Plasma Insulin and All-Cause, Cardiovascular, and Noncardiovascular Mortality

The 22-year follow-up results of the Helsinki Policemen Study

MARJA PYÖRÄLÄ, MD
HEIKKI MIETTINEN, MD
MARKKU LAAKSO, MD
KALEVI PYÖRÄLÄ, MD

OBJECTIVE — To investigate the association of plasma insulin with all-cause, cardiovascular, and noncardiovascular mortality.

RESEARCH DESIGN AND METHODS — We studied 22-year mortality data from the Helsinki Policemen Study. The study population comprised 970 men, 34–64 years of age, who were free of coronary heart disease, other cardiovascular disease, and diabetes. Area under the insulin response curve (AUC insulin) during an oral glucose tolerance test was used to reflect plasma insulin levels.

RESULTS — During the follow-up period, 276 men died: 130 from cardiovascular and 146 from noncardiovascular causes. The hazard ratio (HR) for hyperinsulinemia (highest AUC insulin quintile vs. combined lower quintiles) with regard to all-cause mortality, adjusting for age, was 1.94 (95% CI 1.20–3.13) during the first 10 years of the follow-up period and 1.51 (1.15–1.97) during the entire 22 years; adjusting for other risk factors, the HR was 1.88 (1.08–3.30) and 1.37 (1.00–1.87) during 10 and 22 years, respectively. The corresponding HRs for cardiovascular mortality during 10 and 22 years were 2.67 (1.35–5.29) and 1.73 (1.19–2.53), respectively, for age-adjusted and 2.30 (1.03–5.12) and 1.39 (0.90–2.15), respectively, for multiple-adjusted HRs. A U-shaped association was observed between insulin and noncardiovascular mortality; multiple-adjusted HRs for lowest and highest versus middle AUC insulin quintiles were 1.85 (1.20–2.86) and 1.43 (0.91–2.24), respectively.

CONCLUSIONS — Hyperinsulinemia was associated with increased all-cause and cardiovascular mortality in Helsinki policemen independent of other risk factors, although these associations weakened with the lengthening of the follow-up period. The association of insulin with noncardiovascular mortality was U-shaped.

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Many, although not all, prospective studies have shown an association of hyperinsulinemia with the risk of coronary heart disease (CHD) and some studies with the risk of stroke (1–7). The question of the role of hyperinsulinemia as a cardiovascular risk factor has however proven to be complex because of the close physiological links of hyperinsulinemia and the underlying insulin resistance with other risk factors, such as obesity, impaired glucose tolerance, dyslipidemia, and elevated blood pressure (8).

The Helsinki Policemen Study was one of the first prospective studies to demonstrate the association of hyperinsulinemia with CHD (9). During the 22-year follow-up of the Helsinki Policemen Study, hyperinsulinemia continued to be a predictor of major CHD events (CHD death or nonfatal myocardial infarction), independent of other risk factors, although its predictive power weakened with the lengthening of the follow-up period (2). Hyperinsulinemia was also associated with the risk of stroke (fatal or nonfatal), but this association became nonsignificant after adjustment for other risk factors (5). However, when clusters of baseline risk factors obtained from factor analysis were used as predictors, the cluster of insulin and associated metabolic factors, including obesity, glucose, triglycerides, and blood pressure, predicted CHD and stroke similarly (10).

Thus far, no studies have been published on the associations between plasma insulin and all of the main categories of mortality. Therefore, we investigated the association of plasma insulin with all-cause, cardiovascular, and noncardiovascular mortality and their different subcategories based on 22-year mortality data from the Helsinki Policemen Study.

RESEARCH DESIGN AND METHODS

Study population

The study population comprised 970 men, 34–64 years of age (median 48), who were free of CHD, other heart disease, cerebrovascular disease, and diabetes when they participated in the second examination of the Helsinki Policemen Study in 1971–1972. The formation of the study population, the study protocol, and the diagnostic criteria for prevalent CHD, other heart disease, and cerebrovascular disease at baseline have been described in detail previously (2,5). Diabetes was considered to be present if the subject had been diagnosed previously to have diabetes or if the fasting blood glucose was ≥6.7 mmol/l or the 2-h blood glucose during an oral glucose tolerance test (OGTT) was ≥10.0 mmol/l (11). The study

From the Department of Medicine, University of Kuopio, Kuopio, Finland.
Address correspondence and reprint requests to Kalevi Pyörälä, MD, Department of Medicine, University of Kuopio, P.O. Box 1627, 70211 Kuopio, Finland. E-mail: kalevi.pyorala@uku.fi.
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Abbreviations: AUC glucose, area under the blood glucose response curve; AUC insulin, area under the plasma insulin response curve; CHD, coronary heart disease; HR, hazard ratio; OGTT, oral glucose tolerance test.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Baseline characteristics of the study population (*n *= 970) by quintiles of AUC insulin*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	*P*
n	191	197	194	193	195	—
Age (years)	46 ± 7	47 ± 7	47 ± 8	48 ± 8	48 ± 7	0.001
Height (cm)	179 ± 5	179 ± 5	179 ± 5	178 ± 5	179 ± 6	0.364
Weight (kg)	80 ± 9	81 ± 9	83 ± 10	86 ± 11	91 ± 12	<0.001
BMI (kg/m^2)	24.8 ± 2.4	25.4 ± 2.5	25.7 ± 2.7	27.0 ± 2.9	28.3 ± 3.0	<0.001
Subscapular skinfold (mm)	14 ± 5	16 ± 6	18 ± 6	20 ± 6	22 ± 8	<0.001
Triceps skinfold (mm)	9 ± 3	10 ± 4	10 ± 4	11 ± 4	12 ± 5	<0.001
Systolic blood pressure (mmHg)	132 ± 17	134 ± 17	134 ± 18	139 ± 18	141 ± 19	<0.001
Diastolic blood pressure (mmHg)	82 ± 10	84 ± 11	85 ± 10	87 ± 11	88 ± 11	<0.001
Hypertension (%)*	15.2	23.4	18.6	30.1	34.4	0.001
Cholesterol (mmol/l)	6.10 ± 1.16	6.17 ± 1.11	6.41 ± 1.15	6.24 ± 1.03	6.40 ± 1.22	0.014
Triglycerides (mmol/l)	1.41 ± 0.87	1.60 ± 0.79	1.74 ± 1.04	1.94 ± 1.13	2.04 ± 1.06	<0.001
Fasting glucose (mmol/l)	4.7 ± 0.4	4.8 ± 0.4	4.9 ± 0.4	4.9 ± 0.5	5.1 ± 0.5	<0.001
1-h glucose (mmol/l)	5.2 ± 1.3	6.0 ± 1.8	6.4 ± 1.8	7.0 ± 1.9	7.9 ± 1.8	<0.001
2-h glucose (mmol/l)	3.9 ± 0.9	4.2 ± 1.1	4.2 ± 1.0	4.7 ± 1.1	5.1 ± 1.4	<0.001
AUC glucose (mmol · l^{-1} · h^{-1})	9.5 ± 1.5	10.5 ± 2.1	11.0 ± 2.1	11.8 ± 2.4	13.0 ± 2.4	<0.001
Maximal O_2 uptake (ml · min^{-1} · kg^{-1} body wt)	39.8 ± 9.8	36.5 ± 8.1	35.3 ± 7.6	33.1 ± 6.4	31.9 ± 7.0	<0.001
Physically active in leisure time (%)	50.3	36.5	31.4	28.5	24.1	0.001
Current smokers (%)	45.0	47.2	49.5	47.2	36.4	0.130
Officers (%)	35.1	36.0	46.4	38.9	40.0	0.536

Data are *n* or means ± SD, unless otherwise indicated. The cutoff points for AUC insulin were 237, 337, 437, and 669 pmol · l^{-1} · h^{-1}. *Defined as systolic blood pressure ≥160 mmHg and/or diastolic blood pressure ≥95 mmHg or on antihypertensive drug treatment (29 men).

was approved by the Ethics Committee of the University of Kuopio. All study subjects gave their informed consent.

Baseline risk factors

Methods used in the assessment of risk factors at the baseline examination have been described in detail elsewhere (2,5). The following risk factors were included in present data analyses: BMI, triceps, and subscapular skinfold thicknesses (subscapular skinfold as an index of upper-body obesity); blood pressure; plasma total cholesterol and triglycerides; blood glucose and plasma insulin levels during OGTT; maximal O_2 uptake predicted on the basis of bicycle ergometer exercise test; leisure-time physical activity based on a questionnaire (physically active vs. inactive); current smoking status (smokers vs. nonsmokers); and occupational status (officers vs. nonofficers).

The OGTT was performed during the morning after a minimum of a 12-h fast. The glucose dose was 75 or 90 g, according to the body surface area (847 men received 75 g and 123 men 90 g glucose). Venous blood samples were taken before and 1 and 2 h after the glucose load for the determination of blood glucose by *o*-toluidine method (12) and plasma insulin by the coated-charcoal radioimmunological assay (13). Areas under the blood glucose response curve (AUC glucose) and the plasma insulin response curve (AUC insulin) were calculated from fasting, 1-h, and 2-h blood glucose and plasma insulin concentrations with the trapezoid rule. AUC glucose and AUC insulin were used in data analyses as composite variables reflecting blood glucose and plasma insulin levels.

Mortality data

The follow-up lasted until 1 January 1994. Copies of death certificates of all deceased men were obtained from the national Cause-of-Death Register (Statistics Finland). In addition to the review of death certificates, hospital records and autopsy reports, if available, were also used in the final classification of causes of death. Autopsy had been performed in 142 of the 276 cases of death (51.4%). Underlying cause of death was coded by one of the authors (M.P.) using the *International Classification of Diseases, Ninth Revision* (ICD-9). Cardiovascular deaths included codes 390–459, coronary deaths codes 410–414, and cerebrovascular deaths codes 431–434 and 436. Deaths from subarachnoid hemorrhage (code 430) were included in the subcategory of other cardiovascular deaths, which comprised the remaining codes for cardiovascular disease. Noncardiovascular deaths included codes for causes other than cardiovascular disease with the following subcategories: cancer deaths, codes 140–208; violent deaths, codes 800–999; and other noncardiovascular deaths, codes covered by none of the previous subcategories. Within the subcategory of violent deaths, suicides or accidents with notes on excessive alcohol use or alcohol intoxication in death certificates were considered to be possibly alcohol related, and within the subcategory of other noncardiovascular deaths, deaths from liver cirrhosis and acute pancreatitis without gallstones were considered to be possibly alcohol related.

Statistical analysis

Data analyses were performed with SPSS 6.1.3 and SAS 6.12 software. Because of the skewed distributions of blood glucose and plasma insulin variables, as well as plasma triglycerides, these variables were log-transformed for statistical analyses. Linear trends of baseline characteristics by quintiles of AUC insulin were tested by analysis of variance using age-adjusted values for continuous variables and by Mantel-Haenszel test for categorical variables. Age-standardized mortality rates per 1,000 person-years by AUC insulin quintiles were calculated by direct method using the age structure of the whole study population as a reference, and 95% CIs were computed for these esti-

Table 2—*Distribution of causes of death and age-standardized cause-specific mortality rates by quintiles of AUC insulin during the 22-year follow-up (276 deaths among 970 men)*

	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Distribution of causes of death (% of all deaths)					
n	191	197	194	193	195
All-cause	51 (100.0)	43 (100.0)	58 (100.0)	51 (100.0)	73 (100.0)
Cardiovascular	16 (31.4)	19 (44.2)	28 (48.3)	29 (56.9)	38 (52.1)
Coronary	6 (11.8)	14 (32.6)	17 (29.3)	21 (41.2)	22 (30.1)
Cerebrovascular	5 (9.8)	3 (7.0)	3 (5.2)	5 (9.8)	11 (15.1)
Other	5 (9.8)	2 (4.7)	8 (13.8)	3 (5.9)	5 (6.8)
Noncardiovascular	35 (68.6)	24 (55.8)	30 (51.7)	22 (43.1)	35 (47.9)
Cancer	13 (25.5)	16 (37.2)	15 (25.9)	15 (29.4)	22 (30.1)
Violent	11 (21.6)	4 (9.3)	4 (6.9)	3 (5.9)	7 (9.6)
Other	11 (21.6)	4 (9.3)	11 (19.0)	4 (7.8)	6 (8.2)
Age-standardized mortality rate per 1,000 person-years (95% CI)					
All-cause	13.32 (12.32 to 14.33)	10.65 (9.67 to 11.63)	14.62 (13.64 to 15.61)	13.19 (12.19 to 14.19)	19.89 (18.86 to 20.91)
Cardiovascular	4.18 (3.18 to 5.18)	4.71 (3.73 to 5.68)	7.06 (6.08 to 8.04)	7.50 (6.50 to 8.50)	10.35 (9.33 to 11.37)
Coronary	1.57 (0.57 to 2.57)	3.47 (2.49 to 4.44)	4.29 (3.30 to 5.27)	5.43 (4.44 to 6.43)	5.99 (4.97 to 7.02)
Cerebrovascular*	1.31 (−0.02 to 2.64)	0.74 (−0.51 to 1.99)	0.76 (−0.52 to 2.03)	1.29 (0.36 to 2.23)	3.00 (1.97 to 4.02)
Other*	1.31 (0.24 to 2.37)	0.50 (−2.40 to 3.39)	2.02 (1.03 to 3.00)	0.78 (−1.18 to 2.73)	1.36 (0.34 to 2.38)
Noncardiovascular	9.14 (8.14 to 10.15)	5.94 (4.97 to 6.92)	7.56 (6.58 to 8.55)	5.69 (4.69 to 6.69)	9.53 (8.51 to 10.56)
Cancer	3.40 (2.39 to 4.40)	3.96 (2.99 to 4.94)	3.78 (2.80 to 4.77)	3.88 (2.88 to 4.88)	5.99 (4.97 to 7.02)
Violent*	2.87 (1.87 to 3.88)	0.99 (−0.05 to 2.03)	1.01 (0.02 to 1.99)	0.78 (−0.83 to 2.38)	1.91 (0.88 to 2.93)
Other*	2.87 (1.87 to 3.88)	0.74 (−0.62 to 2.10)	2.77 (1.79 to 3.76)	1.03 (−0.23 to 2.30)	1.63 (0.61 to 2.66)

Data are *n*, %, or CIs. The cutoff points for AUC insulin were 237, 337, 437, and 669 pmol · l^{-1} · h^{-1}. *In some quintiles, the 95% CI includes 0 because of the small number of deaths.

mates. The Cox proportional hazard model was used to estimate the predictive value of AUC insulin with regard to mortality, with adjustment for age and with multiple adjustment for other confounding factors. There was no indication of nonproportional hazards during the 22-year follow-up. In Cox model analyses in which log AUC insulin was entered as a continuous variable, the log-likelihood ratio test was used to examine whether the inclusion of a squared logarithmic term was needed in the model. For multiple-adjusted Cox model analyses, missing values for predicted maximal O_2 uptake in 32 men were substituted in 24 men with the measurement made at an earlier examination and in 8 men with the age-specific mean value. Statistical significance is expressed either as *P* or by giving the 95% CI for the estimates.

RESULTS — Table 1 shows the baseline risk factors by quintiles of AUC insulin. With increasing AUC insulin, there was an increasing trend for age, obesity indexes, blood pressure, cholesterol, triglycerides, and glucose variables, but a decreasing trend for maximal O_2 uptake and the proportion of physically active men.

During the 22-year follow-up, 276 men died (28.5%). Of these, 130 deaths (47.1% of all deaths) were cardiovascular; among them, 80 were coronary deaths, 27 were cerebrovascular deaths, and 23 were other cardiovascular deaths. The remaining 146 deaths (52.9% of all deaths) were noncardiovascular; 81 of these were cancer deaths, 29 deaths were from violence, and 36 were other noncardiovascular deaths.

The distribution of causes of death and age-standardized cause-specific mortality rates per 1,000 person-years and their 95% CIs by quintiles of AUC insulin during the 22-year follow-up period are shown in Table 2. The proportion of cardiovascular deaths to all deaths increased with increasing AUC insulin. The proportion of coronary deaths was particularly low and the proportion of noncardiovascular deaths particularly high in the lowest quintile of AUC insulin. There was a significant excess of all-cause mortality in the highest AUC insulin quintile as compared with lower AUC insulin quintiles. This was mainly a result of an excess in cardiovascular mortality in the highest AUC insulin quintile, which in turn resulted from an excess in coronary and cerebrovascular mortality. The relationship of AUC insulin with noncardiovascular mortality appeared to be U-shaped, with higher mortality rates in the lowest and highest quintiles rather than in the middle.

To assess the association of hyperinsulinemia with all-cause, cardiovascular, coronary, and cerebrovascular mortality, hyperinsulinemia was defined by the cutoff point for the highest AUC insulin quintile (≥669 pmol · l^{-1} · h^{-1}). Age-adjusted and multiple-adjusted hazard ratios (HRs) and their 95% CIs, comparing the highest AUC insulin with the combined lower quintiles, were calculated with the Cox model (Table 3). In addition to age, multiple adjustment included BMI, subscapular skinfold, systolic blood pressure, cholesterol, triglycerides, AUC glucose, maximal O_2 uptake, physical activity, smoking, and occupational status. In the age-adjusted model, hyperinsulinemia was significantly associated with increased all-cause, cardiovascular, coronary, and cerebrovascular mortality

Table 3—*Age-adjusted and multiple-adjusted HRs and 95% CIs for hyperinsulinemia (AUC insulin quintile 5 vs. quintiles 1–4) with regard to all-cause, cardiovascular, coronary, and cerebrovascular mortality during the 10- and 22-year follow-up periods*

	HR (95% CI)	
	10 years	22 years
All-cause (*n*/total deaths)	25/75	73/276
Age-adjusted	1.94 (1.20–3.13)	1.51 (1.15–1.97)
Multiple-adjusted*	1.88 (1.08–3.30)	1.37 (1.00–1.87)
Cardiovascular (*n*/total deaths)	14/34	38/130
Age-adjusted	2.67 (1.35–5.29)	1.73 (1.19–2.53)
Multiple-adjusted*	2.30 (1.03–5.12)	1.39 (0.90–2.15)
Coronary (*n*/total deaths)	10/25	22/80
Age-adjusted	2.54 (1.14–5.65)	1.58 (0.97–2.59)
Multiple-adjusted*	2.77 (1.06–7.23)	1.35 (0.77–2.37)
Cerebrovascular (*n*/total deaths)	3/5	11/27
Age-adjusted	6.12 (1.02–36.80)	3.01 (1.40–6.50)
Multiple-adjusted*	4.38 (0.44–44.00)	1.76 (0.68–4.57)

Data are *n*, ratios, or CIs. *Adjusted for age, BMI, subscapular skinfold, systolic blood pressure, cholesterol, triglycerides (log-transformed), AUC glucose (log-transformed), maximal O_2 uptake, physical activity (yes/no), smoking (yes/no), and occupational status (officers/nonofficers).

during the 10-year follow-up. These associations weakened during the 22-year follow-up but remained statistically significant, except for coronary mortality. In the multiple-adjusted model, hyperinsulinemia was significantly associated with all-cause mortality during both the 10- and 22-year follow-up periods, but this association weakened with the lengthening of the follow-up period. Multiple-adjusted HRs for hyperinsulinemia with regard to cardiovascular and coronary mortality were statistically significant during the 10-year follow-up but no more during the 22-year follow-up; AUC glucose contributed most substantially to this weakening in HRs. Over the 22-year follow-up, independent predictors for all-cause, cardiovascular, and coronary mortality included systolic blood pressure ($P = 0.004$, $P < 0.001$, and $P < 0.001$, respectively) and smoking ($P < 0.001$, $P < 0.001$, and $P = 0.002$, respectively), as well as AUC glucose ($P = 0.049$) for coronary mortality only. The associations between hyperinsulinemia and cerebrovascular mortality became nonsignificant with multiple adjustment, mainly because of the impact of obesity indexes. Subscapular skinfold was an independent predictor of the 22-year cerebrovascular mortality ($P = 0.012$).

Because the association of AUC insulin with noncardiovascular mortality appeared to be U-shaped (Table 2), age-adjusted and multiple-adjusted Cox model HRs and their 95% CIs, comparing the lowest and highest AUC insulin quintiles with the combined middle quintiles (quintiles 2–4), were calculated for noncardiovascular mortality and its subcategories during the 22-year follow-up (Table 4). In AUC insulin quintile 1, the risk of noncardiovascular death, violent death, and other noncardiovascular death was significantly increased in both the age-adjusted and multiple-adjusted models. In AUC insulin quintile 5, the risk of noncardiovascular death was also significantly increased adjusting for age but lost its significance with multiple adjustment. There was an increase in the risk of cancer death and violent death in AUC insulin quintile 5, although these did not reach statistical significance. Smoking was independently associated with noncardiovascular ($P < 0.001$), cancer ($P < 0.001$), and other noncardiovascular mortality ($P = 0.027$), and maximal O_2 uptake was independently and inversely associated with noncardiovascular mortality ($P = 0.030$).

Of the 146 noncardiovascular deaths, 19 (13.0%) were possibly alcohol related (7 suicides, 6 deaths from accidents, 4 from liver cirrhosis, and 2 from acute pancreatitis). In AUC insulin quintile 1, 7 of 35 noncardiovascular deaths (20.0%) were possibly alcohol related; in quintiles 2–4, the corresponding proportion was 8 of 76 (10.5%), and in quintile 5, 4 of 35 (11.4%).

To analyze the association between AUC insulin and all-cause, cardiovascular, coronary, and noncardiovascular mortality during the 22-year follow-up over the whole AUC insulin distribution, we carried out Cox model analyses using base 10–log-transformed AUC insulin as a continuous variable. Adjusting for age alone, log AUC insulin showed a positive statistically significant linear association with all-cause, cardiovascular, and coronary mortality; the HRs for 1 base 10–log-unit increase in AUC insulin were 1.65 (95% CI 1.04–2.61), 3.05 (1.56–5.96), and 3.95 (1.69–9.21),

Table 4—*Age-adjusted and multiple-adjusted HRs and 95% CIs for low (AUC insulin quintile 1) and high (AUC insulin quintile 5) versus middle insulin levels (AUC insulin quintiles 2–4) with regard to noncardiovascular mortality and its subcategories during the 22-year follow-up*

	HR (95% CI)		
	Quintile 1	Quintiles 2–4	Quintile 5
n	191	584	195
Noncardiovascular deaths (*n*)	35	76	35
Age-adjusted	1.59 (1.07–2.38)	1.00	1.50 (1.00–2.24)
Multiple-adjusted*	1.85 (1.20–2.86)	1.00	1.43 (0.91–2.24)
Cancer deaths (*n*)	13	46	22
Age-adjusted	0.97 (0.53–1.81)	1.00	1.57 (0.94–2.61)
Multiple-adjusted*	1.26 (0.65–2.44)	1.00	1.32 (0.74–2.36)
Violent deaths (*n*)	11	11	7
Age-adjusted	3.27 (1.41–7.56)	1.00	2.01 (0.78–5.18)
Multiple-adjusted*	3.13 (1.24–7.91)	1.00	2.43 (0.84–6.99)
Other noncardiovascular deaths (*n*)	11	19	6
Age-adjusted	2.14 (1.01–4.52)	1.00	1.06 (0.42–2.65)
Multiple-adjusted*	2.31 (1.01–5.28)	1.00	1.12 (0.40–3.10)

Data are *n*, ratios, or CIs. *Adjusted for age, BMI, subscapular skinfold, systolic blood pressure, cholesterol, triglycerides (log-transformed), AUC glucose (log-transformed), maximal O_2 uptake, physical activity (yes/no), smoking (yes/no), and occupational status (officers/nonofficers).

respectively. With multiple adjustment, the HRs became nonsignificant for all-cause mortality (1.16 [95% CI 0.65–2.07]) and cardiovascular mortality (2.10 [0.91–4.85]), whereas the HR for coronary mortality remained almost unchanged and significant (3.72 [1.32–10.51]). A model also including a squared term of log AUC insulin, and adjusting for age revealed a statistically significant curvilinear relationship between AUC insulin and noncardiovascular mortality ($\chi^2 = 5.35$, df = 1, $P = 0.021$), but with multiple adjustment, this relationship was no more significant ($\chi^2 = 2.82$, df = 1, $P = 0.093$).

CONCLUSIONS — Our study, based on 22-year mortality data from the Helsinki Policemen Study, is the first prospective study investigating the association of insulin with all major categories of mortality. From this study, 2 main findings emerged. First, elevated plasma insulin during OGTT, expressed as AUC insulin, was associated with increased all-cause mortality, and this was mainly a result of an increase in cardiovascular mortality. Second, a U-shaped association was observed between plasma insulin and noncardiovascular mortality.

In the present study, the association of hyperinsulinemia with all-cause mortality was independent of other risk factors. Information available from other studies on the association of insulin with all-cause mortality is scarce and conflicting. In the Busselton Study, a significant positive association between insulin and all-cause mortality was observed in older men, but the association was inverse in younger men, and there was no association in women (14). In a Finnish study of elderly men and women, a significant inverse association was observed between insulin and all-cause mortality in the oldest age-group and a trend to a positive association in the youngest age-group (15). In the Paris Prospective Study, the association between insulin and all-cause mortality was U-shaped and independent of other risk factors (16).

In the present study, hyperinsulinemia was strongly and independently associated with cardiovascular and coronary mortality during the 10-year follow-up, but during the 22-year follow-up, these associations weakened and were no more independent. However, as a continuous variable, insulin was also an independent predictor of coronary mortality during the 22-year follow-up. A weakening of the predictive value of hyperinsulinemia with regard to cardiovascular and coronary mortality with lengthening follow-up time was also observed in the Busselton Study (17,18) and the Paris Prospective Study (16). In contrast to these findings, 2 prospective studies on elderly subjects—the Finnish study of elderly men and women (15) and the Rancho Bernardo Study (19)—found no association between insulin and cardiovascular mortality or even an inverse association in some subgroups.

The U-shaped relationship of insulin with noncardiovascular mortality in the present study resulted from a significant excess of violent deaths and other noncardiovascular deaths (deaths from noncardiovascular causes other than cancer or violence) in the lowest insulin quintile and from a nonsignificant excess of cancer deaths and violent deaths in the highest AUC insulin quintile. The excess of violent deaths and other noncardiovascular deaths in the lowest AUC insulin quintile was an unexpected finding, and there is no obvious explanation for it. Because there is evidence that regular alcohol use is associated with low insulin concentrations and enhanced insulin sensitivity (20–23), we considered the possibility that the increased noncardiovascular mortality in men with low insulin could at least in part be a result of excessive use of alcohol. Unfortunately, the baseline interview did not include questions on alcohol consumption. However, we made an attempt to identify alcohol-related deaths on the basis of death certificate data. Of all noncardiovascular deaths, the proportion of possibly alcohol-related deaths thus identified was almost 2-fold higher in the lowest AUC insulin quintile than in the higher quintiles. Our data probably underestimate the contribution of alcohol to noncardiovascular mortality but give some support to the view that excessive alcohol use could be one of the factors explaining the increase in noncardiovascular mortality in men with low insulin levels.

Little information is available on the relationship between insulin and cancer mortality. In accordance with our finding of some, although nonsignificant, excess of cancer deaths in the highest AUC insulin quintile, the Busselton Study showed a significant positive association between insulin and cancer mortality in older men (14). In the Cardiovascular Health Study (24), insulin was positively associated with incident colorectal cancer.

The main limitation of our study is the small number of deaths in certain mortality subcategories. Another limitation is the lack of information on certain potential confounders, such as HDL cholesterol and alcohol consumption. No conclusions can be drawn about how our results can be generalized to other populations (e.g., women and other ethnic groups).

In conclusion, during the 22-year follow-up of the Helsinki Policemen Study, hyperinsulinemia was associated with an increase in all-cause and cardiovascular mortality, independent of other risk factors, although these associations weakened with the lengthening of the follow-up period. The association between insulin and noncardiovascular mortality was U-shaped.

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