Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death.

Hedblad, Bo; Nilsson, P; Engström, Gunnar; Berglund, Göran; Janzon, Lars

Published in:
Diabetic Medicine

DOI:
10.1046/j.1464-5491.2002.00719.x

2002

DM

Insulin resistance in non-diabetic subjects is associated with increased incidence of myocardial infarction and death

B. Hedblad*†, P. Nilsson*, G. Engström†, G. Berglund* and L. Janzon†

*Department of Medicine and
†Department of Community Medicine, Lund University, Malmö University Hospital, Malmö, Sweden

Accepted 26 November 2001

Abstract

Aims To compare the incidence of myocardial infarction and death in non-diabetic subjects with and without insulin resistance.

Methods Population-based prospective cohort study, in Malmö, Sweden, of 4748 non-diabetic subjects (60% women), aged 46–68 years, with no history of myocardial infarction or stroke. The prevalence of insulin resistance was established by the homeostasis model assessment (HOMA) and defined as values above the sex-specific 75th percentile (1.80 for women and 2.12 for men). Incidence of myocardial infarction and death is based on record linkage with local and national registers. Cox's proportional hazards model was used to assess the influence of insulin resistance after adjustment for age, sex, hyperglycaemia, raised arterial blood pressure, dyslipidaemia, central obesity, smoking and leisure-time physical activity.

Results Sixty-two subjects suffered a coronary event, and 93 subjects died during the 6-year follow-up period. Insulin resistance was after adjustment for other factors included in the insulin resistance syndrome and other potential confounders, associated with an increased incidence of coronary events (relative risk (RR) 2.18; 95% confidence interval (CI) 1.22–3.87; $P = 0.008$) and deaths (RR 1.62; 1.03–2.55; $P = 0.038$).

Conclusions Insulin resistance, as assessed by the HOMA method, was in this cohort of middle-aged non-diabetic subjects associated with an increased incidence of myocardial infarction and death. This risk remained when smoking, low physical activity and factors included in the insulin resistance syndrome were taken into account in a stepwise regression model.

Diabet. Med. 19, 470–475 (2002)

Keywords insulin resistance, HOMA, coronary heart disease, mortality

Abbrevations HOMA, homeostasis model assessment; HDL, high-density lipoprotein; RR, relative risk; CI, confidence interval

Introduction

During the last 25 years at least 20 prospective studies have been published in which hyperinsulinaemia, as a marker of insulin resistance, has been evaluated as a risk factor for cardiovascular disease and death [1–3]. Although in some studies insulin resistance has been associated with an increased incidence of myocardial infarction and death, results are far from unequivocal [1]. This may be due to differences with regard to rules for inclusion and exclusion of study subjects. In some studies patients with diabetes have been included in the cohort with insulin resistance. Only a few studies have used a random sample from the general population [1].

Based on a sample of non-diabetic subjects from the 'Diet and Cancer' cohort [4] in Malmö, Sweden, in which intima-media thickness and prevalence of asymptomatic stenosis in

Correspondence to: Dr Bo Hedblad, Department of Community Medicine, Malmö University Hospital, 205 02 Malmö, Sweden. E-mail: Bo.Hedblad@smi.mas.lu.se

the carotid arteries were compared in non-diabetic cases with insulin resistance and non-insulin resistance controls, it was concluded that initially observed associations with insulin resistance could be entirely accounted for by covariance with other cardiovascular risk factors, especially hypertension [5].

In order to assess whether insulin resistance may have any relationship with the progression and complications of atherosclerosis we have now compared the incidence of myocardial infarction and death in subjects with and without insulin resistance, as assessed by the homeostasis model assessment (HOMA) [6–8].

Methods

Study population

The 1862 men and 2886 women are a sample from the cohort study on 'Diet and Cancer' in Malmö, Sweden [4]. A random 50% of those who entered the study (n = 11 456) between November 1991 and February 1994, born between 1926 and 1945, were invited to take part in a study of the epidemiology of carotid artery disease [5]. The 5540 subjects who accepted were re-scheduled for blood sampling under standardized circumstances. Subjects with a history of myocardial infarction or stroke (n = 144), diabetes mellitus (n = 136) and subjects whose fasting whole blood glucose were ≥ 6.1 mmol/l (i.e. plasma glucose ≥ 7.0 mmol/l, n = 308) were excluded [9]. Another 204 individuals were excluded because of incomplete data.

The Ethics Committee at Lund University, Sweden, approved the study. Each proband gave his or her written informed consent.

Clinical and physical examination data

Information regarding smoking habits, physical activity, medical history and use of medication is based on a self-administered structured questionnaire. Smoking habits were categorized into never smokers, former smokers and current smokers. The assessment of physical activity during leisure time is based on the average time per week (in minutes) one spends on each of the 17 activities listed in the questionnaire, multiplied by an intensity factor ranging from 4 to 8 [10,11]. The sum of these products is the activity index. In the analysis we have used the following categories: low (Quartile 1), moderate (Q2–3), and high (Q4) physical activity.

Blood pressure (mmHg) in supine position was measured once after 10 min rest. Weight (kg) and height (cm) were measured while the subjects wore light indoor clothing and were without shoes. Waist circumference (cm) was measured at the umbilicus. Overnight fasting blood samples were drawn for determination of serum values for blood lipids (i.e. triglycerides and high-density lipoprotein (HDL) cholesterol), whole blood glucose, ery-HbA_{1c} and plasma insulin. Analyses were carried out at the Department of Clinical Chemistry, Malmö University Hospital, which is attached to a recurrent standardization system. Insulin levels in mIU/l (nmol/l = mIU/L × 7.175/1000) were measured by a non-specific radioimmunoassay [12]. Intra- and interassay coefficients of variation were 5% and 8%, respectively.

Individuals with a fasting whole blood glucose level ≥ 5.6 mmol/l (i.e. plasma glucose ≥ 6.1 mmol/l) were considered to have an impaired fasting glucose regulation or hyperglycaemia. Raised arterial blood pressure was defined as a blood pressure ≥ 140/90 mmHg or use of blood pressure-lowering medication. The cut-off value for definition of central obesity was waist circumference 94 cm for men and 80 cm for women. Presence of dyslipidaemia was defined as a triglyceride level > 2.0 mmol/l or a HDL-cholesterol level < 1.0 mmol/l.

Definition of insulin resistance

Criteria used for the definition of insulin resistance are in accordance with the recently published guidelines proposed by the European Group of the study of Insulin Resistance (EGIR) [13]. Fasting insulin × fasting blood glucose/22.5 were in accordance with the HOMA model calculated for each individual [4]. Subjects whose values exceeded the sex-specific 75th percentile (i.e. 1.80 for women and 2.12 for men) were considered to have insulin resistance (HOMA-IR) [13].

Retrieval of endpoints

Information on morbidity and mortality following the health examination was obtained by record linkage with the National Inpatient Register (Swedish Board on Health and Welfare), the Swedish Causes of Death Register and the Malmö Heart Infarction Registry [14,15]. Underlying cause of death, respectively, hospitalization diagnosis, was coded in accordance with the 9th version of the *International Classification of Diseases* [16]. Incidences of myocardial infarction and deaths have been updated until 31 December 1997.

A coronary event was defined as a fatal or non-fatal myocardial infarction or death from coronary heart disease. Each individual was followed until 31 December 1997, date of a first coronary event or death.

Statistical analysis

SPSS was used for the statistical analyses [17]. The Kaplan–Meier method [18], with the generalized Wilcoxon rank sum test, was used for the computation of incidence of coronary events and overall survival in relation to insulin resistance. Rates were expressed in terms of events per 1000 person-years. Cox's proportional hazards model [19], using a backward likelihood-ratio method (probability for stepwise entry 0.05 and removal 0.10), was used to estimate the influence of insulin resistance on the incidence of coronary events and death after adjustment for differences with regard to age and sex. In a second model further adjustment was made for differences with regard to risk factors included in the insulin resistance syndrome, i.e. hyperglycaemia, raised arterial blood pressure, dyslipidaemia and central obesity [13], and life-style factors, i.e. smoking and leisure time physical activity. Due to a limited number of events, missing values on life-style covariates (n = 157 subjects) were coded into the model as dummy variables. Since fasting blood glucose is included in the HOMA calculation and thus

very strongly correlated ($r = 0.51$, $P < 0.001$) to HOMA [5], we also used HbA_{1c}, which is less correlated to HOMA ($r = 0.13$) as an indicator of hyperglycaemia, in an additional Cox's regression model. Age, systolic blood pressure, HDL-cholesterol, triglycerides, fasting blood glucose, HbA_{1c} and waist circumference were introduced as continuous variables. All other covariates, i.e. sex (males and female), treatment for hypertension (yes vs. no), smoking (yes vs. no) and low level of physical activity (yes vs. no) were fitted as categorical variables. The fit of the proportional hazards model was confirmed by plotting the hazards function in different groups over time. There was no indication that the proportional-hazards assumption was violated. The interaction of waist circumference with sex was investigated by including interaction terms in the regression equations. The results of the test of interaction between sex and waist circumference in the analyses of incidence of coronary events and all-cause mortality were statistically non significant (i.e. $P = 0.123$ and $P = 0.838$, respectively). Relative risk was computed as the antilogarithm of the risk coefficient. All confidence intervals were calculated at the 95% level.

Results

Mortality rates and incidence of coronary events

During a median follow-up time of 5 years (range 0.04–6.23 years), 23 715 person-years were accumulated. Cardiovascular disease (ICD-9: 390–448) was the cause of death for 27 (30%) of the 93 subjects who died, cancer for 51 (54%), and 15 (16%) died from other causes. Cause of death was based on autopsy in 50% of the deceased subjects. There were in all 62 coronary events (43 men and 19 women), of which 17 were fatal.

Incidence of events in relation to insulin resistance

The relative risk of a coronary event was twice as high in the insulin resistance group as it was in the non-insulin resistance control group (relative risk (RR) after adjustment for age and sex 2.06; 95% confidence interval (CI) 1.24–3.41; $P = 0.005$). In terms of the overall rate of mortality the corresponding RR was 2.07; 95% CI 1.37–3.13; $P < 0.001$ (Table 1, Fig. 1).

The relative risk of a coronary event remained statistically significant when other factors included in the insulin resistance syndrome and smoking and physical activity were taken into account (RR 2.18; 95% CI 1.22–3.87; $P = 0.008$). When HbA_{1c} was used in the model instead of fasting blood glucose, the corresponding RR was 1.90; 1.14–3.16; $P = 0.013$.

The influence of insulin resistance on the overall rate of mortality similarly remained statistically significant after adjustment for other factors involved in the insulin resistance syndrome and life-style factors, i.e. smoking and leisure-time physical activity, were taken into account: RR 1.62; 95% CI 1.03–2.55; $P = 0.038$. The corresponding RR when HbA_{1c} was included in the model was 1.94; 1.27–2.94; $P = 0.002$.

Table 1 Incidence and estimated covariate-adjusted relative risk (RR) of coronary events (i.e. fatal and non-fatal myocardial infarction or coronary heart disease (CHD) deaths) and survival in relation to insulin resistance (HOMA-IR) in non-diabetic subjects

	HOMA-IR	
	No	Yes
CHD event		
Events/subjects at risk	36/3559	26/1189
Incidence/1000 person-years	2.02 (1.42–2.80)	4.47 (2.92–6.55)
Age- and sex-adjusted RR	Reference	2.06 (1.24–3.41)
Full model, RR*	Reference	2.18 (1.22–3.87)
All cause mortality		
Events/subjects at risk	54/3559	39/1189
Incidence/1000 person-years	3.02 (2.27–3.94)	6.67 (4.75–9.12)
Age- and sex-adjusted RR	Reference	2.07 (1.37–3.13)
Full model, RR*	Reference	1.62 (1.03–2.55)

*Covariates included in the Cox's model, using a stepwise backward likelihood-ratio, were age, sex and other components involved in the insulin resistance syndrome, i.e. systolic blood pressure, treatment for hypertension, HDL-cholesterol, triglycerides, fasting glucose and waist circumference and life-style factors, i.e. smoking and leisure-time physical activity.

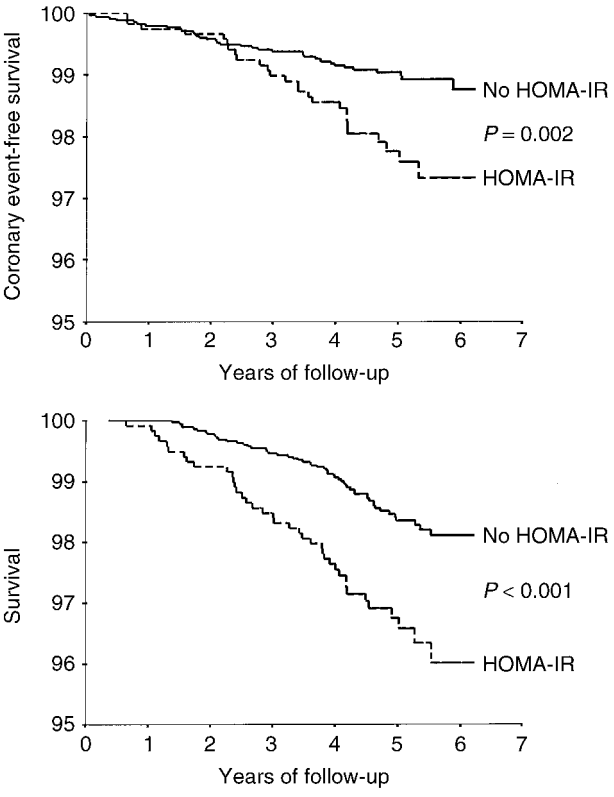

Figure 1 Coronary event rates (fatal and non-fatal myocardial infarction and coronary heart disease deaths, upper panel) and all-cause mortality rates (lower panel) in non-diabetic subjects in relation to insulin resistance as assessed by HOMA.

Prevalence of cardiovascular risk factors in quartiles with regard to insulin sensitivity

Age was somewhat higher in the fourth HOMA quartile (= insulin resistance group) than it was in the first (Table 2). All factors included in the insulin resistance syndrome were similarly more prevalent in that group. Three out of four had, according to the cut-off levels proposed by EGIR [11], raised arterial blood pressure, 67% central obesity, 36% dyslipidaemia and 20% hyperglycaemia. Smoking was less common and low physical activity more common among those with insulin resistance.

Discussion

Our results support the view [1–3] that insulin resistance is associated with an increased incidence of coronary heart disease and death. This risk remained statistically significant when smoking, physical activity and cardiovascular risk factors included in the insulin resistance syndrome were taken into account in a Cox's stepwise regression model.

It has been suggested that insulin contributes to the atherogenetic process [20]. Carotid and femoral intima-media thickness are related to plasma levels of insulin, independent of other components involved in the insulin resistance syndrome [21–23]. No similar independent relationship has yet been demonstrated for pro-insulin [22–24]. Based on a sample of non-diabetes subjects from the 'Diet and Cancer' cohort in Malmö, Sweden, in which intima-media thickness and prevalence of asymptomatic stenosis in the carotid arteries were compared in non-diabetic cases with insulin resistance and non-insulin resistance controls [5], it was concluded that associations with insulin resistance were entirely accounted for by its covariance with other cardiovascular risk factors, especially hypertension. As a number of cross-sectional studies have failed to demonstrate any independent relationship between insulin resistance and ultrasound-assessed measures of atherosclerosis, the exact role insulin may have in the

Table 2 Baseline characateristics in relation to quartiles of HOMA-assessed insulin sensitivity in non-diabetic subjects

	Quartiles of HOMA				
	1 *n* = 1207	2 *n* = 1185	3 *n* = 1167	4 *n* = 1189	Age-adjusted *P* for trend
Age (years)	56.6 ± 6.0	57.2 ± 5.9	57.6 ± 5.9	58.1 ± 5.9	
Male sex (%)	39.0	39.6	39.2	39.0	0.991
Glucose status					
Fasting insulin (mIU/l)	3 (3–5)	5 (4–9)	7 (5–11)	11 (7–186)	**
Fasting glucose (mmol/l)	4.6 ± 0.4	4.8 ± 0.4	5.0 ± 0.4	5.2 ± 0.4	**
Hyperglycaemia* (%)	1.4	3.8	8.7	20.1	**
Ery-HbA_{1c} (%)	4.7 ± 0.4	4.7 ± 0.4	4.8 ± 0.4	4 .8 ± 0.4	< 0.001
Blood pressure status					
Systolic (mmHg)	137 ± 19	139 ± 18	141 ± 18	145 ± 19	< 0.001
Diastolic (mmHg)	85 ± 10	86 ± 10	87 ± 9	89 ± 9	< 0.001
Treatment (%)	8.8	10.4	13.8	22.0	< 0.001
Raised arterial BP*, (%)	52.3	56.7	63.2	73.8	< 0.001
Body composition					
Body mass index (kg/m^2)	23.6 ± 2.8	24.5 ± 3.1	25.7 ± 3.2	28.2 ± 4.1	< 0.001
Waist–hip ratio	0.82 ± 0.08	0.84 ± 0.09	0.85 ± 0.09	0.87 ± 0.10	< 0.001
Waist circumference (cm)	77.3 ± 10.2	80.2 ± 11.1	83.3 ± 11.2	89.9 ± 12.4	< 0.001
Central obesity* (%)	12.1	22.4	38.0	67.1	< 0.001
Blood lipid status					
Total cholesterol (mmol/l)	6.0 ± 1.1	6.1 ± 1.1	6.2 ± 1.1	6.3 ± 1.1	< 0.001
LDL-cholesterol (mmol/l)	4.0 ± 1.0	4.2 ± 1.0	4.2 ± 1.0	4.3 ± 1.0	< 0.001
HDL-cholesterol (mmol/l)	1.5 ± 0.4	1.5 ± 0.4	1.4 ± 0.3	1.3 ± 0.3	< 0.001
Triglycerides (mmol/l)	0.9 (0.3–4.2)	1.2 (0.4–7.6)	1.2 (0.4–6.1)	1.5 (0.4–5.3)	< 0.001
Dyslipidaemia* (%)	9.2	13.9	21.6	35.9	< 0.001
Life-style factors					
Former smokers (%)	35.1	36.4	39.1	37.2	0.203
Current smokers (%)	26.2	22.6	20.2	21.4	0.014
Low physical activity (%)	20.9	21.6	26.1	28.6	< 0.001

BP, Blood pressure.

*Cut-off levels for these conditions were according to the European Group of the study of Insulin Resistance (EGIR) [11]. Fasting hyperglycaemia was defined as fasting whole blood glucose level ≥ 5.6 mmol/l (i.e. plasma glucose ≥ 7.0 mmol/l). Hypertension was defined as blood pressure ≥ 140/90 mmHg or treatment for hypertension. Central obesity was defined as a waist circumference > 94 cm for men and > 80 cm for women. Dyslipidaemia was defined as a triglyceride level > 2.0 mmol/l or a HDL-cholesterol level < 1.0 mmol/l.

**Selection criteria not tested for statistical significance. Figures are shown as mean (SD) or when appropriate as median (range).

early atherosclerotic process remains to be determined [5,24,27].

There is evidence linking insulin resistance to the complications of atherosclerosis. Several prospective studies have shown that hyperinsulinaemia is independently associated with myocardial infarction [1–3]. This is compatible with the hypothesis that insulin contributes to the steps preceding this event [28,29].

Evidence from both clinical and epidemiological studies has shown that hyperinsulinaemia or insulin resistance covaries with several risk factors for cardiovascular disease, i.e. raised arterial blood pressure, lipid abnormalities, impaired glucose tolerance, obesity and certain thrombogenic factors [30,31]. The association between insulin resistance and the occurrence of myocardial infarction was, however, only marginally changed when adjustment was made for differences between cases and controls with regard to markers of the insulin resistance syndrome and life-style factors which may have acted as confounders.

Studies in which the assessment of insulin resistance has been compared with the hyperinsulinaemic-euglycaemic clamp do not indicate that the results could have been confounded by misclassification [7,32]. However, categorization of insulin resistance was based on one sample. By dichotomizing the study group into those with and those without insulin resistance, misclassification due to lack of precision should have been reduced.

As insulin resistance is associated with an increased incidence of Type 2 diabetes, one could question whether this may explain the increased risk of myocardial infarction in that group. Based on the incidence figures in published studies we conclude that, in subjects with insulin resistance, those who sustain a cardiovascular event over 6 years will far exceed those who develop diabetes [8,33].

Vital status at the end of the follow-up was updated on all individuals by data linkage with regional and national registers. The completeness and validity of these registers has been documented in several other studies from the city [15]. About 50% of the death certificates were based on autopsy.

Change of exposure is an inherent problem in long-term studies. It has been shown that the risk of cardiovascular disease in relation to insulin resistance diminishes over time [3,34]. To what extent this relates to treatment of cardiovascular risk factors associated with insulin resistance remains to be evaluated. However, this tends to dilute an existing risk.

The increased cardiovascular morbidity and mortality rates associated with insulin resistance have mainly been shown for men. Although many prospective studies have included both men and women, few have presented sex-specific rates [1–3]. Only one study has demonstrated a positive relationship between hyperinsulinaemia and coronary heart disease in women. However, in that study no similar association was found in men [2]. To assess the influence of insulin resistance on the distribution of cardiovascular disease in the population we need to understand the factors modifying the risk of exposure.

Acknowledgements

The study was supported by grants from the Swedish Cancer Society, the Medical Research Council, the Swedish Heart and Lung Foundation, the King Gustav V Jubilee Foundation, and by the Ernhold Lundström Foundation.

References

1 Ruige JB, Assendelft JJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease. A meta-analysis. *Circulation* 1998; **97**: 996–1001.
2 Folsom AR, Szklo M, Stevens J, Liao F, Smith R, Ekfeldt JH. A prospective study of coronary heart disease in relation to fasting insulin, glucose, and diabetes: the Atherosclerosis Risk in Communities (ARIC) Study. *Diabetes Care* 1997; **20**: 935–942.
3 Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men. The 22-year follow-up results of the Helsinki Policemen Study. *Circulation* 1998; **98**: 398–404.
4 Berglund G, Elmståhl S, Janzon L, Larsson SA. The Malmö Diet, Cancer Study. Design and feasibility. *J Intern Med* 1993; **233**: 45–51.
5 Hedblad B, Nilsson P, Janzon L, Berglund G. Relation between insulin resistance and carotid intima-media thickness and stenosis in non-diabetic subjects. Results from a cross-sectional study in Malmö, Sweden. *Diabet Med* 2000; **17**: 299–307.
6 Matthews DR, Hosker JP, Rudsenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and β-cell function from fasting plasma glucose and insulin concentrations in man. *Diabetologia* 1985; **28**: 412–419.
7 Haffner SM, Miettinen H, Stern MP. The homeostasis model in the San Antonio Heart Study. *Diabetes Care* 1997; **20**: 1087–1092.
8 Haffner SM, Kennedy E, Gonzalez C, Stern MP, Miettinen H. A prospective analysis of the HOMA model. The Mexico City Diabetes Study. *Diabetes Care* 1996; **19**: 1138–1141.
9 Alberti KGMM, Zimmet P for the WHO Consultation. 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**: 539–553.
10 Taylor HL, Jacobs D, Schucker B, Knudsen J, Leon AS, Debacker G. A questionnaire for the assessment of leisure time physical activities. *J Chron Dis* 1978; **31**: 741–755.
11 Richardsson MT, Leon AS, Jacobs DR Jr, Ainsworth BE, Serfass R. Comprehensive evaluation of the Minnesota leisure time physical activity questionnaire. *J Clin Epidemiol* 1994; **47**: 271–281.
12 Thorell JI, Larson SM. *Radioimmunoassay and Related Techniques*. St Louis: CV Mosby Co., 1978: 205–211.
13 Balkau B, Charles M for the European Group for the Study of Insulin Resistance (EGIR). Comment on the provisional report from the WHO Consultation. *Diabet Med* 1999; **16**: 442–443.
14 Anonymous. *Causes of Death 1995*. Stockholm: The National Board of Health and Welfare, Centre of Epidemiology, 1997.
15 Tydén P, Hansen O, Janzon L. Intra-urban variations in incidence and mortality in myocardial infarction. A study from the myocardial infarction register in the city of Malmö, Sweden. *Eur Heart J* 1998; **19**: 1795–1801.
16 Anonymous. *Classification of Causes of Death in Swedish Statistics*, Reports on Statistical Co-ordination 1990, 3. Stockholm: Statistics Sweden, 1990.
17 Norusis MJ. *SPSS/PC + Statistics 4.0 for the IBM PC/XT/AT and PS/2*. Chicago: SPSS, 1990.
18 Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc* 1958; **53**: 457–481.

19 Cox DR. Regression models in life tables. *J R Stat Soc* 1972; **34**: 187–220.
20 Stout RW. Insulin and atheroma: 20-yr perspective. *Diabetes Care* 1990; **13**: 956–654.
21 Folsom AR, Eckfeldt JH, Weitzman S, Ma J, Chambless L, Barnes R *et al.* for the Atherosclerosis Risk in Communities (ARIC) Study Invesigators. Relation of carotid artery wall thickness to diabetes mellitus, fasting glucose and insulin, body size, and physical activity. *Stroke* 1994; **25**: 66–73.
22 Haffner SM, D'Augustino R, Mykkänen L, Hales CN, Savage PJ, Bergman R *et al.* Proinsulin and insulin concentrations in relation to carotid wall thickness. *Stroke* 1998; **29**: 1498–1503.
23 Bokemark L, Wikstrand J, Fagerberg B. Intact insulin, insulin propeptides, and intima-media-thickness in the femoral artery in 58-year-old clinical healthy men—the Atherosclerosis and Insulin Resistance Study. *Angiology* 2001; **52**: 237–245.
24 Howard G, O'Leary D, Zaccaro D, Haffner S, Rewers M, Hamman R *et al.* Insulin sensitivity and atherosclerosis. *Circulation* 1996; **93**: 1809–1817.
25 Bonora E, Tessari R, Micciolo R, Zenere M, Targher G, Padovani R *et al.* Intima-media thickness of the carotid artery in nondiabetic and NIDDM subjects. *Diabetes Care* 1997; **4**: 627–631.
26 Suzuki M, Shinozaki K, Kanazawa A, Hara Y, Hattori Y, Tsushima M *et al.* Insulin resistance as independent risk factor for carotid wall thickening. *Hypertension* 1996; **28**: 593–598.
27 Bokemark L, Wikstrand J, Attvall S, Hulthe J, Wedel H, Fagerberg H. Insulin resistance and intima-media thickness in the carotid and femoral arteries of clinically healthy 58-year-old men. The Atherosclerosis and Insulin Resistance study (AIR). *J Intern Med* 2001; **249**: 59–67.
28 Båvenholm P, Proudler A, Silveira A, Crook D, Blomback M, de Faire U *et al.* Relationship of insulin and intact and split proinsulin to haemostatic function in young men with and without coronary artery disease. *Thromb Haemost* 1995; **73**: 568–575.
29 Agewall S, Bokemark L, Wikstrand J, Lindahl A, Fagerberg B. Insulin sensitivity and hemostatic factors in clinically healthy 58-year-old men. *Thromb Haemost* 2000; **84**: 571–575.
30 Reaven GM. The role of insulin resistance in human disease. *Diabetes* 1988; **37**: 1595–1607.
31 Haffner SM. Cardiovascular risk factors and the prediabetic syndrome. *Ann Med* 1996; **28**: 363–370.
32 Bonora E, Kiechl S, Willeit J, Oberhollenzer F, Egger G, Targher G *et al.* Prevalence of insulin resistance in metabolic disorders. *Diabetes* 1998; **47**: 1643–1649.
33 Haffner SM, Valdez RA, Hazuda HP, Mitchell BD, Morales PA, Stern MP. Prospective analysis of the insulin-resistance syndrome (Syndrome X). *Diabetes* 1992; **41**: 715–722.
34 Balkau B, Eschwege E. Insulin resistance: an independent risk factor for cardiovascular disease? *Diabetes, Obesity Metab* 1999; **1**: S23–S31.