Hyperinsulinaemia as long-term predictor of death and ischaemic heart disease in nondiabetic men: The Malmö Preventive Project.

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Hyperinsulinaemia as long-term predictor of death and ischaemic heart disease in nondiabetic men: The Malmö Preventive Project

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Abstract. Nilsson P, Nilsson J-Å, Hedblad B, Eriksson K-F, Berglund G. (University Hospital, Malmö, Sweden) Hyperinsulinaemia as long-term predictor of death and ischaemic heart disease in nondiabetic men: The Malmö Preventive Project. *J Intern Med* 2003; **253:** 136–145.

Objectives. Prospective studies have indicated that hyperinsulinaemia/insulin resistance is a risk factor for ischaemic heart disease (IHD), the risk decreasing with time of follow-up. Few studies have so far investigated the role of hyperinsulinaemia in the prediction of long-term total mortality.
Setting. Section of Preventive Medicine, Department of Medicine, University Hospital, Malmö, Sweden.
Subjects. A total of 6074 nondiabetic, middle-aged, healthy Swedish males.
Screening examination. We determined IHD risk factors including blood glucose and plasma insulin before and 2 h after an oral glucose tolerance test (OGTT). Total follow-up time was 19 years. Hyperinsulinaemia was defined as values above the 10th decentile of fasting or 2 h insulin concentration.
Main outcome measures. Total mortality and cardiac event (CE) rate for IHD.
Results. Unadjusted relative risks (RRs) for both death and CE were J-shaped with the highest relative risk (RR: 1.4–1.6) in the hyperinsulinaemic group compared with all other men. The RRs for death and CE were significant for fasting insulin but became nonsignificant after adjustment for other risk factors and also with a longer follow-up. The risk of death in hyperinsulinaemic men, defined on the basis of 2-h insulin level, increased with time of follow-up and was still significantly increased after 19 years [RR: 1.32 (95% CI: 1.05–1.65], even after adjustment for other risk factors.
Conclusions. Fasting hyperinsulinaemia was a predictor of total mortality and IHD in nondiabetic men, although not more significantly after adjustment for other risk factors and with lengthening of follow-up time. The 2-h postglucose hyperinsulinaemia appeared to be a stronger and independent predictor of mortality over long-term follow-up. These findings support the view that insulin resistance with associated cluster of risk factors predicts increased long-term risk of mortality and IHD.

Keywords: cardiovascular, epidemiology, insulin, mortality, obesity, risk factors.

Introduction

Hyperinsulinaemia, a marker of insulin resistance [1], has been proposed to be a risk factor for ischaemic heart disease (IHD) in certain age groups of nondiabetic, Caucasian males [2–9], but not in ethnically mixed male populations [10]. During the last decade, however, the role of hyperinsulinaemia as a risk factor for IHD has been disputed [11–15]. In one study of elderly subjects only hyperinsulinaemic subjects with concomitant microalbuminuria were at higher risk [16]. Power problems [14, 15], differences in insulin assays, e.g. including or excluding proinsulin [7, 8], blood-sampling in the fasting or nonfasting state [8], inclusion of subjects with prevalent IHD [8], and lack of adjustment for glucose levels [7] are some possible explanations for the discrepant results. According

to one meta-analysis, insulin is a weak, but significant, cardiovascular risk factor for IHD [17].

One major analytical problem is to disentangle the role of hyperinsulinaemia *per se* from other related risk factors, e.g. age, blood pressure, body mass index (BMI), total cholesterol, HDL cholesterol, triglycerides, and glucose levels. In a recent 22-year follow-up of Finnish policemen, hyperinsulinaemia – defined as the top quintile of area under the curve (AUC) insulin after an oral glucose tolerance test (OGTT) – was an independent predictor of IHD events and both total and cardiovascular mortality [18, 19]. However, the predictive power of hyperinsulinaemia decreased with longer time of follow-up.

Thus, several studies have addressed the issue of insulin as a risk factor for IHD and – to a lesser extent – mortality [18], but the analyses have been troubled with statistical power problems and varying definitions of hyperinsulinaemia and other key variables, and time of follow-up. The aim of this study was, therefore, to investigate the predictive role of hyperinsulinaemia, defined as the top decentile of fasting or 2-h insulin concentration, in a large population-based sample of nondiabetic males free of cardiovascular disease and type 2 diabetes at baseline, for ischaemic cardiac events (CE) and mortality during 19 years of follow-up, adjusting for possible confounders (age, systolic blood pressure, lipid levels, smoking, glycaemia and BMI).

Subjects and methods

Subjects

This observational, population-based, prospective study was carried out in Malmö, the third largest city of Sweden. Men belonging to certain age cohorts and living in Malmö were invited to a baseline examination between 1974 and 1984 at the Department of Preventive Medicine, Malmö University Hospital [20]. In all, 22 444 males (aged 25–63 years; mean age 44 years) were recruited, with an overall attendance rate of 75%. An OGTT was carried out in most participants, but not in patients with known type 2 diabetes. In 6256 subjects belonging to some age-cohorts, fasting and 2-h insulin were also determined, thus making them eligible for this study. This subsample was not biased in any way from the original cohort, because they were selected only based on their year of birth. Financial restrictions made it impossible to measure insulin in all birth cohorts.

Exclusion criteria

All subjects with a self-reported or registered medical history of myocardial infarction ($n = 56$), or stroke/transitory ischaemic attack (TIA) ($n = 16$) at baseline were excluded from further analyses, the reason being that they might have adapted new lifestyles that could influence insulin levels. However, no men with self-reported chest pain as a medical symptom were excluded because of the unreliable mixture of cardiac and noncardiac origins for this symptom.

Additionally, all subjects with a self-reported history of diabetes mellitus ($n = 5$), or an elevated fasting blood glucose >6.7 mmol L^{-1} at the baseline visit ($n = 105$) were excluded. Using a single fasting glucose measurement for definitions, we choose to use the cut-off level of 6.7 mmol L^{-1} for definition of diabetes instead of 6.1 mmol L^{-1}, more recently stated in the World Health Organization (WHO) criteria for diabetes when multiple measurements are recommended before a diagnosis is made [21].

The final study group thus consisted of 6074 nondiabetic men with fasting insulin, of whom 5484 also had 2-h insulin measured. The fasting and 2-h insulin concentrations were divided into decentiles of distribution for further analyses.

Definitions of hyperinsulinaemia, hypertension, hyperlipidaemia and smoking

Hyperinsulinaemia was defined as the highest decentile of fasting insulin or 2-h insulin concentration, respectively, according to previously established risk relationships [8, 18, 19]. The definition of hypertension was based on a single visit blood pressure ≥160/95 mmHg and/or being on antihypertensive medication at baseline. Hyperlipidaemia was defined as a total cholesterol ≥6.5 mmol L^{-1} and/or triglyceride levels ≥2.3 mmol L^{-1}. Subjects were classified according to smoking habits as daily smokers or nonsmokers (never smokers and former smokers).

Clinical examination

The clinical procedures and investigations employed have previously been described in detail [22–24] and included the following aspects.

A trained nurse measured weight (kg) with the subjects in light indoor clothing, and height (m) without shoes. The BMI was calculated (kg m^{-2}). Blood pressure (Korotkoff V) was determined as a mean of two readings (mmHg) after 10 min of rest in the supine position, using a cuff of appropriate size. The mean heart rate (beats per minute) was registered. Blood samples were drawn after an overnight fast for the determination of blood glucose, serum total cholesterol and serum triglycerides in all participants. An OGTT was carried out with the ingestion of 30 g glucose m^{-2} body surface area within 5 min [20]. Fasting and 2-h-values of insulin and glucose were determined.

Laboratory analyses

Blood glucose levels were automatically analysed using the glucose-oxidase method (1974–77) or the hexokinase-oxidase method (1977–87). All serum samples were analysed at the Department of Clinical Chemistry at Malmö University Hospital, using routine methods for lipids. Because these two methods give rather similar results, we used the blood glucose data as such – without trying to apply a conversion factor. Plasma insulin was analysed by a nonspecific radioimmunoassay (RIA) method [25], the detection limit being 3 mIU L^{-1} (nmol L^{-1} = mIU $L^{-1} \times 7.175/1.000$). Intra- and inter-assay coefficients of variation were on average 5 and 8%, respectively. The Department of Clinical Chemistry in Malmö, where the RIA method was originally developed, was attached to a continuing standardization programme.

Follow-up for mortality and cardiac events

The cohort was followed for incident ischaemic CE caused by IHD until 31 December 1997, by means of national and a local register, the Malmö Heart Infarct Register [26]. The average follow-up time was 19 years (shortest follow-up 13 years and the longest 23 years), contributing to a total of 115 802 person-years (p.y.).

Mortality follow-up was based on the national register on causes of mortality at the Central Bureau of Statistics, Sweden. In all, 1012 deaths were recorded.

The first CE was defined as the first nonfatal or fatal myocardial infarction, or sudden cardiac death, thus representing the incidence of IHD. The IHD diagnoses were classified according to ICD-9, numbers 410–414 [27]. A total of 677 ischaemic CEs were recorded during a total of 19 years of follow-up.

Statistics

The SAS package program was used for statistical analyses [28]. Mean values and standard deviations (SD) are given for baseline variables in men with fasting insulin concentration above and below the 10th decentile, and for men with an incident CE compared with other men. Kaplan–Meyer's curves have been used to illustrate the risk of mortality and CE associated with hyperinsulinaemia. Cox proportional hazard models have been used for the calculation of relative hazard ratios for total mortality and CEs based on insulin levels, when the top decentile (hyperinsulinaemic) group (fasting insulin: ≥21 mIU L^{-1}; or 2-h insulin: 84–860 mIU L^{-1}) was compared with the rest of the men after 6, 12 and 19 years of follow-up, respectively. Stepwise adjustments were made for smoking and the continuous variables age, systolic blood pressure, cholesterol, triglycerides, blood glucose levels, and BMI, in models A–H (see Table 3). A *P*-value of less than 0.05 was considered significant.

Results

Insulin levels and risk of cardiac event and death

In all, 6074 men were evaluated with a full set of baseline variables, including fasting serum insulin, and 5484 of these men also had an additional OGTT with measurement of 2-h insulin. Mean levels of fasting insulin was 10.5 (SD: 9.3; median 8.0) mIU L^{-1}, and 2-h insulin 38 (SD: 42; median 25) mIU L^{-1}. Subjects were divided into decentiles of fasting and 2-h insulin levels for definition of the hyperinsulinaemic groups (10th decentile). The total number of CE ($n = 677$) and deaths ($n = 1012$) in

each decentile of the fasting insulin distribution, and person-years of follow-up for CE and total mortality are shown in Fig. 1(a,b). The total follow-up time (p.y.) was for deaths at 6 years, 36 305 p.y.; at 12 years, 70 868 p.y. and at 19 years, 115 802 p.y. The corresponding figures for total follow-up time calculated for CEs were at 6 years 35 780 p.y., at 12 years 69 734 p.y., and at 19 years 112 652 p.y. The relationships between fasting insulin and 2-h insulin, respectively, and risk of CE and death were rather flat for both end-point categories, but with an increase in the 10th decentile.

Baseline characteristics of subjects with fasting insulin above or below the 10th decentile, and with or without cardiac event

Baseline characteristics of all men with fasting insulin above or below the 10th decentile, or with a CE during the follow-up period are shown in Tables 1 and 2. Large differences were noted in the variables included in the metabolic syndrome (BMI, blood pressure, hyperlipidaemia) between men in the 10th decentile compared with the rest of the men. The hyperinsulinaemic men were less often current smokers than other men ($P < 0.05$).

Men with an incident CE differed from other men in most of the variables including age, BMI, blood pressure, insulin levels, cholesterol, triglycerides, the proportion of hypertensives, smokers and subjects with hyperlipidaemia. No difference was detected for fasting glucose or 2 h-glucose at baseline.

Risk of cardiac event and mortality in the hyperinsulinaemic group

Graphs of the Kaplan–Meyer curves for total mortality and CE in the hyperinsulinaemic group, based

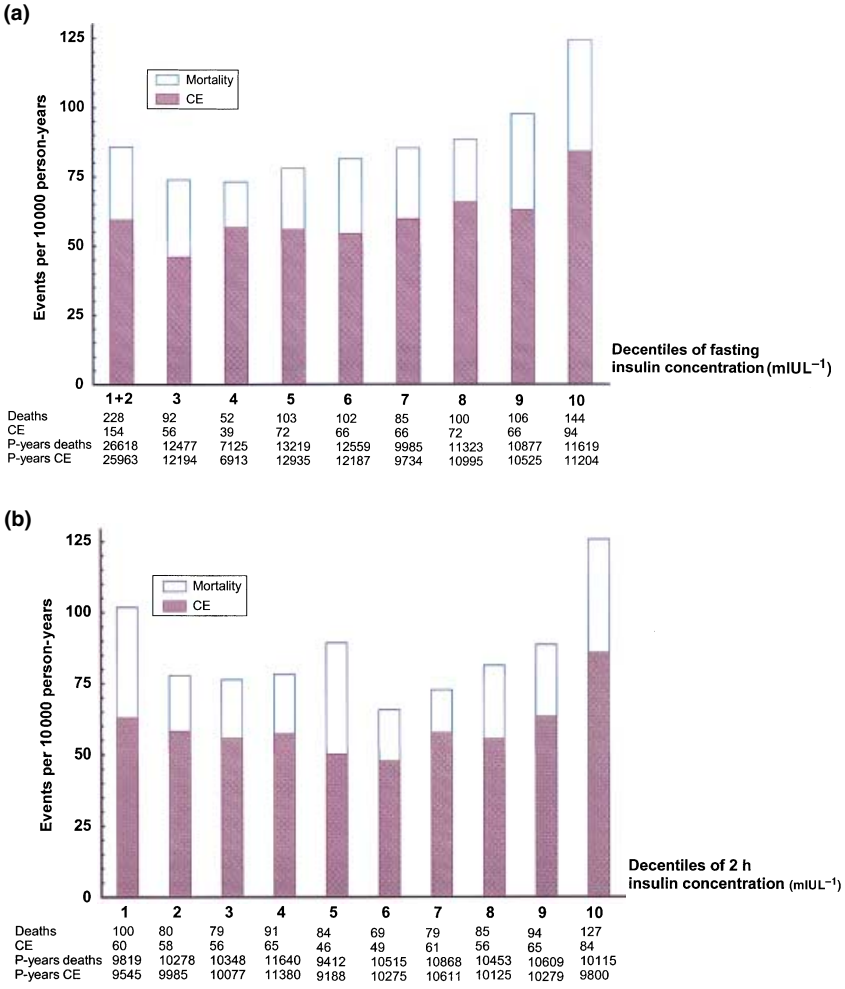

Fig. 1 Mortality and cardiac event rates per 10 000 person-years in decentiles of fasting (a) and 2 h (b) plasma insulin concentrations at baseline. Test for curvilinear relation: fast insulin ($P = 0.091$), and 2-h insulin ($P = 0.03$).

Table 1 Baseline characteristics of groups (based on decentiles) according to fasting insulin levels. The hyperinsulinaemic group (10th decentile) is compared with the rest of the study group. Mean (SD). Median (*) values are given when appropriate

	Fasting insulin		
Variable	1–9th decentile (1–20 mU L^{-1})	10th decentile (21–140 mU L^{-1})	Difference (95% CI)
n	5.457	617	
Age (years)	47.2 (2.5)	47.7 (1.7)	0.4 (0.2–0.6)
BMI (kg/m^2)	24.5 (3.0)	28.0 (4.1)	3.4 (3.2–3.7)
Smoking (%)			
Nonsmokers	25.4	27.4	
Former smokers	23.0	26.1	
Current smokers	51.6	46.6	$P = 0.049$
SBP (mmHg)	128.9 (15.7)	136.5 (17.0)	7.5 (6.2–8.9)
DBP (mmHg)	87.1 (10.1)	92.4 (11.1)	5.2 (4.4–6.1)
Cholesterol (mmol L^{-1})	5.7 (1.0)	5.9 (1.0)	0.2 (0.1–0.3)
Triglycerides (mmol L^{-1}) *	1.5 (0.8), 1.4	2.2 (1.7), 1.8	0.7 (0.6–0.8)
Glucose (mmol L^{-1})			
Fasting	4.9 (0.6)	5.1 (0.7)	0.2 (0.1–0.2)
2 h	5.4 (1.5)	6.4 (1.8)	1.0 (0.9–1.1)
Insulin (mIU L^{-1})*			
Fasting	8.2 (4.8) 7.0	31.0 (13.3) 27.0	NA
2 h	31 (29), 22	99 (78) 86	NA

NA, not applicable.

Table 2 Baseline characteristics, cardiovascular risk factors and risk categories in patients with or without a cardiac event (CE) during follow-up. Differences between non-CE and CE cases ($n = 677$) in risk factor levels. Mean (SD), and median values (*) for triglycerides, glucose 120 min, and insulin levels. Proportions (%) of cardiovascular risk categories

Variable	Non-CE	First CE	Difference (95% CI)
Age (years)	47.2 (2.6)	47.6 (1.4)	0.4 (0.2–0.6)
BMI (kg m^{-2})	24.8 (3.3)	25.5 (3.6)	0.7 (0.5–1.0)
SBP (mmHg)	129.1 (15.5)	134.4 (19.2)	5.3 (4.0–6.6)
DBP (mmHg)	87.3 (10.1)	90.7 (11.7)	3.5 (2.6–4.3)
Fasting glucose (mmol L^{-1})	4.9 (0.6)	4.9 (0.6)	0.0 (0.0–0.1)
Glucose-120 min*	5.5 (1.5), 5.4	5.6 (1.7), 5.2	0.1 (−0.1–0.2)
Cholesterol (mmol L^{-1})	5.7 (1.0)	6.1 (1.1)	0.4 (0.4–0.5)
Triglyc (mmol L^{-1})*	1.6 (0.9), 1.4	1.8 (1.0), 1.6	0.3 (0.2–0.3)
Fasting insulin (mIU L^{-1})*	10.3 (8.9), 8	12.1 (12.0), 9	1.8 (1.0–2.5)
Insulin-120 min (mIU L^{-1})*	37.3 (39.8), 25	43.1 (54.2), 27	5.8 (2.3–9.3)
Hypertension (%)	26.5	39.4	12.9 (9.2–17.0)
Hyperlipidaemia (%)	27.8	43.9	16.1 (12.2–20.0)
Smokers (%)	49.0	67.7	18.7 (14.8–22.3)

For definitions of hypertension, hyperlipidaemia and smoking habits: see Subjects and methods.

on fasting insulin, compared with the rest of the cohort, Fig. 2a,b, show that the hyperinsulinaemic group had an increased risk from 5-years follow-up onwards. The corresponding findings based on the 2-h insulin were similar.

The relative risk of mortality and cardiac events after 6, 12 and 19 years of follow-up

The RR ratios for total mortality and CEs in hyperinsulinaemic men (10th decentile) versus all other men changed not only according to whether the analyses were based on fasting or 2-h insulin levels, but also with increasing time of follow-up (Table 3). Four different models were used. Stepwise adjustments for age, systolic blood pressure, cholesterol, triglycerides, smoking, glucose and BMI generally reduced the risk ratios which finally became nonsignificant for fasting insulin. Furthermore, for fasting insulin the RR ratios decreased with a longer follow-up period, from 6 to 12 and 19 years. For hyperinsulinaemia, defined by 2-h insulin concentrations, the RR ratios, however, increased with time of follow-up. The risk of death in hyperinsulinaemic men, based on the 2-h insulin distribution, was still significantly increased after 19 years, 1.32

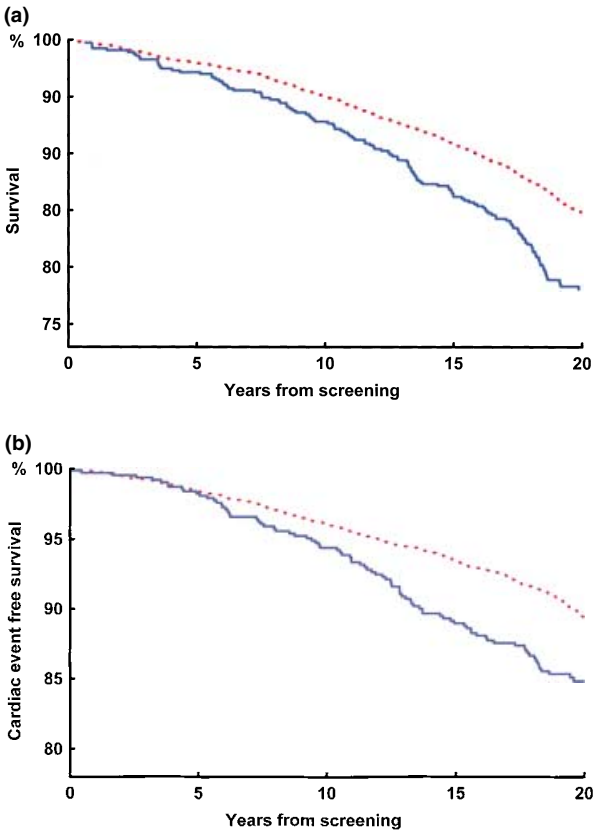

Fig. 2 Kaplan–Myer's curves for survival (a) and cardiac event free survival (b) in hyperinsulinaemic (10th decentile) men (solid line) compared with all other men (dotted line).

(1.05–1.65), even after full adjustment for covariates (Table 3). The significantly increased risk of IHD remained after adjustment for age, systolic blood pressure, cholesterol, triglycerides and 2-h glucose, but disappeared when BMI was introduced as a covariate in the final model.

Discussion

This study has shown that both fasting and 2-h insulin are predictors of mortality and CE (IHD) in nondiabetic men. The relationship was nonlinear with the highest risk in the top decentile of the insulin distribution, similar to previous findings of risk associated with stimulated insulin levels during OGTT [2, 18, 19], and nonfasting insulin levels [8]. It should be pointed out that hyperinsulinaemia in this study was not an independent risk factor for CEs after full adjustment for other risk factors. The long-term prediction of all-cause mortality was, however, independent of adjustment for most risk factors, including glycaemia, which has not routinely been carried out in other studies. In fact, 2-h insulin values in the top decentile of the distribution independently predicted long-term total mortality after 19 years, even when full adjustment for other risk factors was made. The finding that hyperinsulinaemia in the population-based Malmö Prevention Project predicts total mortality is a confirmation of previous results in the Helsinki Policemen Study, a smaller study in a selected group of men but with somewhat longer follow-up 22 years [18]. As high plasma insulin level (hyperinsulinaemia) is a marker of insulin resistance [29], at least in nondiabetic males, these findings support the view that insulin resistance with concomittant risk factor cluster [1, 30, 31] is associated with increased total mortality. Most male deaths in the studied age-groups were cardiovascular by origin (data not shown).

It is well-known that the predictive power of cardiovascular risk factors tends to decrease with the lengthening of follow-up time. This is evidently because of selective mortality and competing causes of death, and the possible influence of external factors during the time course, e.g. change in lifestyle habits or drug treatment. Therefore, it is of interest that the 2-h hyperinsulinaemia was still predictive of total mortality after 19 years.

A possible shortcoming of the present study is that we measured plasma insulin with a conventional (unspecific) laboratory assay. Only few studies, e.g. the British Regional Heart Study [8], have so far used a truly specific insulin assay [17], but this method seems to be more relevant to use in subjects with established type 2 diabetes, when conventional assays may substantially overestimate insulin levels because of a relative predominance of proinsulin and split-products [32]. In our study, however, subjects with self-reported diabetes mellitus or fasting hyperglycaemia in the diabetic range (>6.7 mmol L^{-1}) were excluded making the question of using a specific insulin assay less relevant.

We did not include HDL cholesterol in our analyses, because this variable was never measured in the total cohort, which was performed in some other studies [4–9]. As there exists a well-known inverse correlation between levels of HDL cholesterol and triglycerides [33], it should be relevant to adjust for either fasting triglyceride levels or HDL cholesterol. Adjustment for triglycerides was carried out in

Table 3 Risk ratios [(RR), 95% CI] for total mortality and cardiac events (CE) in nondiabetic, hyperinsulinaemic (>10th decentile) middle-aged men, as defined by use of fasting or 2-h insulin levels, compared with all other men

	6 years	12 years	19 years
Total mortality (fasting insulin)	(n = 148)	(n = 417)	(n = 1012)
A	1.49 (0.95–2.35)	1.43 (1.08–1.88)	1.40 (1.17–1.67)
B	1.36 (0.64–2.18)	1.30 (0.97–1.73)	1.23 (1.02–1.48)
C	1.33 (0.83–2.13)	1.28 (0.96–1.71)	1.22 (1.01–1.47)
D	1.34 (0.82–2.20)	1.24 (0.92–1.67)	1.17 (0.96–1.41)
Cardiac events (fasting insulin)	(n = 181)	(n = 464)	(n = 677)
A	1.56 (1.04–2.33)	1.49 (1.15–1.93)	1.40 (1.12–1.74)
B	1.33 (0.87–2.02)	1.29 (0.99–1.69)	1.15 (0.91–1.44)
C	1.30 (0.85–1.98)	1.28 (0.97–1.67)	1.14 (0.91–1.43)
D	1.27 (0.82–1.90)	1.19 (0.90–1.58)	1.03 (0.81–1.30)
Total mortality (2-h insulin)	(n = 148)	(n = 417)	(n = 1012)
E	1.28 (0.77–2.12)	1.55 (1.17–2.07)	1.53 (1.27–1.85)
F	1.16 (0.68–2.00)	1.48 (1.09–2.01)	1.37 (1.12–1.67)
G	1.14 (0.63–2.05)	1.43 (1.02–2.00)	1.37 (1.10–1.71)
H	1.12 (0.61–2.07)	1.40 (0.99–1.98)	1.32 (1.05–1.65)
Cardiac events (2-h insulin)	(n = 181)	(n = 464)	(n = 677)
E	1.29 (0.81–2.03)	1.55 (1.18–2.04)	1.50 (1.19–1.89)
F	1.10 (0.67–1.78)	1.38 (1.03–1.85)	1.28 (1.00–1.64)
G	1.06 (0.62–1.80)	1.39 (1.01–1.92)	1.41 (1.08–1.85)
H	1.01 (0.59–1.74)	1.31 (0.94–1.82)	1.26 (0.96–1.67)

Stepwise adjustments of RRs have been made for (A) age only (B) age + systolic blood pressure + cholesterol + triglycerides + smoking, (C) B + fasting glucose and (D) C + body mass index. The RRs after 6 years were based on 148 deaths and 181 CEs, the corresponding numbers after 12 and 19 years were 417 deaths and 464 CEs and 1012 deaths and 677 CEs, respectively. Stepwise adjustments of RRs have been made for (E) age only, (F) age + systolic blood pressure + cholesterol + triglycerides + smoking, (G) F + 2-h glucose, and (H) G + body mass index.

the Canadian case–control study [7] and in the Helsinki Policemen Study [2], but not in the British Regional Heart Study [8] because of the overall use of nonfasting blood samples in the latter study, and thus their alternative inclusion of HDL cholesterol instead of triglyceride levels in statistical analyses [8]. Specific syndromes of insulin resistance, e.g. with the combination morbid obesity and hypertriglyceridaemia, were not investigated, but these syndromes are rare in the general population and should therefore not influence our findings to a substantial degree. The polycystic ovary (PCO) syndrome is only relevant to women, not included in this study.

Insulin has been proposed to be potentially atherogenic in itself [34], but there is currently not much clinical evidence to support this notion [10–12]. Instead arguments have been raised that it is the underlying insulin resistance that matters [35, 36]. Which mechanisms could possibly link hyperinsulinaemia and insulin resistance to cardiovascular risk and total mortality, independent of age, hypertension, hyperlipidaemia, obesity, hyperglycaemia and smoking? Defects in fibrinolysis and endothelial dysfunction may be causally related to both insulin resistance and outcome measures. The tissue plasminogen activator (tPA) antigen, as a marker of the tPA–PAI-1 complex indicating defect fibrinolysis, has been shown to correlate with fasting insulin and other metabolic abnormalities, and independently with blood pressure levels [37]. Another factor of importance is abdominal (central) obesity that is strongly associated with insulin resistance and other metabolic, fibrinolytic and haemodynamic abnormalities [38]. However, as BMI correlates fairly well with abdominal obesity, at least in males [39], this was regarded as a useful surrogate variable in our study group of middle-aged men. Furthermore, fat mass itself may interact with insulin sensitivity because of the secretion of leptin and pro-inflammatory cytokines such as tumour necrosis factor-α (TNF-α), interleukin-6 and interleukin-10 [40]. BMI is, however, also a useful surrogate variable for total body fat. Finally, it is well-documented that fasting insulin levels and the insulin resistance syndrome, to a large extent, are determined by genetic factors [41, 42], thus linking family traits with cardiovascular risk.

One proof of the hypothesis that hyperinsulinaemia, or rather the underlying insulin resistance, are true risk factors for mortality and IHD [43] would be beneficial results of a randomized intervention trial, aimed at lowering hyperinsulinaemia through improving insulin sensitivity. Such intervention-derived data on insulin metabolism and clinical outcomes do not exist today, and therefore the Hill's criteria of causality [44] have so far not been fulfilled. New drugs that improve insulin sensitivity, such as the thiazolidinediones (glitazones), with beneficial effects on cardiovascular risk factors have recently been developed [45–47]. We currently lack long-term data on progress of atherosclerosis or clinical outcomes during use of these drugs, but several new studies are underway.

The J-shaped risk pattern of insulin in relation to future mortality or IHD found in this prospective study resembles what had previously been reported from a cross-sectional study in Italy, the Bruneck Study [48], and in the Paris Prospective Study [49], where multiple adjustments for covariates were also made. All three studies are population-based and can conclude that a somewhat higher risk also seems to be associated with low insulin levels (hypoinsulinaemia) maybe as a marker for impaired β-cell function. In the Bruneck study, known diabetes patients (77 of 888) were included in the analysis but results were adjusted for hyperglycaemia [48]. We choose instead to exclude all known diabetes patients at baseline.

Proinsulin has recently been proposed as a risk factor for cardiovascular morbidity in its own right, independent of insulin levels [50–52]. We have no data to compare these variables for predictive power. No studies have so far shown prediction of proinsulin for all-cause mortality.

Future studies should also investigate the potential role of hyperinsulinaemia as a risk factor in women. In the Malmö Preventive Project we have data from fewer women than men, and they have a shorter follow-up time why the number of CE and deaths is still not sufficient for a similar analyses [24]. In a previous study from Busselton, Australia, insulin was not a marker for prospective cardiovascular risk in women [5].

In conclusion, fasting hyperinsulinaemia is a significant risk factor for mortality and IHD events in nondiabetic men although the independent risk disappears after full adjustment for traditional risk factors and with time. The 2-h hyperinsulinaemia may be a stronger risk factor for mortality and IHD, the risk increasing with time of follow-up. This supports the role of insulin resistance as a cardiovascular risk factor. Intervention studies based on lifestyle changes, in particular dietary changes aiming at reduction and control of body weight and regular physical activity, or use of insulin-sensitizing drugs, might give further information about the role of insulin resistance as a determinant of cardiovascular risk. Contemplation of such trials has got support from the recent demonstration of the effectiveness of lifestyle changes in the prevention of the progression of impaired glucose tolerance to type 2 diabetes in one Finnish [53] and one American [54] intervention trial.

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