The association between blood glucose value and long-term mortality

PE Wändell, H Theobald

SUMMARY

This study aims at estimating the association between different fasting blood glucose levels (FBG) and total mortality during a long-term follow-up. In all 2,300 subjects were health examined, out of a stratified sample of 32,185 individuals aged 18—64 years drawn from the population in Stockholm County from the years 1969—70. FBG values were divided into following groups: < 3.0, 3.0-4.4, 4.5-5.5, 5.6-6.0, 6.1-6.6, and > 6.6 mmol/l (corresponding to fasting plasma glucose, FPG, < 3.5, 3.5-4.9, 5.0-6.0, 6.1-6.9, 7.0-7.7 and > 7.7 mmol/l), and known diabetes mellitus. All participants were followed up in the National Cause of Death Register up to the end of 1996. Multivariate analysis was performed by Cox regression, with three models, the first age- and sex-adjusted, the second also adjusted for care need category and hypertension, and the third with added BMI-category, with hazard ratios (HR) and 95% confidence interval (CI). Smoking habits were available for around half of the sample. Compared to the FBG showing the lowest mortality, i.e. FBG 5.6-6.0 mmol/l, we found an age- and sex-adjusted excess risk for subjects with known diabetes (HR 7.39, 95% CI 3.78-14.45), with FBG > 6.6 mmol/l (HR 2.30, 95% CI 1.20-4.39), and with FBG < 3.0 mmol/l (HR 3.44, 95% CI 1.47-8.06). The excess risk persisted when adjusting for care need, hypertension, BMI, and also for smoking. The cause of the increased mortality risk with low FBG values is unclear, but low FBG value seems to be a risk marker of poor health.

Key-words: Blood glucose · Diabetes mellitus · Mortality · Follow-up studies · Sweden.

Wändell PE, Theobald H. The association between blood glucose value and long-term mortality
Diabetes Metab 2005;31:588-594

RÉSUMÉ

Association entre glycémie à jeun et mortalité à long terme

Cette étude avait pour but d'évaluer l'association entre les différents niveaux de la glycémie à jeun (FBG) et la mortalité toutes causes confondues à long terme. L'état de santé d'un échantillon de 2 300 sujets issus d'une sélection stratifiée de 32 185 sujets âgés de 18 à 64 ans de la population du Département de Stockholm des années 1969-70 a été examiné. Les valeurs de FBG ont été réparties selon les groupes suivants : < 3,0, 3,0-4,4, 4,5-5,5, 5,6-6,0, 6,1-6,6, et > 6,6 mmol/l (correspondant aux glycémies à jeun plasmatiques, FPG, < 3,5, 3,5-4,9, 5,0-6,0, 6,1-6,9, 7,0-7,7 et > 7,7 mmol/l), et diabète sucré connu. Tous les participants ont pu être suivis grâce au Registre National des Causes de Décès jusqu'à la fin de 1996. Une analyse multivariée a été réalisée avec une régression de Cox, avec trois modèles, le premier ajusté sur l'âge et le sexe, le deuxième ajusté en outre sur la catégorie du besoin de soins et sur l'hypertension, et le troisième sur le niveau d'indice de masse corporelle, avec détermination du risque relatif (HR) et de l'intervalle de confiance à 95 % (CI). Les données concernant le tabagisme était disponibles pour la moitié environ de l'échantillon. Par comparaison au niveau de FBG associé à la mortalité la plus basse (FBG 5,6-6,0 mmol/l), il existe un risque élevé de mortalité, ajusté sur l'âge et le sexe, chez les sujets qui avaient un diabète connu (HR 7,39, CI 95 % 3,78-14,5), chez les sujets qui avaient une FBG supérieure 6.6 mmol/l (HR 2,30, CI 95 % 1,20-4,39), et chez les sujets qui avaient une FBG inférieure à 3,0 mmol/l (HR 3,44, CI 95 % 1,47-8,06). L'excès de mortalité persistait après ajustement pour la catégorie de besoin des soins, l'hypertension artérielle, l'indice de masse corporelle, et le tabagisme. Les causes de l'augmentation de mortalité associée au niveau glycémique le plus faible ne sont pas claires, mais ce niveau semble être le marqueur d'un mauvais état général.

Mots-clés : Glycémie à jeun · Diabète sucré · Mortalité · Étude longitudinale · Suède.

Address correspondence and reprint requests to:
PE Wändell. Center of Family Medicine, Alfred Nobels allé 12, S-141 83 Huddinge, Sweden.
per.wandell@ki.se

Center of Family and Community Medicine, Karolinska Institutet, Stockholm.

Received: April 21st, 2005; revised: September 18th, 2005

Diabetes mellitus and impaired glucose tolerance (IGT) are both associated with increased mortality, especially cardiovascular mortality. However, the glucose thresholds used to define diabetes were chosen without regard to the risk of cardiovascular disease or mortality, but to identify people at risk of eye and kidney disease [1,2].

Regarding all-term mortality and fasting glucose level, either measured as fasting plasma glucose (FPG) or fasting blood glucose (FBG), earlier studies have found a J-shaped relation between the lowest death rates and FPG values in the intervals centred around 5.5 mmol/l, or around 4.75 mmol/l [3,4]. Regarding cardiovascular mortality, a study of Norwegian men found an increase only in the highest glucose quartile (FBG > 85 mg/100 ml, corresponding to > 4.7 mmol/l) [5]. In contrast to that study, several other studies have found a graded and increasing relation between FPG/FBG values and cardiovascular risk factors, including cardiovascular mortality, without any sign of a clear threshold [6-8]. These findings are also observed for HbA_{1c} values [9].

The aim of this study was to study the effect on total mortality in different categories of fasting blood glucose values.

Materials and methods

During the years 1969-70, a stratified sample of 32,185 individuals aged 18-64 years was drawn out of the population in Stockholm County, which then had about 445,000 inhabitants in this age range. The population was stratified into three age groups, 18-24 years, 25-44 years and 45-64 years. From each of the strata a random sample was drawn, in the ratios of 3 to 2 to 1, as the primary purpose was an investigation of the need for care. The 32,185 sampled individuals received a postal questionnaire with 30 questions concerning physical and social difficulties in daily life, and health needs. The response rate was 87%. The individuals in the three age groups were classified in four different groups according to their estimated needs of services. This selection was made on the basis of the questionnaire and data obtained from registers containing information regarding hospitalisation and sick leave. Individuals with high needs were taken in a higher proportion in the subsequent randomisation procedure, as these were expected to be rather few, especially in the younger age groups. In this way a group of 3064 individuals was obtained. They were invited to the health-screening programme on average one year after the questionnaire survey and 2578 (84%) attended. 2407 individuals underwent an extensive health examination including blood test for fasting blood glucose. Data as regards blood pressure were available for 2300 of those. Thus the study group was composed of these 2300 subjects, i.e. 75% of the invited sample.

Blood glucose values

Subjects were classified into different groups according to the FBG value obtained, using a lower level, the median value in the actual study sample, and cut-off values for impaired fasting glucose (IFG) and diabetes according to WHO guidelines from 1999 and 1985, respectively [10-12]. The commonly used lower limit for the reference interval for fasting glucose values is set at FBG 3.0 mmol/l (FPG 3.5 mmol/l). The median value in the total sample was 4.5 mmol/l (FPG 5.0 mmol/l). Thus, the following groups were obtained: low FBG values, i.e. beneath 3.0 mmol/l (FPG < 3.5 mmol/l), normal FBG values beneath the median values, i.e. 3.0-4.4 mmol/l (FPG 3.5-4.9 mmol/l), normal FBG values above the median values, i.e. 4.5-5.5 mmol/l (FPG 5.0-6.0 mmol/l), impaired fasting glucose (IFG) according to WHO guidelines from 1999 [10,11], i.e. 5.6-6.0 mmol/l (FPG 6.1-6.9 mmol/l), diabetes according to WHO guidelines from 1999 but not according to WHO guidelines from 1985 [12], i.e. 6.1–6.6 mmol/l (FPG 7.0-7.7 mmol/l), diabetes according to the WHO guidelines from 1985, i.e. above 6.6 mmol/l (FPG 7.7 mmol/l), and already known and pharmacologically treated diabetes mellitus.

Covariates

Age adjustment was performed by 5-year groups. Care need group was defined as no, low or high need group, or not known, based on data on hospitalisation, sick leave and answers of questionnaire, estimating levels of expected care need. Hypertension was defined as systolic blood pressure above 140 and/or diastolic blood pressure above 90 mm Hg, or known diagnosis and treatment of hypertension. Smoking habits values were available only for 47.8% (n = 1100). BMI was calculated from measured weight and height, and expressed in kg/m^2. Overweight was defined as BMI 25-30, and obesity as above 30, according to WHO guidelines. Blood lipid values were not available.

Follow-up

All participants were followed up in the National Cause of Death Register up to the end of 1996. The National Cause of Death Register contains records of all deaths among the people of Sweden and is more than 99% complete except for some emigrants. Causes of death and main diagnoses during hospitalisation were recorded according to the International Statistical Classification of Diseases, Injuries and Causes of Death (8th and 9th revisions), based on certificates issued by physicians and coded at Statistics Sweden. The autopsy rate was about 40% during the study period.

Statistical analysis

Multivariate analysis was performed, utilising a Cox regression [13]. The results are shown as hazard ratios (HR)

for the exposure variable, with 95% confidence intervals (CI). In the statistical analyses the individuals were categorised into 5-year intervals of age, which also takes the sampling proportions in the strata into consideration, although they are not exactly in agreement with the sampling strata [14]. As reference level regarding FBG values the interval showing the lowest total mortality was chosen, i.e. FBG 5.6-6.0 mmol/l (FPG 6.1-6.9 mmol/l). From the death certificates the "underlying cause of death" was used for the calculations, and was available for all subjects in the study sample. The analyses were performed by the PHREG procedure in the SAS data package (SAS Institute Inc., Cary, NC, USA).

Ethics

The study was approved by the Research Ethics Committee at Karolinska Institutet.

Results

Descriptive data of the study population by sex are shown in Table I. Of the 2300 individuals in this study, 0.7% had known diabetes mellitus. According to the guidelines from 1985 the diabetes prevalence in the sample would be 1.8%, and to the guidelines from 1999 3.4%. The

Table I

Descriptive data of the study sample (n = 2300), by sex, and with number of deaths, are shown. FBG are fasting blood glucose levels, measured in mmol/l, hypertension is known hypertension or measured high blood pressure (systolic > 140 mmHg and/or diastolic > 90 mmHg), BMI is category of body mass index in kg/m^2, care need category is according to predicted care needs. Percentage is given as regards distribution for men and women, respectively.

	Men		Women	
Variable	***n***	**No. of deaths**	***n***	**No. of deaths**
Total	1130	328	1170	219
Age groups:				
18-24 years	293 (25.9%)	17	314 (26.8%)	7
25-44 years	445 (39.4%)	65	445 (38.0%)	41
45-64 years	392 (34.7%)	246	411 (35.1%)	171
Glucose levels:				
FBG –2.9	9 (0.8%)	2	18 (1.5%)	5
FBG 3.0–4.4	445 (39.4%)	111	677 (57.9%)	101
FBG 4.5–5.5	553 (48.9%)	165	423 (36.2%)	96
FBG 5.6–6.0	69 (6.1%)	19	28 (2.4%)	5
FBG 6.1–6.6	31 (2.7%)	13	6 (0.5%)	1
FBG 6.7–	16 (1.4%)	12	9 (0.8%)	3
Known diabetes	7 (0.6%)	6	9 (0.8%)	8
Blood pressure:				
Hypertension	277 (24.5%)	148	249 (21.3%)	115
No hypertension	853 (75.5%)	180	921 (78.7%)	104
BMI-groups:				
BMI < 25	775 (69.0%)	186	866 (75.3%)	115
BMI 25-30	304 (27.1%)	114	230 (20.0%)	69
BMI > 30	44 (3.9%)	26	45 (4.7%)	27
BMI missing	7	2	20	8
Care need groups:				
High care need	309 (27.3%)	133	303 (25.9%)	89
Low care need	269 (23.8%)	82	345 (29.5%)	60
No care need	428 (37.9%)	90	429 (36.7%)	60
Unknown care need	124 (11.0%)	23	93 (7.9%)	10

overall mortality after 26 years of follow-up was 23.8% (n = 547), 29.0% (n = 328) for men and 18.7% (n = 219) for women, and CVD-mortality was 10.0% (n = 229), 12.4% (n = 140) for men and 7.6% (n = 89) for women. Total hypertension rate was 22.9% (n = 526), and rate of known hypertension 4.5% (n = 103), 3.6% (n = 41) among men, and 5.3% (n = 62) among women. Smoking rate was 51.5%, 57.8% (n = 312/540) among men and 45.4% (n = 254/560) among women.

Results of Cox regression are shown in Table II for total and CVD-mortality, respectively. Three models are shown, Model I age- and sex-adjusted, Model II also including adjustment for hypertension and care need category, and Model III also with addition of BMI-category. Consistent, significant findings in the models as regards total mortality were the excess risk for subjects with known diabetes, with FBG over 6.7 mmol/l (however, not when adjusting for BMI-category) and FBG beneath 3.0 mmol/l. For subjects with FBG 6.1-6.6 mmol/l a non-significant excess risk was found. For CVD-mortality significant values was found only as regarded known diabetes. Excess risk for total and CVD-mortality was found for men, subjects with hypertension, and for subjects in the high care need group, and to some extent also for those in the low care group. Analyses for cancer death were also performed, showing figures essentially of the same levels as for total and CVD-mortality, however, not statistically significant.

When using a model including smoking habits (n = 1078) in addition to all others factors, the excess risk for all-cause mortality remained relatively stable for subjects with FBG beneath 3.0 mmol/l (HR 3.18, 95% CI 0.86-11.70), for those with FBG over 6.7 mmol/l (HR 1.81, 95% CI 0.63-5.20) and those with known diabetes (HR 8.17, 95% CI 2.93-22.75), while the risk decreased for subjects with FBG 6.1-6.6 mmol/l (HR 0.72, 95% CI 0.20-2.63), and it did not change any more for cardiovascular mortality. Test for interaction between smoking and FBG-levels for both total and CVD-mortality showed no statistical significance. The hazard ratio for smokers in the multivariate model was 1.79 (95% CI 1.36-2.36) for total mortality, and 1.72 (95% CI 1.12-2.64) for CVD-mortality.

Models for men and women separately are shown in Table III. Significant excess mortality risk was present for known diabetes for both men and women, and for low FBG only for women. For women, the lowest mortality was found for FBG 6.1-6.6 mmol/l.

Table II

Cox regression models assessing all and cardiovascular (CVD) mortality risk, respectively, during 26 years of follow-up among subjects with different levels of fasting blood glucose (FBG), measured in mmol/l. Three models are presented, Model I with adjustment for age and sex, and Model II also including adjustment for hypertension and category of care need, and Model III also with addition of BMI-categories (BMI-values were missing for 27 persons). Reference groups were as regards sex women, as regards hypertension normotensive subjects, as regards BMI-level those with BMI < 25, and as regards care need level those with no care needs.

	All deaths			**CVD-deaths**		
	Model I:	**Model II:**	**Model III:**	**Model I:**	**Model II:**	**Model III:**
Variable	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)
n	2300	2300	2273	2300	2300	2273
FBG –2.9	3.44 (1.47-8.06)	3.39 (1.44-7.99)	3.22 (1.37-7.60)	2.54 (0.56-11.56)	2.95 (0.64-13.62)	2.85 (0.62-13.20)
FBG 3.0–4.4	1.26 (0.82-1.92)	1.28 (0.83-1.97)	1.22 (0.79-1.88)	1.15 (0.63-2.10)	1.25 (0.67-2.33)	1.16 (0.62-2.18)
FBG 4.5–5.5	1.31 (0.86-1.99)	1.32 (0.86-2.02)	1.30 (0.85-1.99)	1.08 (0.59-1.96)	1.14 (0.62-2.12)	1.12 (0.60-2.09)
FBG 5.6–6.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
FBG 6.1–6.6	1.45 (0.75-2.81)	1.41 (0.73-2.75)	1.37 (0.70-2.66)	1.48 (0.58-3.79)	1.52 (0.59-3.94)	1.47 (0.57-3.80)
FBG 6.7–	2.30 (1.20-4.39)	2.02 (1.04-3.90)	1.80 (0.92-3.52)	1.63 (0.61-4.37)	1.77 (0.64-4.84)	1.56 (0.56-4.35)
Known diabetes	7.39 (3.78-14.45)	4.56 (2.31-9.02)	4.17 (2.10-8.27)	11.48 (4.86-27.12)	6.95 (2.85-16.94)	6.17 (2.51-15.17)
Hypertension	-	1.43 (1.19-1.72)	1.44 (1.19-1.75)	-	2.45 (1.83-3.29)	2.45 (1.81-3.31)
BMI 25-30	-	-	0.87 (0.72-1.05)	-	-	1.01 (0.76-1.36)
BMI >30	-	-	1.16 (0.85-1.58)	-	-	1.56 (0.56-4.35)
High care need	-	2.26 (1.83-2.80)	2.32 (1.87-2.87)	-	2.16 (1.54-3.03)	2.28 (1.16-3.22)
Low care need	-	1.33 (1.06-1.68)	1.32 (1.05-1.67)	-	1.79 (1.26-2.54)	1.80 (1.26-2.56)
Unknown care need	-	1.36 (0.92-1.99)	1.35 (0.92-1.99)	-	1.49 (0.79-2.82)	1.50 (0.79-2.84)
Male	2.01 (1.69-2.40)	2.05 (1.72–2.45)	2.07 (1.73-2.45)	2.27 (1.73-2.98)	2.44 (1.86-3.21)	2.44 (1.84-3.22)

Table III
Cox regression models assessing total mortality risk during 26 years of follow-up among men and women, respectively, with different levels of fasting blood glucose (FBG), measured in mmol/l. Three models are presented, Model I with adjustment for age and sex, and Model II also including adjustment for category of care need and hypertension, and Model III also addition of BMI-categories (BMI-values were missing for a few persons). Reference groups were: as regards hypertension, normotensive subjects; as regards BMI-level, those with BMI < 25, and as regards care need level, those with no care need.

	Men			Women		
	Model I:	**Model II:**	**Model III:**	**Model I:**	**Model II:**	**Model III:**
Variable	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)	Hazard Ratio (95%CI)
n	1130	1130	1123	1170	1170	1150
FBG-2.9	3.01 (0.69-13.09)	2.98 (0.68-13.06)	2.91 (0.66-12.74)	4.77 (1.37-16.60)	4.25 (1.21-14.93)	4.12 (1.17-14.56)
FBG 3.0-4.4	1.22 (0.75-1.99)	1.22 (0.74-2.02)	1.20 (0.73-1.99)	1.52 (0.62-3.75)	1.52 (0.61-3.79)	1.39 (0.55-3.46)
FBG 4.5-5.5	1.20 (0.74-1.93)	1.21 (0.74-1.97)	1.21 (0.74-1.98)	1.71 (0.70-4.22)	1.66 (0.67-4.13)	1.60 (0.64-4.00)
FBG 5.6-6.0	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
FBG 6.1-6.6	1.58 (0.78-3.22)	1.67 (0.82-3.41)	1.62 (0.80-3.31)	0.64 (0.07-5.53)	0.45 (0.05-3.95)	0.42 (0.05-3.68)
FBG 6.7-	2.30 (1.10-4.82)	1.80 (0.84-3.87)	1.62 (0.73-3.60)	2.20 (0.52-9.27)	2.79 (0.65-12.06)	2.74 (0.62-12.03)
Known diabetes	5.49 (2.15-14.03)	3.23 (1.24-8.41)	2.87 (1.07-7.65)	12.01 (3.88-37.22)	7.21 (2.28-22.79)	7.23 (2.27-23.07)
Hypertension	-	1.41 (1.11-1.79)	1.46 (1.14-1.86)	-	1.40 (1.03-1.92)	1.32 (0.95-1.82)
BMI 25-30	-	-	0.84 (0.66-1.08)	-	-	0.93 (0.67-1.29)
BMI >30	-	-	1.12 (0.70-1.78)	-	-	1.39 (0.88-2.18)
High care need	-	2.32 (1.76-3.06)	2.38 (1.80-3.14)	-	2.26 (1.61-3.19)	2.32 (1.64-3.30)
Low care need	-	1.42 (1.05-1.93)	1.42 (1.05-1.93)	-	1.23 (0.85-1.77)	1.18 (0.82-1.73)
Unknown care need	-	1.35 (0.84-2.16)	1.36 (0.85-2.19)	-	1.39 (0.70-2.78)	1.32 (0.66-2.63)

When excluding deaths occurring during the first five years of follow-up, the excess risk of total mortality, when adjusting for age, sex, hypertension, care need level and BMI-category, for low FBG values persisted (HR 3.38, 95% CI 1.42-8.02), while the risk further decreased for FBG > 6.6 mmol/l (HR 1.39, 95% CI 0.66-2.93).

Discussion

The main finding was a J-curved risk of long-term mortality in relation to FBG values. The excess risk associated with high FBG values was seen both in the group with already known diabetes, and in the group with diabetic FBG values according to the WHO diagnostic criteria from 1985, while the excess risk was not significant among those with diabetic FBG values according to the WHO diagnostic criteria from 1999 only. We also found an excess risk in subjects with low FBG values. This J-shaped relationship between glucose levels and mortality is found in earlier studies, e.g. in studies from the European DECODE Study [4,15], in a French study by Balkau et al. [3], and in an American study by Wei et al. [16]. The lowest total mortality in the DECODE study published in 2003 was found in subjects with a FPG of 4.5-5.0 mmol/l [4], in the study by Balkau et al in the interval 5.25-5.75 mmol/l [3], and in the study by Wei et al (after adjustment) in the interval 4.4-6.1 mmol [16].

In our study, the lowest mortality was found was shown for subjects classified as IFG, i.e. FBG values 5.6-6.0 mmol/l, corresponding to FPG values 6.1-6.9 mmol/l, thus higher than in the earlier mentioned studies. We have no satisfactory explanation to this finding. The classification into IFG has been also been questioned earlier [15,17,18], and our findings seem to strengthen those concerns. Thus, an IFG diagnosis does not in itself seem to denote an increased risk, but indicates a need for further clinical investigation, i.e. repeated fasting glucose values or oral glucose tolerance test, to identify high-risk individuals. Diabetes and high fasting glucose values are associated with increased morbidity and mortality, both CVD and non-CVD. However, as regards subjects diagnosed with diabetes according to the WHO criteria from 1999, i.e. in the FBG interval 6.1-6.6 mmol/l (FPG 7.0-7.7 mmol/l), we were only able to demonstrate a moderate but non-significant excess risk in total mortality. These criteria, however, were based on the risk of eye and kidney disease, and not on risk of death [10,11].

As regards the excess risk in low fasting glucose values, the DECODE Study Group showed an excess risk at FPG

values beneath 4.5 mmol/l, especially regarding non-cardiovascular mortality at FPG values below 4.0 mmol/l [4,15]. In the DECODE study subjects with FPG < 4.4 mmol/l were younger, had lower BMI, cholesterol and blood pressure, and were more often non-smokers [4]. Wei et al. found an increased risk of all-cause mortality, including a 3.3-fold increased risk of cardiovascular mortality, among subjects with FPG < 3.89 mmol/l, after multivariate adjustment for confounding factors [16]. Balkau et al found more men with suspected cirrhosis in the group with FPG beneath or equal to 4.75 mmol/l [3]. We found no specific pattern regarding underlying cause of death, and the excess risk was stable even when adjusting for other risk factors, and with exclusion of deaths during the first five years of follow-up. Otherwise the low FPG/FBG values could have been a sign of life-threatening clinical or sub-clinical disease, e.g., cancer. Thus, the adverse effect of low fasting glucose values on mortality remains obscure, but it may serve as a general marker of poor general health.

As regards gender, mortality of men was double that of women, i.e. the pattern usually found. Otherwise it is impossible to draw conclusions on gender differences of the mortality associated with the FBG-groups, due to an insufficient number of subjects in the most important groups.

The influence of the covariates is also of interest. The group with highest care need also showed the highest mortality risk, which is natural and merely an evidence of the accuracy of this categorization. As diabetic subjects are expected to have high care needs, this would explain the decreased mortality risk found among those subjects when adjusting for care need. As regards hypertension, the increased total and especially CVD-mortality is also natural. The increased mortality associated with smoking is also well known. However, smoking is also shown to increase the risk of type 2 diabetes [19,20], even if the most important predictive factor for smoking-associated mortality is the substantially increased risk of CVD, respiratory diseases and cancers. On the other hand obesity was found to show a rather low predictive effect.

There are some limitations in this study. Some important risk factors especially for cardiovascular disease and death were not available for all subjects, e.g. smoking habits was noticed for around half of the sample, and blood lipid values were not measured. The number of subjects in some of the groups, i.e. with FBG values beneath 3.0 mmol/l and above 6.0 mmol/l, including the subjects with known diabetes, was too small to allow secure evaluations. Thus, the analyses in further sub-groups, e.g., into men and women, and regarding CVD- and cancer-mortality, should be interpreted with caution, as the numbers were too low to yield enough statistical power. However, the general tendencies could be seen in these sub-groups as well, even if no conclusions could be drawn between differences between men and women, or between total, CVD and cancer-mortality. Glucose values were measured on one single occasion, and no oral glucose tolerance test (OGTT) was performed. Otherwise, it is recommended that the 2-hour glucose value at a 75-g OGTT be used rather than the FBG value for the diabetes diagnosis, as around 30% of the diabetic subjects will not be diagnosed because of normal FBG while having a diabetic 2-h glucose [21,22]. However, the test reliability is worse for OGTT than for fasting blood glucose [23]. In one large study the test-retest reproducibility was 66%, with the prevalence of diabetes decreasing from 19.3% with one OGTT to 11.3% on repeated testing of initial positive results [24]. Thus, using FBG value alone for diabetes diagnosis can be justified.

The strengths of the study are the high attendance rate and the long follow-up time, 26 years, and high quality of data from the National Cause of Death Register.

In conclusion, a J-shaped curve was found for all-cause mortality regarding FBG levels, with highest mortality among subjects with known diabetes at baseline, and also an excess mortality for subjects with FBG of 6.7 mmol/l (FPG 7.8 mmol/l) and above, and FBG below 3.0 mmol/l (FPG 3.5 mmol/l). The cause of the increased mortality risk for low FBG values is unclear, however low FBG values must be seen as a risk marker of poor health.

Acknowledgements – This study was supported with grants from Stockholm County Council.

References

1. European Arterial Risk Policy Group. A strategy for arterial risk assessment and management in type 2 (non-insulin-dependent) diabetes mellitus. European Arterial Risk Policy Group on behalf of the International Diabetes Federation European Region. Diabet Med 1997;14:611-21
2. DECODE Study Group. Consequences of the new diagnostic criteria for diabetes in older men and women. DECODE Study (Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe). Diabetes Care 1999;22:1667-71
3. Balkau B, Bertrais S, Ducimetiere P, Eschwege E. Is there a glycemic threshold for mortality risk? Diabetes Care 1999;22:696-9
4. DECODE Study Group European Diabetes Epidemiology Group. Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and noncardiovascular diseases? Diabetes Care 2003;26:688-96
5. Bjornholt JV, Erikssen G, Aaser E, et al. Fasting blood glucose: an underestimated risk factor for cardiovascular death. Results from a 22-year follow-up of healthy nondiabetic men. Diabetes Care 1999; 22:45-9
6. Coutinho M, Gerstein HC, Wang Y, Yusuf S. The relationship between glucose and incident cardiovascular events. A metaregression analysis of published data from 20 studies of 95,783 individuals followed for 12.4 years. Diabetes Care 1999;22:233-40
7. Shaw JE, Zimmet PZ, Hodge AM, et al. Impaired fasting glucose: how low should it go? Diabetes Care 2000;23:34-9
8. Kim DJ, Kim KW, Cho NH, Noh JH, Lee MS, Lee MK. The cutoff value of fasting plasma glucose to differentiate frequencies of cardio-

vascular risk factors in a Korean population. Diabetes Care 2003;26:3354-6

9. Khaw K-T, Wareham N, Bingham S, Luben R, Welch A, Day N. Association of hemoglobin A_{1c} with cardiovascular disease and mortality in adults: The European Prospective Investigation into Cancer in Norfolk. Ann Intern Med 2004;141:413-20

10. Alberti KG, Zimmet PZ. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. Diabet Med 1998;15:539-53

11. WHO. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva: World Health Organization. Department of Noncommunicable Disease Surveillance; 1999.

12. WHO Study Group. Diabetes Mellitus. Geneva: WHO; 1985. Report No.: WHO Technical Report Series 727

13. Cox DR. Regression models and life-tables. J R Stat Soc 1972;34: 187-220

14. Nordberg L. Generalized linear modelling of sample survey data. J Official Statistics 1989;3:223-39

15. DECODE Study Group the European Diabetes Epidemiology Group. Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. Arch Intern Med 2001;161: 397-405

16. Wei M, Gibbons LW, Mitchell TL, Kampert JB, Stern MP, Blair SN. Low fasting plasma glucose level as a predictor of cardiovascular disease and all-cause mortality. Circulation 2000;101:2047-52

17. Davies M. New diagnostic criteria for diabetes--are they doing what they should? Lancet 1999;354:610-1

18. DECODE Study Group. Glucose tolerance and mortality: comparison of WHO and American Diabetes Association diagnostic criteria. The DECODE study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe. Lancet 1999;354:617-21

19. Rimm EB, Chan J, Stampfer MJ, Colditz GA, Willett WC. Prospective study of cigarette smoking, alcohol use, and the risk of diabetes in men. BMJ 1995;310:555-9

20. Wannamethee SG, Shaper AG, Perry IJ. Smoking as a modifiable risk factor for type 2 diabetes in middle-aged men. Diabetes Care 2001;24: 1590-5

21. DECODE Study Group. Is fasting glucose sufficient to define diabetes? Epidemiological data from 20 European studies. The DECODE-study group. European Diabetes Epidemiology Group. Diabetes Epidemiology: Collaborative analysis of Diagnostic Criteria in Europe. Diabetologia 1999;42:647-54

22. The DECODE Study Group. Age- and sex-specific prevalences of diabetes and impaired glucose regulation in 13 European cohorts. Diabetes Care 2003;26:61-9

23. Barr RG, Nathan DM, Meigs JB, Singer DE. Tests of glycemia for the diagnosis of type 2 diabetes mellitus. Ann Intern Med 2002;137:263-72

24. Ko GT, Chan JC, Woo J, et al. The reproducibility and usefulness of the oral glucose tolerance test in screening for diabetes and other cardiovascular risk factors. Ann Clin Biochem 1998;35 (Pt 1):62-7