 1988

Dr. L.-O. Ohlson
Department of Medicine I
Sahlgren's Hospital
S-413 45 Gothenburg
Sweden