Hyperinsulinemia, Risk Factors, and Coronary Heart Disease
The Zutphen Elderly Study

Edith J.M. Feskens, Daan Kromhout

Abstract We investigated the association between fasting insulin concentration—an indicator of insulin resistance in nondiabetic individuals—cardiovascular risk factors, and coronary heart disease in a study of 390 men in the town of Zutphen. In 1990, an extensive examination was carried out on the participating men (aged 70 to 89 years). Fasting insulin levels were determined and a number of other risk factors measured. Known and newly diagnosed diabetics were excluded from the data analyses. Fasting insulin concentration was significantly associated with levels of glucose, triglycerides, uric acid, serum albumin, creatinine, and fibrinogen as well as resting heart rate. Inverse associations with high-density lipoprotein cholesterol and factor VII activity were observed. These results were independent of confounding factors such as age, body mass index, ratio of subscapular to triceps skinfold thicknesses, cigarette smoking, physical activity, and alcohol consumption. Men with a fasting insulin level higher than 80 pmol/L (highest quartile of the distribution) had a significantly higher prevalence of coronary heart disease and especially of myocardial infarction. This result was independent of potential confounding variables as well as of possible intermediates (total and high-density lipoprotein cholesterol, hypertension, serum triglycerides, fasting glucose, and other risk factors related to fasting insulin) (odds ratio, 2.2; 95% confidence interval, 1.2-4.0). No association between fasting insulin level and hypertension or blood pressure was observed. These results show that fasting insulin is an important indicator of coronary heart disease in elderly men. Clotting factors, resting heart rate, uric acid, serum albumin, and creatinine may also play a role in this metabolic syndrome. (Arterioscler Thromb. 1994;14:1641-1647.)

Key Words: • coronary heart disease • diabetes mellitus, non-insulin-dependent • hypertension • insulin • serum lipids

It has been appreciated for a long time that a number a cardiovascular risk factors tend to cluster in the same individuals.\(^{1-7}\) Recently, an etiologic framework for this observation was provided by Reaven,\(^8\) who referred to this clustering as "syndrome X." The basic components of this syndrome are insulin resistance, hyperinsulinemia, hyperglycemia, dyslipidemia (notably high levels of triglycerides and low levels of high-density lipoprotein [HDL] cholesterol), and hypertension, predisposing to coronary heart disease and non-insulin-dependent diabetes mellitus (type 2). In this view, insulin resistance, hyperinsulinemia, or both are the main underlying metabolic deteriorations, and this cluster is now more frequently referred to as the insulin-resistance syndrome or multiple metabolic syndrome.\(^8-12\)

However, some elements of this hypothesis remain controversial. Several epidemiological studies failed to show an association between insulin and hypertension.\(^{13-16}\) Only a few studies showed an association between insulin and the risk of coronary heart disease,\(^{17-19}\) and results varied according to the subgroup studied or the insulin measurement used.\(^20\) Other cardiovascular risk factors have also been put forward as part of the cluster.\(^9\) Finally, the extent to which the clustering of risk factors is caused by underlying associated determinants such as overweight, physical activity, smoking, and alcohol consumption is unclear.\(^20\)

In 1990 an extensive examination was carried out on all members of the Zutphen Study, a longitudinal study on chronic disease risk factors. The relation of fasting insulin, an indicator of insulin resistance in nondiabetic individuals, to coronary heart disease and its risk factors, including clotting factors, was studied in this cohort of elderly men, a population generally prone to these disorders. Special attention was paid to the potential confounding effects of obesity, physical activity, cigarette smoking, and alcohol consumption.

Methods

Study Population

The Zutphen Study is a longitudinal study on chronic disease risk factors that was initiated in 1960 as the Dutch contribution to the Seven Countries Study.\(^{21,22}\) In 1985, 555 men of this cohort were still alive and invited for a new examination. In addition, a random sample of 2 of 3 of all other men of the same age, 65 to 84 years, and living in Zutphen was selected (n=711). This resulted in a total population of 1266 men, of which 939 (74.2%) finally took part in the survey and formed the cohort of the Zutphen Elderly Study. In the spring of 1990, 718 of these 939 men were alive and invited for participation in a new survey, of which 560 did (response rate, 76%). For the present analyses, all men with diabetes (known and newly diagnosed during the survey) were excluded, together with 93 men with incomplete information on fasting insulin.

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and confounding variables. This resulted in a study population of 389 nondiabetic men.

Examinations

The men were examined according to the protocol used in previous surveys of the Seven Countries Study. The physical examination was carried out by trained physicians from March through June 1990. Weight and height were measured with participants dressed in underwear only. Height was measured with a stadiometer and rounded to the nearest millimeter. Body weight was recorded to the nearest 0.5 kg on a calibrated scale. Body mass index was calculated from weight and height (kilograms per meter squared). Subscapular skinfold and tricipital skinfold thicknesses were measured with a Harpenden caliper in duplicate. Blood pressure was measured with the men in a supine position and the cuff on the right arm. Systolic and diastolic (5th Korotkoff phase) pressures were recorded, and the mean value of two repeated measurements was used in the analyses. The use of antihypertensive drugs was also recorded. The presence of hypertension was defined as systolic blood pressure equal to or greater than 160 mm Hg, diastolic blood pressure equal to or greater than 95 mm Hg, or the use of antihypertensive drugs. Resting heart rate was determined from the electrocardiogram (ECG), which was taken after subjects had rested 10 minutes in a supine position. The physician asked questions regarding smoking using a standardized questionnaire.

An OGTT was carried out during a second visit of the participants to the study center. Procedures were according to guidelines of the World Health Organization. Subjects treated with insulin or oral hypoglycemic agents were excluded from the test. The first blood sample was obtained in the morning after an overnight fast. Second and third samples were obtained 1 and 2 hours after a glucose load of 75 g. Samples were collected in tubes with sodium fluoride. Plasma glucose was determined using the hexokinase method. Fasting glucose levels of 7.8 mmol/L or higher and/or 2-hour glucose levels of 11.1 mmol/L were considered as indicative of diabetes, as recommended. Insulin was measured in serum collected from subjects in a fasting state using a radioimmunoassay from Pharmacia Diagnostics. Within- and between-run coefficients of variation ranged from 6% to 7%.

Other blood samples were obtained by venipuncture after minimal stasis. Triglycerides were determined in serum collected from subjects in a fasting state of the OGTT; whereas other analyses were done on nonfasting samples obtained during another visit of the participants to the study center. Serum total and HDL cholesterol and triglycerides were determined enzymatically at the standardized Lipid Laboratory at the Department of Human Nutrition, Agricultural University, Wageningen, Netherlands. Serum albumin, uric acid, and creatinine were determined at the Central Clinical and Chemical Laboratory of the University Hospital of Leiden (Netherlands), using standard procedures on an autoanalyzer (SMAC, Technicon). Factor VII and factor X activities were determined enzymatically in citrate plasma obtained after immediate centrifugation at 4°C at the Laboratory of the Department of Human Biology, University of Limburg, Maastricht, Netherlands. Fibrinogen analyses were carried out in the same laboratory according to the method of Clauss.

Information on alcohol intake was collected by the cross-check dietary history method adapted to the Dutch situation. Physical activity was assessed with a questionnaire designed for retired men made available by Prof J.N. Morris, London School of Hygiene and Tropical Medicine. The questionnaire was pilot tested for the present study to become a 15-item sequence. Time estimates for time spent on activities (walking, cycling, gardening, doing odd jobs, sports, hobbies, and work) were converted to minutes per week for each type of activity and summed to get total weekly minutes of activity.

### Table 1. Selected Background Characteristics of 389 Men Aged 70 to 89 Years According to Fasting Insulin Level, the Zutphen Elderly Study, 1990

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Quartiles 1-3 (n=294)</th>
<th>Quartile 4* (n=96)</th>
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<tbody>
<tr>
<td>Age, y</td>
<td>75.2 (4.8)</td>
<td>74.8 (4.2)</td>
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<tr>
<td>Body mass index, kg/m²</td>
<td>24.9 (2.8)</td>
<td>27.5 (3.1)</td>
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<tr>
<td>Subscapula-triceps ratio</td>
<td>1.44 (0.38)</td>
<td>1.47 (0.37)</td>
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<tr>
<td>Physical activity, h/wk</td>
<td>11.4 (9.6)</td>
<td>9.0 (7.5)</td>
</tr>
<tr>
<td>Alcohol, g/d</td>
<td>10.3 (13.2)</td>
<td>12.4 (13.3)</td>
</tr>
<tr>
<td>Cigarette smoking, %</td>
<td>24.1</td>
<td>16.5</td>
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</table>

Values are mean (SD).
*Fasting insulin >80 pmol/L.
†P<.05, ‡P<.001.

This was recalculated to hours of activity per day. Socioeconomic status was derived from the profession carried out for the largest part of the subject's working life and was divided into three categories (low, middle, high).

Coronary heart disease history was determined by the physician using a standardized questionnaire developed by the London School of Hygiene and Tropical Medicine. Information was verified with the ECG, hospital discharge data, and written information from general practitioners. Coronary heart disease was assumed to be present when a history of either myocardial infarction or angina pectoris was established. Definite myocardial infarction was assumed to be present when two of the following three criteria were fulfilled: a specific medical history, ie, severe chest pain lasting for more than 20 minutes and not disappearing at rest; characteristic ECG changes (major or lesser Q waves and minor T findings); and specific enzyme elevations. Probable myocardial infarction was diagnosed when one of the three criteria was met. The diagnosis of angina pectoris was based on criteria of the questionnaire: chest pain or discomfort located at the sternum or left chest plus left arm caused by the effort of walking or hurrying, compelling the patient to slow down or take nitroglycerin, and relieved within 10 minutes after the effort was stopped.

### Statistical Analyses

Statistical analyses were carried out using the SAS program (version 6.07). Since several variables were not normally distributed, Spearman's rank correlations were used to investigate bivariate and multivariate associations. Logistic regression analysis was used to investigate the association between fasting insulin and the presence of hypertension and coronary heart disease. Hyperinsulinemia was assumed for the highest quartile of fasting insulin. This cutoff point was confirmed by cluster analysis (PROC FASTCLUS on standardized values of fasting insulin), showing that 95 of the 389 men could be designated to a cluster characterized by high fasting insulin levels. For simplicity and comparative purposes, the classification according to quartiles was preferred. All probability values were based on two-sided tests of statistical significance.

### Results

In spring 1990, 389 nondiabetic men aged 70 to 89 years were investigated. Mean age was 75.1 years. Fasting insulin levels in this population ranged from 21.6 to 254 pmol/L, with a median value of 60 pmol/L. Men with insulin levels higher than 80 pmol/L (highest quartile) were considered to be hyperinsulinemic. These men had significantly higher levels of body mass...
index and a lower mean level of physical activity (Table 1). The proportion of men using alcohol and smoking cigarettes did not differ between the two groups.

Investigation of the selected metabolic risk factors found that fasting and 2-hour glucose, serum triglycerides, creatinine, albumin, and uric acid as well as diastolic blood pressure were significantly higher among men with hyperinsulinemia (Table 2). The mean level of HDL cholesterol was 0.17 mmol/L lower compared with men without hyperinsulinemia (P < .001).

Fasting insulin levels were significantly associated with fasting and 2-hour glucose levels, serum triglycerides, uric acid, albumin, creatinine, diastolic blood pressure, and resting heart rate, whereas significant inverse associations were observed with HDL cholesterol and factor VII activity (Table 2). After adjustment for potential confounding variables such as age, body mass index, subscapular-to-triceps skinfold ratio, physical activity, cigarette smoking, and alcohol consumption, the associations remained statistically significant except for the association with diastolic blood pressure, which disappeared. The adjusted association between fasting insulin and fibrinogen reached statistical significance. When adjustments were made for socioeconomic status, 2-hour glucose levels, presence of coronary heart disease, or use of antihypertensive medication (mostly diuretics or \( \beta \)-blockers), the correlation coefficients remained essentially the same.

No independent association between hyperinsulinemia and blood pressure levels was observed. Twelve percent of the men used antihypertensive drugs. The overall prevalence of hypertension (systolic blood pressure \( \geq 160 \) mm Hg and/or diastolic blood pressure \( \geq 95 \) mm Hg or use of antihypertensive drugs) was 38.5% and amounted to 45.8% among the highest quartile of fasting insulin and 36.4% among the other men. The odds ratio was 1.44 (95% confidence interval [CI], 0.79-2.29). After adjustment for potential confounders, the odds ratio amounted to 2.8, whereas after additional adjustments for all related cardiovascular disease risk factors, the odds ratio was 2.4 (95% CI, 1.33-4.47). Additional adjustments for other factors such as socioeconomic status or use of antihypertensive medication resulted in similar effect estimates. When the different components of coronary heart disease were investigated separately, the strongest associations were found for definite and probable myocardial infarction (Table 3). For angina pectoris, no significant association with hyperinsulinemia was ob-

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Fasting</th>
<th>2-Hour</th>
<th>Serum total cholesterol, mmol/L</th>
<th>Serum HDL cholesterol, mmol/L</th>
<th>Serum triglycerides, mmol/L</th>
<th>Systolic blood pressure, mm Hg</th>
<th>Diastolic blood pressure, mm Hg</th>
<th>Resting heart rate, bpm</th>
<th>Serum creatinine, mmol/L</th>
<th>Serum albumin, g/L</th>
<th>Serum uric acid, mmol/L</th>
<th>Fibrinogen, g/L</th>
<th>Factor VII, %</th>
<th>Factor X, %</th>
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<tbody>
<tr>
<td>Glucose, mmol/L</td>
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<tr>
<td>Fasting</td>
<td>5.6</td>
<td>5.6</td>
<td>6.10</td>
<td>1.21</td>
<td>1.30</td>
<td>148</td>
<td>81</td>
<td>74.0</td>
<td>108.0</td>
<td>43.0</td>
<td>0.34</td>
<td>3.69</td>
<td>121.4</td>
<td>98.2</td>
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<td>2-Hour</td>
<td>5.6</td>
<td>5.6</td>
<td>6.10</td>
<td>1.21</td>
<td>1.30</td>
<td>148</td>
<td>81</td>
<td>74.0</td>
<td>108.0</td>
<td>43.0</td>
<td>0.34</td>
<td>3.69</td>
<td>121.4</td>
<td>98.2</td>
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<td>Serum total cholesterol, mmol/L</td>
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<td>Serum HDL cholesterol, mmol/L</td>
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<td>Serum triglycerides, mmol/L</td>
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<td>Systolic blood pressure, mm Hg</td>
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<td>Diastolic blood pressure, mm Hg</td>
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<td>Resting heart rate, bpm</td>
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<td>Serum creatinine, mmol/L</td>
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<td>Serum albumin, g/L</td>
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<td>Serum uric acid, mmol/L</td>
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<td>Fibrinogen, g/L</td>
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<td>Factor VII, %</td>
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<td>Factor X, %</td>
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</table>
TABLE 3. Association Between Fasting Insulin and Prevalence of Coronary Heart Disease, the Zutphen Elderly Study, 1990

<table>
<thead>
<tr>
<th>Fasting Insulin</th>
<th>Quartiles 1-3</th>
<th>Quartile 4*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coronary heart disease, %</td>
<td>21.4</td>
<td>35.4§</td>
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<tr>
<td>Odds ratio</td>
<td></td>
<td></td>
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<tr>
<td>Crude</td>
<td>1.0</td>
<td>2.04 (1.24-3.35)</td>
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<tr>
<td>Adjusted 1†</td>
<td>1.0</td>
<td>2.72 (1.54-4.80)</td>
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<tr>
<td>Adjusted 2‡</td>
<td>1.0</td>
<td>2.43 (1.33-4.47)</td>
</tr>
<tr>
<td>Definite myocardial infarction, %</td>
<td>10.9</td>
<td>21.7§</td>
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<tr>
<td>Odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>2.27 (1.24-4.17)</td>
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<tr>
<td>Adjusted 1†</td>
<td>1.0</td>
<td>2.80 (1.41-5.57)</td>
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<tr>
<td>Adjusted 2‡</td>
<td>1.0</td>
<td>2.22 (1.02-4.80)</td>
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<tr>
<td>Probable myocardial infarction, %</td>
<td>9.5</td>
<td>16.5</td>
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<tr>
<td>Odds ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.88 (0.97-3.77)</td>
</tr>
<tr>
<td>Adjusted 1†</td>
<td>1.0</td>
<td>2.63 (1.23-5.62)</td>
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<tr>
<td>Adjusted 2‡</td>
<td>1.0</td>
<td>2.30 (1.01-5.25)</td>
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<tr>
<td>Angina pectoris, %</td>
<td>13.2</td>
<td>16.5</td>
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<td>Odds ratio</td>
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<tr>
<td>Crude</td>
<td>1.0</td>
<td>1.30 (0.69-2.55)</td>
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<tr>
<td>Adjusted 1†</td>
<td>1.0</td>
<td>1.72 (0.84-3.53)</td>
</tr>
<tr>
<td>Adjusted 2‡</td>
<td>1.0</td>
<td>1.28 (0.57-2.88)</td>
</tr>
</tbody>
</table>

Values in parentheses are 95% confidence intervals.
*Fasting insulin ≥80 pmol/L.
†Adjusted for age, body mass index, subscapular-to-triceps skinfold ratio, physical activity, cigarette smoking, and alcohol consumption.
‡Adjusted for total and high-density lipoprotein cholesterol, hypertension, triglycerides, resting heart rate, 2-hour glucose, fibrinogen, factor VII, uric acid, serum albumin, and serum creatinine.
§P < .01.

Discussion

The results of our study show that fasting insulin is an important indicator of coronary heart disease prevalence in the elderly independent of potential confounding variables such as body mass index, physical activity, alcohol consumption, and cigarette smoking. In addition, whereas hyperinsulinemia was associated with postload glucose, dyslipidemia, resting heart rate, fibrinogen, factor VII, uric acid, serum albumin, and serum creatinine, these metabolic intermediates could not account for the relation with coronary heart disease. Among nondiabetics, fasting insulin is an indicator of insulin resistance, and thus our results can be interpreted as associations with the insulin-resistant state. The full effect of insulin resistance on coronary heart disease may even be underestimated to some extent because we excluded men with diabetes from our analyses. Insulin was measured with a conventional immunoassay known to cross-react with proinsulin. Proinsulin levels are increased in diabetics and subjects with impaired glucose tolerance, and some authors argue that this causes a false observation of an association between hyperinsulinemia and glucose tolerance. However, when proinsulin is taken into account, subjects with impaired glucose tolerance are still shown to have increased insulin concentrations. In fact, proinsulin constitutes only a minor part of the total insulin measured by the assay and thus cannot account for our observations.

Our study population consisted of elderly men. Elderly subjects are in general prone to diabetes and glucose intolerance as well as to cardiovascular diseases and therefore form an appropriate study population for the investigation of the hypothesis of the insulin-resistance syndrome. This is confirmed by the high prevalence of the syndrome as indicated by our cluster analysis (25%) and the high prevalence of the combination of one or more risk factors in the men with hyperinsulinemia. Theoretically, it is possible that selective mortality would have favored relatively mild cases of coronary heart disease to survive up to this age, having consequences for associations with risk factors.
However, associations between insulin and other risk factors such as serum lipids are as expected,\textsuperscript{4,7} and therefore the results are unlikely to be biased.

Insulin was strongly associated with dyslipidemia, notably with increasing levels of triglycerides and decreasing levels of HDL cholesterol. This has been observed by others,\textsuperscript{4,7} and recently Haffner and coworkers\textsuperscript{12} confirmed this association in a prospective study: subjects with hyperinsulinemia had the highest risk of developing hypertriglyceridemia and low HDL cholesterol levels after 8 years of follow-up and also after adjustment for overweight and body fat distribution. Several mechanisms for this observation have been suggested,\textsuperscript{6-9} such as an increased very-low-density lipoprotein (VLDL) production by increased availability of free fatty acids, a reduced VLDL clearance, or reduced adipose tissue lipoprotein lipase activity. Theoretically, impaired insulin action may also be a result of increased VLDL triglycerides or free fatty acids, described as the Randle cycle.\textsuperscript{5,8}

No association between hyperinsulinemia and total cholesterol was observed. This has also been confirmed by others, although in some studies weak positive associations were noticed.\textsuperscript{28,29} In our earlier longitudinal study, changes in glucose tolerance were independently associated with changes in total cholesterol, suggesting an association with insulin resistance.\textsuperscript{30} However, this could also have been due to underlying changes in common determinants, such as fat intake,\textsuperscript{31} and this issue requires further study.

Fasting insulin tended to be associated with blood pressure and the prevalence of hypertension, but the results were not statistically significant. Insulin resistance has been found among lean hypertensive individuals in a number of studies.\textsuperscript{8,9,40} Several mechanisms have been proposed to explain this observation, including effects on renal sodium absorption, cation transport, proliferation of vascular smooth muscle cells, and effects on the sympathetic nervous system.\textsuperscript{9} Also, confounding effects caused by the use of antihypertensive medication such as diuretics or \(\beta\)-blockers could play a role.\textsuperscript{41} However, epidemiological population-based studies have until now produced conflicting results. Modan and coworkers\textsuperscript{2} observed an association between postload insulin levels and hypertension independent of age and overweight or presence of coronary heart disease or hematocrit. Little is known about the relation between serum albumin and chronic disease. Recently, Hu and coworkers\textsuperscript{49} reported an association between serum albumin and blood pressure independent of serum calcium, hematocrit, and antihypertensive drug use. The authors postulated that this could be related to a blood pressure-lowering effect of tryptophan, the only amino acid binding noncovalently to serum albumin.\textsuperscript{49,51} However, vascular permeability, and thus possibly intravascular volume, has been associated with serum albumin concentrations.\textsuperscript{49,51} Although the associations between insulin and albumin and between albumin and blood pressure remain to be confirmed by others, they suggest that some biological relations between these metabolic and vascular factors exist.

In addition to well-known associated factors such as serum lipids and blood pressure, insulin was shown to be independently associated with other cardiovascular risk factors such as fibrinogen and factor VII in our study. This suggests that the clotting system is involved in the insulin-resistance syndrome. Several studies have
shown that fibrinogen is a risk factor for coronary heart disease and cerebrovascular accident. Barker and coworkers observed increased levels of fibrinogen and factor VII among individuals with syndrome X. For fibrinogen, the results of our study point in the same direction, providing further evidence for an important link between metabolic risk factors and thrombogenesis. On the basis of former studies indicating a positive association between serum triglycerides and factor VII activity, factor VII was expected to increase with increasing insulin levels. In contrast, an inverse relation was observed independent of other risk factors and prevalence of coronary heart disease. This may be due to confounding by underlying determinants, although additional analyses showed that they could not be explained by, for instance, differential associations with dietary factors such as fat intake or by the presence of cardiovascular disorders or the use of anticoagulants. Methodological aspects may have played a role, such as cold activation during the preparation of plasma, but it is not clear to what extent this may have affected our results. This issue remains to be explored in further studies.

Besides associations with cardiovascular disease risk factors, we showed that fasting insulin level was significantly related to the prevalence of coronary heart disease and especially the presence of myocardial infarction. This relation could not be explained by factors such as age, overweight, fat distribution, physical activity, alcohol use, and cigarette smoking nor by associated biological risk factors such as dyslipidemia, hypertension, hemodynamic activity, and clotting factors. This suggests that these variables do not mediate the relation. Thus, other explanations should be considered. It has been suggested that insulin and glucose may have a direct atherogenic effect. The process could also be mediated by other unmeasured risk factors, such as tissue plasminogen activator and plasminogen activator 1 activity, low-density lipoprotein subclass, or modified (glycosylated) low-density lipoprotein. Common underlying genetic determinants also could be involved. Since the present study is of a cross-sectional nature, it cannot be excluded that insulin levels are increased because of the presence of coronary heart disease, because it is well established that glucose tolerance deteriorates directly after an infarction. However, this usually is a temporary phenomenon, and it is unlikely that this has played a major role in the present situation because most of the men had their myocardial infarction several years before the survey.

Until now, three prospective studies have shown that insulin is an independent risk factor for coronary heart disease. Prospective studies in the elderly are scarce, however, additional analyses showed that they could not be explained by, for instance, differential associations with dietary factors such as fat intake or by the presence of cardiovascular disorders or the use of anticoagulants. Methodological aspects may have played a role, such as cold activation during the preparation of plasma, but it is not clear to what extent this may have affected our results. This issue remains to be explored in further studies.

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