Hyperinsulinemia Predicts Coronary Heart Disease Risk in Healthy Middle-aged Men
The 22-Year Follow-up Results of the Helsinki Policemen Study

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Background—The Helsinki Policemen Study is one of the first prospective epidemiological studies demonstrating an association of hyperinsulinemia to the risk of coronary heart disease (CHD). The aim of the present study was to investigate the predictive value of hyperinsulinemia with regard to CHD risk during a 22-year follow-up of the Helsinki Policemen Study population.

Methods and Results—The study was based on a cohort of 970 men who were 34 to 64 years of age and free of CHD, other cardiovascular disease, and diabetes. Risk factor measurements at baseline examination included an oral glucose tolerance test (OGTT) with blood glucose and plasma insulin measurements at 0, 1, and 2 hours. Area under the plasma insulin response curve (AUC insulin) during OGTT was used as a composite variable reflecting plasma insulin levels. During the 22-year follow-up, 164 men had a major CHD event (CHD death or nonfatal myocardial infarction). Age-adjusted hazard ratios for a major CHD event comparing men in the highest AUC insulin quintile with those in the combined 4 lower quintiles during 5-, 10-, 15-, and 22-year follow-up periods were 3.29 (95% CI, 1.56 to 6.91), 2.72 (95% CI, 1.67 to 4.42), 2.14 (95% CI, 1.43 to 3.21), and 1.61 (95% CI, 1.14 to 2.27), respectively. Further adjustment for other risk factors attenuated these hazard ratios to 2.36 (95% CI, 1.00 to 5.57), 2.29 (95% CI, 1.31 to 4.02), 1.76 (95% CI, 1.09 to 2.82), and 1.32 (95% CI, 0.89 to 1.97), respectively.

Conclusions—Hyperinsulinemia predicted CHD risk in Helsinki policemen over the 22-year follow-up, and to a large extent independently of other CHD risk factors, but its predictive value diminished with lengthening follow-up time. (Circulation. 1998;98:398-404.)

Key Words: coronary disease ■ epidemiology ■ insulin ■ risk factors

The association of hyperinsulinemia to atherosclerosis and CHD has been a subject of interest but also of controversy for more than 3 decades.1-7 The Helsinki Policemen Study,8 the Busselton Study,9 and the Paris Prospective Study10 were the first prospective epidemiological studies showing that high plasma insulin, fasting or after oral glucose load, was associated with increased risk of major CHD events independently of other conventional cardiovascular risk factors. The results of other subsequent prospective epidemiological studies on this subject, however, have been conflicting.11-30 A positive association of plasma insulin level1 and insulin resistance32-34 to ultrasonographically assessed atherosclerosis has been observed in cross-sectional studies. Some evidence has also accumulated from studies on the cell biology of the arterial wall and animal experiments, suggesting that insulin might have a direct enhancing effect on atherogenesis.1

In 1988, Reaven35 introduced the concept of “insulin resistance syndrome” or “metabolic syndrome.” Collecting threads of evidence from experimental, clinical, and epidemiological studies, he pointed out that hyperinsulinemia clusters with several cardiovascular risk factors, including low HDL cholesterol, high triglycerides, impaired glucose tolerance, elevated blood pressure, and obesity and its central distribution. An upsurge of interest in insulin resistance syndrome has led to a renewed attention to prospective epidemiological studies on the association between hyperinsulinemia and CHD.

We have now extended the follow-up of the Helsinki Policemen Study to 22 years, and the aim of the present study was to investigate whether the predictive value of hyperinsulinemia with regard to major CHD events changes with lengthening follow-up time.

Methods

Study Population
This study is based on a cohort of 970 men who were 34 to 64 years of age (median, 48 years) and free of CHD, other clinically significant cardiovascular disease, and diabetes while participating in the second examination of the Helsinki Policemen Study in 1971 to 1972. The initial examination of the Helsinki Policemen Study took place in 1966 to 1967 and comprised a total of 1326 men ≥30 years of age who were employed by the Police Department of the city of Helsinki or by the National Police Force units in Helsinki.36 The participation rate in the initial examination was 98.4%. In 1971 to
AUC glucose = area under the blood glucose response curve
AUC insulin = area under the plasma insulin response curve
BMI = body mass index
CHD = coronary heart disease
ICD = International Classification of Diseases
MI = myocardial infarction
OGTT = oral glucose tolerance test

1972, a total of 1259 men were reexamined, representing 98.5% of the surviving men. The cohort of the present study was formed as follows: Men who had been ≥60 years at the time of the initial examination were excluded because that age group was already highly selected owing to the retirement age in the Finnish Police Force (58 years, with the exception of high-ranking police officers). Of the remaining 1230 men, 190 had definite or possible CHD, 12 had other clinically significant heart disease, 8 had a history of stroke, and 47 had diabetes. Exclusion of 236 men with 1 or several of these diseases, 2 men who had moved out of the country, and 22 men with missing values for the variables used in the analyses led to the final study cohort of 970 men.

Study Program and Methods at 1971 to 1972 Examination

The study program included a questionnaire concerning previously diagnosed diseases, drug therapy, physical activity, and smoking habits; Rose cardiovascular questionnaire; measurement of height, weight, and other anthropometric measures, including subscapular skin-fold thickness; clinical examination, including measurement of blood pressure; resting and exercise ECGs; assessment of physical fitness by a bicycle ergometer exercise test; and laboratory examinations, including determination of plasma total cholesterol and triglycerides, as well as an OGTT with plasma insulin determinations.

Clinical examination was carried out by the same physician throughout the 1971 to 1972 examination. BMI, weight (kilograms)/height (meters) squared, was used as an index of the degree of overall obesity, and subscapular skin-fold thickness was the index of upper-body obesity. Seated blood pressure on the right arm was measured twice (interval, 5 minutes) with a mercury sphygmomanometer; the average of 2 measurements was used in data analyses. Hypertension was considered to be present when systolic blood pressure was ≥160 mm Hg and/or diastolic blood pressure was ≥95 mm Hg or if the subject was using antihypertensive drugs. Resting ECGs were interpreted according to the Minnesota Code.

Smoking history was considered in the data analyses by use of a dichotomous classification: current nonsmokers (those who never smoked and ex-smokers) versus current smokers. Leisure-time physical activity was graded by use of a questionnaire modified from that described by Saltin and Grimby into 4 classes: 1 = inactive, 2 = slightly active, 3 = active, and 4 = highly active. For the data analyses, a dichotomous classification was used: inactive (classes 1 and 2) versus active (classes 3 and 4). Predicted maximal O₂ uptake (milliliters per minute per kilogram of body weight) was used as an objective estimate of physical fitness. It was determined by use of the nomogram of Åstrand and Ryhming on the basis of the heart rate achieved in a bicycle ergometer exercise test in which the subject pedaled at a workload of 150 W for 4 minutes.

The OGTT and collection of blood samples for biochemical measurements were carried out between 8 and 10 AM after a minimum 12-hour fast. The glucose dose used in the OGTT was 75 or 90 g according to body surface area in a 20% solution (847 men received 75 g of glucose; 123 men, 90 g). Venous blood samples for blood glucose and plasma insulin determinations were taken before the glucose load and 1 and 2 hours afterward. Blood glucose was determined by o-toluidine method and plasma insulin was determined by the "coated charcoal" radioimmunological assay described by Herbert et al. AUC glucose was calculated from fasting and 1- and 2-hour blood glucose concentrations by use of the trapezoid rule. Similarly, AUC insulin was calculated from fasting and 1- and 2-hour plasma insulin concentrations. Plasma total cholesterol was determined by the method of Abell et al., and plasma total triglycerides were determined by the method of Björkstén.

Definite or possible CHD was diagnosed if the subject had, either at the 1966 to 1967 or 1971 to 1972 examination, (1) a history of MI verified at hospital (hospital records were checked), (2) major Q/QS waves in the resting ECG (Minnesota Code 1.1 to 1.2), or (3) angina pectoris or chest pain attack by the Rose cardiovascular questionnaire.

Diabetes was considered to be present if the subject had previously diagnosed diabetes or if the fasting blood glucose was ≥6.7 mmol/L or the 2-hour blood glucose in the OGTT was ≥10.0 mmol/L at either the 1966 to 1967 or 1971 to 1972 examination.

Collection of Follow-up Data

The follow-up period extended from the date of the 1971 to 1972 examination for each subject until January 1, 1994. The median follow-up time for those surviving over the whole follow-up period was 22.3 years (range, 21.9 to 22.9 years). Information on the vital status of all men and copies of death certificates of all deceased men were obtained from the Statistical Office of Finland. In the final classification of the causes of death, hospital records and death certificates were used; death certificates also were used if available. Autopsy had been made in 142 of 276 cases of death (51.4%). Underlying cause of death was coded by use of the ninth revision of the ICD (ICD-9). ICD codes 390 through 459 formed the cardiovascular disease death category; ICD codes 410 through 414, the CHD death category.

For the ascertainment of hospital-verified MIs occurring during the follow-up, we obtained from the computerized National Hospital Discharge Register information on hospitalizations of all men belonging to the study cohort over the period from January 1, 1971, until January 1, 1994. From this register, we identified hospitalizations with ICD codes 410 through 413 as discharge diagnoses (ICD-8 until 1986; ICD-9 since 1987). Patient records on these hospitalizations were reviewed by 1 of the authors (M.P.). The diagnosis of a nonfatal MI was confirmed if at least 2 of the following criteria were fulfilled: (1) chest pain attack lasting ≥20 minutes or its equivalent (acute left ventricular failure, syncope), (2) development of ECG changes diagnostic or suggestive of MI, or (3) elevation of serum levels of cardiac enzymes. Thus, we were able to have a complete ascertainment of MIs leading to hospital treatment, including nonfatal MIs occurring in men who later died of CHD or other causes.

The Finnish Social Insurance Institution maintains a central register of diabetic subjects receiving reimbursement of hypoglycemic drugs. We obtained from this register the dates of the beginning of such reimbursement for men belonging to the study cohort.

Statistical Methods

Data analyses were performed with SPSS 6.1.3 and SAS 6.10 software. Because of the skewed distribution of blood glucose, plasma insulin, and triglycerides variables, these variables were log transformed for statistical analyses. Age-adjusted Pearson’s partial correlation coefficients were calculated to examine the correlations of plasma insulin variables with other continuous risk factors. ANCOVA or the Mantel-Haenszel test was used in comparisons between groups as appropriate. Age-adjusted incidences and significances for their trends were calculated by general linear modeling of the SAS system. Kaplan-Meier survival curves for remaining free of major CHD events (CHD death or nonfatal MI) were calculated to describe the occurrence of such events by quintiles of AUC insulin over the 22-year follow-up period, and differences between and over quintiles were tested by the log-rank test. The Cox proportional hazards model was used to estimate the contribution of AUC insulin to the prediction of CHD risk during 5-, 10-, 15-, and 22-year follow-up periods, with adjustment for age and other risk factors. One subject became censored from Cox models because early noncoronary death. There was no indication of nonproportional hazards during the 22-year follow-up period. Statistical significance
TABLE 1. Baseline Characteristics of the Study Population (n=970)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD/Frequency</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>47.4±7.5</td>
</tr>
<tr>
<td>Height, cm</td>
<td>179±5</td>
</tr>
<tr>
<td>Weight, kg</td>
<td>84.1±10.8</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td>26.2±3.0</td>
</tr>
<tr>
<td>Subscapular skin fold, mm</td>
<td>18±7</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>136±18</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>85±11</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>24.3</td>
</tr>
<tr>
<td>Cholesterol, mmol/L</td>
<td>6.27±1.14</td>
</tr>
<tr>
<td>Triglycerides, mmol/L</td>
<td>1.74±1.01</td>
</tr>
<tr>
<td>Fasting glucose, mmol/L</td>
<td>4.9±0.5</td>
</tr>
<tr>
<td>1-h glucose, mmol/L</td>
<td>6.5±1.9</td>
</tr>
<tr>
<td>2-h glucose, mmol/L</td>
<td>4.4±1.2</td>
</tr>
<tr>
<td>AUC glucose, mmol/L·hour</td>
<td>11.2±2.4</td>
</tr>
<tr>
<td>Fasting insulin, pmol/L</td>
<td>44±28</td>
</tr>
<tr>
<td>1-h insulin, pmol/L</td>
<td>372±260</td>
</tr>
<tr>
<td>2-h insulin, pmol/L</td>
<td>160±159</td>
</tr>
<tr>
<td>AUC insulin, pmol/L·hour</td>
<td>475±321</td>
</tr>
<tr>
<td>Current smokers, %</td>
<td>45.1</td>
</tr>
<tr>
<td>Physically active (leisure time), %</td>
<td>34.1</td>
</tr>
<tr>
<td>Maximal O₂ uptake, mL · min⁻¹ · kg⁻¹ body weight</td>
<td>35.3±8.3</td>
</tr>
</tbody>
</table>

is expressed either as P values for two-tailed tests or by giving 95% CI for the estimates.

Approval of the Ethics Committee
This study was approved by the Ethics Committee of the University of Kuopio. All study subjects had given informed consent.

Results
Baseline characteristics of the study population are shown in Table 1, and age-adjusted Pearson’s partial correlation coefficients between plasma insulin variables and other continuous baseline variables are given in Table 2. Blood glucose variables, indexes of obesity, systolic and diastolic blood pressures, and triglycerides correlated positively and significantly with all insulin variables, whereas cholesterol was slightly lower 2-hour insulin in smokers (geometric means, 38 versus 32 pmol/L, P<0.001; 1-hour, 330 versus 261 pmol/L, P<0.001; 2-hour, 121 versus 91 pmol/L, P<0.001; AUC insulin, 427 versus 337 pmol/L·hour, P<0.001).

During the 22-year follow-up, 276 men died. Cardiovascular disease was the cause of death in 130 (47.1%) and CHD in 80 (29.0%) of these men. The number of men who had a major CHD event (CHD death or nonfatal MI) during 5-, 10-, 15-, and 22-year follow-up periods was 28, 68, 105, and 164, respectively. During the 22-year follow-up, CHD death was the first major CHD event in 51 of the 164 men (31.1%).

Age-adjusted incidence of major CHD events by quintiles of fasting and 1- and 2-hour insulin and AUC insulin during different follow-up periods is shown in Figure 1. There was no significant association between fasting insulin and CHD incidence, whereas 1-hour insulin and AUC insulin showed a statistically significant positive association to CHD incidence during all follow-up periods and 2-hour insulin during 5- and 22-year follow-up periods. For 1- and 2-hour insulin and AUC insulin, the highest incidence was observed during all follow-up periods in the highest quintiles of these insulin variables.

In subsequent analyses on the associations between insulin and CHD risk, we used AUC insulin, which reflects the magnitude of insulin response to glucose challenge. Kaplan-Meier survival curves for remaining free of major CHD events during 22-year follow-up by quintiles of AUC insulin are shown in Figure 2.

The predictive value of hyperinsulinemia, defined by the cutoff point for the highest AUC insulin quintile (≥ 669 pmol/L·hour), with regard to the risk of major CHD events was assessed by calculating hazard ratios (highest quintile versus combined lower quintiles) and their 95% CIs by use of the Cox proportional hazards model (Table 3). The age-adjusted hazard ratios for the risk of a major CHD event were statistically significant for all follow-up periods and decreased from 3.29 to 1.61 with lengthening follow-up time. When other risk factors were entered into the Cox model separately, besides age, AUC glucose was the only variable leading to a substantial reduction in the hazard ratios (5 years, 2.26 [95% CI, 1.01 to 5.04]; 10 years, 2.09 [95% CI, 1.23 to 3.55]; 15 years, 1.80 [95% CI, 1.16 to 2.80]; and 22 years, 1.31 [95% CI, 0.90 to 1.90]). Therefore, multiple adjustment for other risk factors was carried out with and without AUC glucose. Multiple adjustment without AUC glucose had very

<table>
<thead>
<tr>
<th>Variable</th>
<th>Mean±SD/Frequency</th>
</tr>
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<tbody>
<tr>
<td>Glucose and insulin variables and triglycerides log transformed.</td>
<td>*P&lt;0.05; †P&lt;0.01; ‡P&lt;0.001.</td>
</tr>
</tbody>
</table>
little effect on the hazard ratios, whereas the inclusion of AUC glucose substantially attenuated them, although they still remained statistically significant, with the exception of that for the 22-year follow-up period.

The multiple-adjusted hazard ratios for major CHD events obtained by replacing the degree of physical activity by predicted maximal O$_2$ uptake (available for 938 men) were as follows: 5 years, 2.42 (95% CI, 0.97 to 6.04); 10 years, 2.16 (95% CI, 1.18 to 3.93); 15 years, 1.65 (95% CI, 1.01 to 2.73); and 22 years, 1.28 (95% CI, 0.85 to 1.93).

Table 4 shows the results of analyses of predictors of the risk of a major CHD event during different follow-up periods using Cox models in which age, BMI, subscapular skin fold, systolic blood pressure, cholesterol, triglycerides, AUC insulin, and AUC glucose were entered as continuous variables, and smoking and physical activity were entered as dichotomous variables. To compare the predictive power of AUC insulin with that of other continuous variables, the hazard ratios were calculated for 1-SD differences in these variables. As a continuous variable, AUC insulin was a statistically significant predictor of the CHD risk over the 22-year follow-up, after adjustment was made for age (model 1). With additional adjustment for other risk factors (model 2), AUC insulin remained, with the exception of the first 5 years, a significant independent predictor of CHD risk, with some attenuation of the hazard ratio in the last part of the follow-up. Cholesterol was a statistically significant predictor of CHD risk over the whole follow-up period, its predictive power being of the same magnitude as that for AUC insulin. AUC glucose predicted CHD risk only during the first 5 years. Systolic blood pressure became a statistically significant predictor with lengthening follow-up time. Smoking predicted CHD risk from 10 years onward. BMI, subscapular skin fold, triglycerides, and physical activity showed no association to CHD risk (data not shown).

We also analyzed the association of insulin to the risk of CHD death using the Cox model approaches shown in Tables 3 and 4. The results were, in the main aspects, similar as those for major CHD events (data not shown).

Information on the beginning of drug treatment of diabetes during the follow-up was used to examine the possibility that hyperinsulinemia would be associated with CHD risk, because it may be an antecedent of diabetes. Altogether, 63 men developed drug-treated diabetes during the follow-up. In the whole study cohort, this occurred more frequently in the top than in the lower AUC insulin quintiles (12.8% versus 4.9%, $P_{\text{adj}}<0.001$) but not among men who developed a major CHD event compared with those who did not (9.8% versus 5.8%, $P_{\text{adj}}=0.115$). In the combined 4 lower AUC insulin quintiles, diabetes requiring drug treatment developed in 9.2% of men with a major CHD event compared with 4.1% of men remaining free of such an event ($P_{\text{adj}}=0.031$), whereas in the highest AUC insulin quintile, drug-treated diabetes emerged equally often in men developing and not developing a major CHD event (11.4% versus 13.2%, $P_{\text{adj}}=0.456$). We also carried out multiple-adjusted Cox model analyses of the risk of a major CHD event (highest AUC insulin quintile versus combined lower quintiles), excluding those 63 men who developed drug-treated diabetes during the follow-up; the hazard ratios shown in Table 3 remained essentially unaltered (data not shown).
Discussion

Our results based on the 22-year follow-up of the Helsinki Policemen Study showed that elevated plasma insulin levels during OGTT, expressed as AUC insulin, were associated with an increased risk of a major CHD event (CHD death or nonfatal MI). This association was largely independent of other cardiovascular risk factors, including blood glucose, cholesterol, triglycerides, blood pressure, indexes of obesity and its distribution, smoking, and physical activity. The predictive power of AUC insulin, however, decreased with lengthening follow-up time. Nevertheless, over 22 years of follow-up, the predictive power of AUC insulin was of the same magnitude as that of cholesterol when these variables were entered as continuous variables into multivariate analyses.

Including our study, results on the relationship between plasma insulin and the risk of CHD or cardiovascular disease are available from 19 prospective epidemiological studies. By study design, 2 of these studies were nested case-control studies, whereas all other studies were prospective cohort studies in which insulin measurements were carried out on all study subjects. A positive association between insulin and CHD risk was observed in 10 studies, and in 8 of them, the association was found to be independent of other cardiovascular risk factors. Nine studies found no association or even an inverse association between insulin and the risk of CHD or cardiovascular disease.

To consider possible explanations for conflicting results of different studies, at least 3 different aspects have to be considered: (1) methodological aspects related to insulin measurements, (2) problems related to study size and statistical power of data analyses, and (3) differences in the characteristics of study populations.

Methodological aspects related to insulin measurements include circumstances of blood sampling, handling of samples before actual insulin assays, differences in the performance of OGTTs in those studies in which post–glucose insulin levels were measured, and differences in the radioimmunological methods used in the measurement of insulin concentrations.

Six studies based their observations on fasting only. Fasting insulin has, in fact, been found in clinical studies to show an even stronger correlation than 1- or 2-hour post–glucose insulin levels to insulin resistance measured by euglycemic clamp technique. The precision of radioimmunological methods used for insulin measurements in early studies was, however, not as good as that of more modern methods at low insulin concentrations. This may explain in part why in our study fasting insulin showed no association to CHD risk, in contrast to a clear association found between post–glucose insulin levels and CHD risk.

Another methodological aspect related to insulin measurements is the cross-reactivity of the earlier reagent kits for radioimmunological assays of insulin to the intact or split proinsulins. Concentrations of these molecules, however, comprise only about 10% of all insulinlike molecules in nondiabetic subjects; therefore, this nonspecificity of insulin

<table>
<thead>
<tr>
<th>Variables</th>
<th>Follow-up Time, y</th>
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<tbody>
<tr>
<td></td>
<td>5</td>
</tr>
<tr>
<td>Age adjusted</td>
<td>3.29 (1.56–6.91)</td>
</tr>
<tr>
<td>Multiple adjusted*</td>
<td>3.07 (1.31–7.20)</td>
</tr>
<tr>
<td>With AUC glucose</td>
<td>2.36 (1.00–5.57)</td>
</tr>
</tbody>
</table>

*Adjustment for age, BMI, subscapular skin fold, cholesterol, triglycerides (log transformed), systolic blood pressure, smoking (yes/no), physical activity (yes/no), and without and with AUC glucose (log transformed).

TABLE 4. Hazard Ratios and 95% CIs for AUC Insulin and Other Risk Factors as Continuous Variables* With Regard to Risk of Major CHD Event During Different Follow-up Periods

<table>
<thead>
<tr>
<th>Variables</th>
<th>5-y HR (95% CI)</th>
<th>10-y HR (95% CI)</th>
<th>15-y HR (95% CI)</th>
<th>22-y HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Model 1, adjusting for age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC insulin</td>
<td>1.77 (1.22–2.57)</td>
<td>1.64 (1.30–2.09)</td>
<td>1.56 (1.28–1.88)</td>
<td>1.38 (1.19–1.61)</td>
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<tr>
<td>Model 2, adjusting for age and</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>other risk factors</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUC insulin</td>
<td>1.51 (0.96–2.37)</td>
<td>1.54 (1.16–2.06)</td>
<td>1.50 (1.18–1.90)</td>
<td>1.32 (1.09–1.60)</td>
</tr>
<tr>
<td>AUC glucose</td>
<td>1.58 (1.04–2.41)</td>
<td>1.30 (0.99–1.71)</td>
<td>1.10 (0.88–1.37)</td>
<td>1.14 (0.95–1.37)</td>
</tr>
<tr>
<td>Systolic blood pressure</td>
<td>1.08 (0.77–1.49)</td>
<td>1.15 (0.93–1.42)</td>
<td>1.17 (0.98–1.39)</td>
<td>1.19 (1.03–1.38)</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>1.68 (1.14–2.47)</td>
<td>1.50 (1.18–1.92)</td>
<td>1.45 (1.19–1.78)</td>
<td>1.30 (1.11–1.54)</td>
</tr>
<tr>
<td>Smoking</td>
<td>1.45 (0.67–3.13)</td>
<td>2.08 (1.26–3.44)</td>
<td>1.89 (1.27–2.81)</td>
<td>1.95 (1.42–2.68)</td>
</tr>
</tbody>
</table>

*Hazard ratios (HR) calculated for 1 SD differences in continuous variables: AUC insulin (0.26 logarithm), AUC glucose (0.09 logarithm), systolic blood pressure (18 mm Hg), and cholesterol (1.1 mmol/L). Smoking was entered as a dichotomous variable. In model 2, adjustment was also made for BMI, subscapular skin fold, and physical activity.
assays cannot have had any major effect on the relationship between plasma insulin and CHD risk observed in prospective epidemiological studies. Furthermore, 2 studies using methods specific for true insulin\textsuperscript{13,18} have demonstrated a positive relationship between insulin and CHD risk.

Studies showing no association between insulin and CHD risk have, on average, been smaller than studies showing a positive association (median number of subjects and CHD end-point events, 624 and 49 versus 1728 and 97, respectively). Thus, statistical power problems may in part explain the negative results of some studies.

Differences in the characteristics of study populations probably offer the most likely explanation for the conflicting results of different studies. Characteristics to be considered include ethnic origin, sex, age, inclusion or exclusion of subjects with chronic illnesses or conditions that might influence plasma insulin levels or insulin sensitivity of peripheral tissues, and the pattern of other cardiovascular risk factors in each study population.

Eight studies have included both men and women\textsuperscript{9,14–16,19,25–27} but in only 3 of them have data been reported separately for men and women, and their results have been conflicting. In 1 of these studies, a positive association between insulin and CHD and cardiovascular disease risk was observed in men but not in women\textsuperscript{15}, another study demonstrated no association in men but a positive association in women\textsuperscript{19}, and the third study showed an inverse association in men and no association in women.\textsuperscript{29}

The association between insulin and CHD risk may become weaker or disappear with aging. Of the 4 studies carried out in elderly populations,\textsuperscript{16,22,29,30} only 1 study\textsuperscript{16} showed a positive association.

Insulin resistance and hyperinsulinemia and the associated cluster of risk factors are known to precede the development of non–insulin-dependent diabetes.\textsuperscript{48} It has been suggested that the association of hyperinsulinemia to CHD risk could be a reflection of common causal factors that link CHD and non–insulin-dependent diabetes.\textsuperscript{17} We analyzed our data with regard to the links between hyperinsulinemia at baseline, future development of diabetes, and the occurrence of major CHD events. The information available on the development of diabetes was based on the beginning of drug treatment for diabetes that was based on a national registry of drug reimbursements; thus, we did not get information on an unknown number of milder new cases of diabetes. With their limitations, however, our results do not support the view that the association between hyperinsulinemia and CHD risk would be explained mainly by the occurrence of CHD in hyperinsulinemic subjects who will later develop diabetes.

We found that the predictive value of hyperinsulinemia with regard to CHD risk diminished with lengthening follow-up time, more clearly when hyperinsulinemia was defined by the cutoff point for the highest AUC insulin quintile than when AUC insulin was entered into multivariate analyses as a continuous variable. In the Busselton Study\textsuperscript{9,15} and the Paris Prospective Study\textsuperscript{16,12,17} the association between insulin and CHD risk also became weaker during lengthening follow-up, although their data were not analyzed in a uniform way for different lengths of follow-up. A similar trend was also observed in the British Regional Heart Study.\textsuperscript{17} At least 2 explanations have to be considered for the decrease in the predictive value of hyperinsulinemia with lengthening follow-up time. First, a relatively strong association of hyperinsulinemia to CHD risk during the early part of the follow-up, as was the case in our study, may lead to selective morbidity and mortality, and this may, during long periods of follow-up, weaken the predictive value of hyperinsulinemia.

Second, the cumulative impact of other risk factors may override the impact of hyperinsulinemia or insulin resistance during long follow-up periods.

In earlier reports on the Helsinki Policemen Study,\textsuperscript{8,11} we emphasized the nonlinear nature of the relationship between post–glucose insulin levels and CHD risk, because the excess risk appeared to be confined to the highest quintile or decile for plasma insulin variables. The analyses reported in this paper with a slightly different statistical approach (Figures 1 and 2) are compatible with that observation for the 5- and 10-year follow-up periods, whereas during the 15- and 22-year follow-up periods, the association appeared to extend over the whole distribution of post–glucose insulin levels and AUC insulin.

Caution is needed in the interpretation of the finding in our study and other studies that insulin is an independent predictor of CHD risk when adjusted for other cardiovascular risk factors. Because insulin has physiological links with several other risk factors, particularly blood glucose, indexes of obesity, triglycerides, HDL cholesterol, and blood pressure, inclusion of all these covariates in multivariate analyses may lead to overadjustment, and thus the interpretation of the results is complex. Our study, like other early studies on this issue, did not include HDL cholesterol measurement in the baseline study program. Fourteen studies have, however, measured HDL cholesterol: in 5 studies, a positive association between insulin and CHD risk remained statistically significant in multivariate models including HDL cholesterol\textsuperscript{14,16–19}, in 2 studies, it lost its statistical significance\textsuperscript{20,21}, and in 7 studies, no positive association was observed at all.\textsuperscript{23,25,27–30} Again demonstrating the complexity of the interpretation of epidemiological data on insulin and CHD risk. Therefore, although the results of our study clearly demonstrated a statistically independent association of hyperinsulinemia to CHD risk, we want to emphasize that this association may still be explained through other factors clustering with hyperinsulinemia and insulin resistance.

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Hyperinsulinemia Predicts Coronary Heart Disease Risk in Healthy Middle-aged Men: The 22-Year Follow-up Results of the Helsinki Policemen Study
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