

Insulin Resistance Syndrome Predicts the Risk of Coronary Heart Disease and Stroke in Healthy Middle-Aged Men

The 22-Year Follow-Up Results of the Helsinki Policemen Study

Marja Pyörälä, Heikki Miettinen, Pirjo Halonen, Markku Laakso, Kalevi Pyörälä

Abstract—The interpretation of conventional multivariate analyses concerning the relation of insulin to the risk of atherosclerotic disease is complex because of correlations of insulin with other risk factors. Therefore, we applied factor analysis to study the clustering of risk factors in the baseline data of the Helsinki Policemen Study (970 healthy men aged 34 to 64 years) and investigated whether these clusterings predict coronary heart disease (CHD) and stroke risk. Areas under the glucose and insulin response curves (AUC glucose and AUC insulin) were used to reflect glucose and insulin levels during oral glucose tolerance tests. During the 22-year follow-up, 164 men had a CHD event, and 70 men had a stroke. Factor analysis of 10 risk factor variables produced 3 underlying factors: insulin resistance factor (comprising body mass index, subscapular skinfold, AUC insulin, AUC glucose, maximal O₂ uptake, mean blood pressure, and triglycerides), lipid factor (cholesterol and triglycerides), and lifestyle factor (physical activity and smoking). In multivariate Cox models, the age-adjusted hazard ratio for insulin resistance factor during the 22-year follow-up was 1.28 (95% CI 1.10 to 1.50) with regard to CHD risk and 1.64 (95% CI 1.29 to 2.08) with regard to stroke risk. Lipid factor predicted the risk of CHD but not that of stroke, and lifestyle factor predicted a reduced CHD risk. Factor analysis including only 6 risk factor variables proposed to be central components of insulin resistance syndrome (body mass index, subscapular skinfold, AUC insulin, AUC glucose, mean blood pressure, and triglycerides) produced only a single insulin resistance factor that predicted the risk of CHD and stroke independently of other risk factors. (*Arterioscler Thromb Vasc Biol.* 2000;20:538-544.)

Key Words: coronary disease ■ epidemiology ■ insulin ■ insulin resistance syndrome ■ stroke

The association of hyperinsulinemia with the risk of coronary heart disease (CHD) has been demonstrated in several, but not in all, prospective studies.^{1,2} Some prospective studies have also shown an association between hyperinsulinemia and the risk of stroke.³⁻⁶ However, the results of those prospective studies that have shown a positive association between insulin and the risk of CHD and stroke have varied with regard to the outcome of multivariate analyses, with some studies finding and other studies not finding insulin to predict the risk independently of other cardiovascular risk factors.

Two main mechanisms have been proposed to explain the association of hyperinsulinemia with atherosclerotic vascular disease: (1) a direct effect of insulin on the arterial wall⁷ and (2) an effect mediated through a clustering of several other risk factors with hyperinsulinemia.⁸ In 1988, Reaven⁹ introduced the concept of syndrome X, which was later named insulin resistance syndrome (IRS) or metabolic syndrome. According to this concept, the underlying factor is the resistance of peripheral tissues, mainly skeletal muscle, to insulin-mediated glucose disposal, leading to hyperinsulinemia. Other risk factors clustering with insulin resistance and

hyperinsulinemia include impaired glucose tolerance, elevated triglycerides, decreased HDL cholesterol, elevated blood pressure, and obesity and its central distribution. There is still debate involving the definition of IRS, and several new components have been suggested, such as increased levels of plasminogen activator inhibitor-1,¹⁰ fibrinogen,¹¹ factor VII,¹² and uric acid.¹³ Some investigators have even questioned the existence of a distinct IRS.¹⁴

There is some evidence from cell biology and experimental research supporting the direct effect of insulin on atherosclerosis,⁷ but the current balance of evidence gives more support to the view that the association of hyperinsulinemia with atherosclerotic vascular diseases is mediated through the clustering of other cardiovascular risk factors with hyperinsulinemia and the underlying insulin resistance.^{8,15}

In the 22-year follow-up of the Helsinki Policemen Study,² hyperinsulinemia was found to predict the risk of CHD independently of other risk factors, whereas the positive association between hyperinsulinemia and the risk of stroke became nonsignificant after adjustment for other risk factors.⁵ Because of problems in the interpretation of conventional multivariate analyses including several closely correlated risk

Received June 16, 1999; revision accepted August 30, 1999.

From the Department of Medicine (M.P., H.M., M.L., K.P.) and Computing Centre (P.H.), University of Kuopio, Kuopio, Finland.

Correspondence to Kalevi Pyörälä, MD, Department of Medicine, University of Kuopio, Puijonlaaksontie 2, PO Box 1627, 70211 Kuopio, Finland. E-mail kalevi.pyoral@uku.fi

© 2000 American Heart Association, Inc.

Arterioscler Thromb Vasc Biol. is available at <http://www.atvbaha.org>

factor variables, it was not possible to decide whether the difference in our results with regard to the role of hyperinsulinemia as a predictor of CHD and stroke was real or only apparent. Factor analysis provides a method for investigating interrelated variables and reducing them to a smaller number of uncorrelated composite variables. Therefore, we applied factor analysis for the investigation of the clustering of cardiovascular risk factors, particularly those proposed to belong to IRS, in the baseline data of the Helsinki Policemen Study and examined whether these clusterings predicted the risk of CHD and stroke during the 22-year follow-up.

Methods

Study Population

The present study is based on a cohort of 970 men aged 34 to 64 years (median 48 years) who were free of CHD and cerebrovascular disease, other cardiovascular disease, and diabetes when they participated in the second examination of the Helsinki Policemen Study in 1971 to 1972. The formation of the study population, the study protocol, and the diagnostic criteria for prevalent CHD, cerebrovascular disease, and other cardiovascular disease at the baseline examination in 1971 to 1972 have been described in detail previously.^{2,5} 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 oral glucose tolerance test (OGTT) was ≥ 10.0 mmol/L.¹⁶

Assessment of Risk Factors at Baseline Examination

Weight and height were measured with subjects in light clothing without shoes. Body mass index (BMI) was calculated as weight (kilograms)/height (meters) squared. Subscapular and triceps skinfold thicknesses were measured with the Harpenden caliper (John Bull, British Indicators). BMI was used as an index of the degree of overall obesity, and subscapular skinfold thickness was used as an index of upper-body obesity.

Seated blood pressure was measured on the right arm twice at the interval of 5 minutes with a mercury sphygmomanometer, and the averages of 2 measurements of systolic and diastolic blood pressure were used in data analyses. Mean blood pressure was calculated from the formula $([2 \times \text{diastolic}] + \text{systolic})/3$. Hypertension was considered to be present when the systolic blood pressure was ≥ 160 mm Hg and/or diastolic blood pressure was ≥ 90 mm Hg or if the subject was receiving drug treatment for hypertension. Only 29 men used antihypertensive drugs at baseline; 23 of them took diuretics.

Smoking history was considered in the data analyses by use of a dichotomous classification: current nonsmokers (those who never smoked and exsmokers) versus current smokers. Leisure time physical activity was assessed by use of a questionnaire modified from that described by Saltin and Grimby¹⁷ and graded into 4 classes: 1 indicated inactive; 2, slightly active; 3, active; and 4, highly active. For the data analyses, a dichotomous classification was used: inactive (classes 1 and 2 combined) versus active (classes 3 and 4 combined). Predicted maximal O_2 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 Ryhming¹⁸ 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.

OGTT and collection of blood samples for other biochemical measurements were performed between 8 and 10 AM after a minimum of a 12-hour fast. The glucose dose used in the OGTT was 75 or 90 g, according to the body surface area (847 men received 75 g and 123 men received 90 g of glucose). Venous blood samples for blood glucose and plasma insulin determinations were taken before and 1 and 2 hours after the glucose load. Blood glucose was determined by the *o*-toluidine method,¹⁹ and plasma insulin was determined by the "coated charcoal" radioimmunological assay

described by Herbert et al.²⁰ The area under the blood glucose response curve (AUC glucose) was calculated from the fasting, 1-hour, and 2-hour blood glucose concentrations with the trapezoid rule. Similarly, the area under the plasma insulin response curve (AUC insulin) was calculated from fasting, 1-hour, and 2-hour insulin concentrations. Plasma total cholesterol was determined by the method of Abell et al,²¹ and plasma total triglycerides was determined by the method of Björkstén.²²

Combined World Health Organization¹⁶ and American Diabetes Association²³ criteria (fasting blood glucose < 5.6 mmol/L and 2-hour blood glucose < 6.7 mmol/L) were used for the definition of strictly normoglycemic men.

Collection of Follow-Up Data

The follow-up lasted until January 1, 1994, from the date of the 1971 to 1972 examination for each study subject. 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 national Cause-of-Death Register (Statistics Finland). In the final classification of causes of death, in addition to the review of death certificates, hospital records and autopsy reports were also used, if available. Autopsy was performed in 142 (51.4%) of the 276 instances of death. The underlying cause of death was coded by one of the authors (M.P.), who used the *International Classification of Diseases, Ninth Revision* (ICD-9). ICD-9 codes 410 through 414 formed the CHD death category. With regard to the stroke death category, subarachnoid hemorrhage was not included as an end point; therefore, death from stroke included ICD-9 codes 431 through 434 and 436.

For the ascertainment of hospital-verified myocardial infarctions (MIs) and strokes 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 ranging from January 1, 1971, to January 1, 1994. From this register, we identified hospitalizations for acute CHD events with ICD codes 410 through 413 and for acute cerebrovascular disease events with ICD codes 431 through 436 as discharge diagnoses (ICD-8 was used until 1986; ICD-9 has been used since 1987). The hospital records on these hospitalizations were reviewed by one 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.

The diagnosis of a nonfatal stroke was ascertained according to the World Health Organization criteria for stroke²⁴: a neurological deficit observed by a physician and persisting > 24 hours, without other diseases explaining the symptoms. Thromboembolic and hemorrhagic strokes, but not subarachnoid hemorrhage, were included in the diagnosis of stroke. Strokes occurring within 28 days after a hospital-verified MI were interpreted as secondary complications of MI and therefore excluded.

Statistical Methods

Data analyses were performed with SPSS 8.0 and SAS 6.12 software. Because of the skewed distribution of blood glucose and plasma insulin levels, as well as plasma triglycerides, these variables were logarithmically transformed for statistical analyses. Pearson correlation coefficients were calculated to examine the intercorrelations between risk factor variables. The Student 2-tailed *t* test for independent samples, ANCOVA, or Mantel-Haenszel test was used for comparisons between groups, as appropriate.

Factor analysis was used to investigate intercorrelations between baseline risk factor variables and to reduce them into a smaller set of underlying uncorrelated factors. The basic assumption of factor analysis is that the identification of these hypothetical underlying factors can be used to explain complex phenomena. A successful factor analysis represents the relations among sets of variables parsimoniously; ie, the observed correlations are explained by as few factors as possible, and the factors can be meaningfully interpreted. In practice, factor analysis consists of 3 steps: (1) extraction of the

initial factors, (2) rotation of the factors, and (3) interpretation of the factors.²⁵

Principal component analysis was used for the extraction of the initial factors. Principal component analysis transforms the original variables into a new set of uncorrelated components (initial factors) that account for the maximum proportion of the variance in the data, with each component being a linear combination of the original observed variables. The first principal component is the linear combination of variables that accounts for the largest proportion of variance in the data, and the second component is the combination that accounts for the next largest proportion, and so on. Only components with eigenvalues (the sum of the squared factor loadings, representing the variance attributable to each principal component) >1.0 were retained in the analysis. The initial factors (components) obtained in this way were then subjected to Varimax rotation, an orthogonal rotation, to facilitate their interpretation. The orthogonal rotation maintains the independence between the factors; ie, the correlation between factors remains zero. The proportion of variance explained by each factor is recalculated after rotation, because rotation reallocates the proportion of total variance explained by each factor. The interpretation of factors is based on factor loadings, equivalent to a Pearson correlation coefficient between each variable and each factor, and involves the identification of those variables for which the loading is strong on a particular factor. Each factor may then be named descriptively on the basis of variables with high loadings on it. Conventionally, variables with loadings ≥ 0.40 on a particular factor (sharing at least 15% of the variance with the factor) are used for its interpretation, although significant correlations ($P < 0.01$) between other variables and the factor, corresponding to loadings ≥ 0.30 , are also noted.²⁵ Different sets of risk factor variables were entered into factor analysis. The largest set of 10 variables included BMI, subscapular skinfold, mean blood pressure, logarithmically transformed AUC glucose, logarithmically transformed AUC insulin, cholesterol, logarithmically transformed triglycerides, and maximal O_2 uptake as continuous variables and current smoking and leisure time physical activity as dichotomous variables. Missing values for maximal O_2 uptake for 32 subjects were imputed by using the study population mean value. Of the 2 strongly correlated skinfold measurements, only subscapular skinfold was included in the factor analysis as an index of upper body obesity. Mean blood pressure was included because it combines information involving both the systolic and diastolic pressures.

Scores for the factors obtained in the factor analysis were retained and used in Cox model and Kaplan-Meier analyses for the prediction of the risk of CHD and stroke, either as continuous variables or as categorical variables dividing the distribution of factor scores into tertiles. As a result of standardization, the mean value for each factor score is 0, and the standard deviation is 1.

Ethical Considerations

The present study was approved by the Ethics Committee of the University of Kuopio, Kuopio, Finland. All study subjects had given informed consent.

Results

The number of men who had a CHD event (CHD death or nonfatal MI) during 5-, 10-, 15-, and 22-year follow-up periods was 28, 68, 105, and 164, respectively. Corresponding numbers of men who had a fatal or nonfatal stroke were 7, 21, 33, and 70. Nineteen men had both a CHD event and a stroke during the follow-up; the CHD event preceded stroke in 13 of these men, and in 6 men, stroke was the first event.

Table 1 shows the baseline characteristics of men without CHD event or stroke, men with CHD event only, men with stroke only, and men with both events during the follow-up. Compared with the reference group of men remaining free of CHD event or stroke, men with CHD event only were somewhat older; had higher blood pressure levels; were more often smokers; and had higher cholesterol and triglyceride levels, higher postload glucose and AUC glucose levels, and

higher fasting and postload insulin and AUC insulin levels. Relative to the reference group, men with stroke only were older and had higher body weight and BMI, thicker subscapular skinfold, and higher blood pressure and triglyceride levels. Their fasting, 2-hour postload and AUC insulin levels were higher than those for men in the reference group. Baseline characteristics of men with both CHD and stroke were more closely similar to those of men with stroke only than to those of men with CHD event only, but because of the small size of this subgroup, it differed significantly from the reference group only with regard to age and indices of obesity.

Table 2 (which can be accessed online at <http://atvb.ahajournals.org/cgi/content/full/20/2/538/DC1>) shows univariate intercorrelations between 10 baseline risk factor variables. BMI and subscapular skinfold were strongly correlated with each other, were somewhat less strongly correlated with AUC insulin and maximal O_2 uptake (inversely), and were also correlated with AUC glucose, triglycerides, and mean blood pressure. AUC glucose and AUC insulin were strongly intercorrelated, and both were positively correlated with triglycerides and mean blood pressure and inversely correlated with maximal O_2 uptake. As expected, cholesterol was positively correlated with triglycerides.

Of these 10 risk factor variables, the following 4 variables showed statistically significant correlations ($P < 0.01$) with age: mean blood pressure ($r = 0.27$), AUC glucose ($r = 0.17$), AUC insulin ($r = 0.11$), and maximal O_2 uptake ($r = -0.29$). Therefore, we carried out factor analyses in 2 different ways: (1) by using risk factor variable data adjusted to the median age of the study cohort with the use of the univariate regression coefficient for each variable and (2) by using the data without age adjustment. The results obtained by these 2 approaches were virtually similar; therefore, the factor analysis results reported in the present study are based on the original, actually measured risk factor data.

We carried out factor analyses with different sets of variables. Factor analysis including all the 10 variables (Table 3, which can be accessed online <http://atvb.ahajournals.org/cgi/content/full/20/2/538/DC1>) yielded 3 factors, explaining 54.4% of the total variance: Factor 1, explaining 28.7% of the variance, comprised BMI, subscapular skinfold, AUC insulin, maximal O_2 uptake, AUC glucose, mean blood pressure, and triglycerides. Because AUC insulin demonstrated loading on factor 1, it was named the insulin resistance factor. Factor 2 had strong loadings for cholesterol and triglycerides and was thus named the lipid factor. Smoking and leisure time physical activity demonstrated loadings on factor 3, with a negative loading for smoking; accordingly, we named this factor the lifestyle factor.

In our study population, cholesterol and smoking showed very little correlation with AUC insulin. Factor analysis excluding these variables produced only 2 factors (Table 3): Factor 1 was rather similar to the insulin resistance factor described above but with a stronger loading for triglycerides, and Factor 2 had a strong loading for physical activity. Maximal O_2 uptake and physical activity correlated with AUC insulin, but traditionally, they are not considered to belong to the insulin resistance cluster. Exclusion of physical activity, leaving 7 variables, as well as further exclusion of

TABLE 1. Baseline Characteristics of Men Without or With CHD Event or Stroke or Both Events During the 22-Year Follow-Up

	Without Either CHD Event or Stroke (n=755)	With CHD Event Only (n=145)	With Stroke Only (n=51)	With CHD Event and Stroke (n=19)
Age, y	46.4±7.5	49.9±7.0*	53.0±6.1*	52±6†
Height, cm	179±5	179±6	178±7	178±4
Weight, kg	83.8±10.5	83.9±11.2	87.4±12.2†	88.8±12.3‡
BMI, kg/m ²	26.1±2.9	26.3±3.0	27.4±3.2†	28.0±3.7‡
Subscapular skinfold, mm	18±7	19±7	21±7*	22±6‡
Triceps skinfold, mm	10±4	10±4	11±4	11±4
Systolic blood pressure, mm Hg	134±17	141±21†	146±22†	142±20
Diastolic blood pressure, mm Hg	84±10	88±13*	91±11†	89±11
Mean blood pressure, mm Hg	101±11	106±15*	109±14*	107±14
Hypertension, % (No.)	21.1 (159)	34.5 (50)‡	39.2 (20)	36.8 (7)
Cholesterol, mmol/L	6.19±1.13	6.66±1.25*	6.33±0.93	6.27±0.85
Triglycerides, mmol/L	1.70±0.97	1.91±1.20†	1.91±0.96‡	1.95±1.14
Fasting glucose, mmol/L	4.9±0.5	5.0±0.5	4.9±0.4	5.0±0.5
1-h glucose, mmol/L	6.4±1.9	7.1±2.2†	6.8±2.0	7.1±2.2
2-h glucose, mmol/L	4.4±1.2	4.7±1.2†	4.7±1.2	4.8±1.5
AUC glucose, mmol · L ⁻¹ · h ⁻¹	11.0±2.3	11.9±2.8†	11.6±2.4	12.0±3.0
Fasting insulin, pmol/L	43±27	48±28‡	54±24†	53±36
1-h insulin, pmol/L	353±248	442±285*	442±316	417±265
2-h insulin, pmol/L	149±150	184±151†	228±228†	208±257
AUC insulin, pmol · L ⁻¹ · h ⁻¹	449±304	558±337*	583±417‡	547±389
Current smokers, % (No.)	42.8 (323)	54.5 (79)†	45.1 (23)	63.2 (12)
Physically active in leisure time, % (No.)	34.8 (263)	33.1 (48)	25.5 (13)	36.8 (7)
Maximal O ₂ uptake, mL · min ⁻¹ · kg body wt ⁻¹	35.8±8.6	33.7±7.1	32.8±6.9	34.1±6.6

Values are mean±SD and percentages, with number of subjects in parentheses.

*P<0.001, †P<0.01, and ‡P<0.05 by t test for age and by ANCOVA or Mantel-Haenszel test for other variables, with adjustment for age.

maximal O₂ uptake, leaving 6 variables considered to belong to the core components of IRS, resulted in only 1 factor.

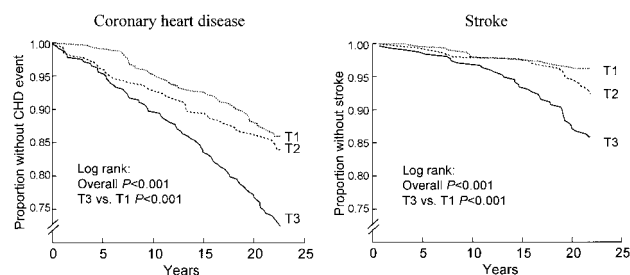
Factor scores for the 3 factors obtained from factor analysis with 10 variables were entered into Cox models, in addition to age, to assess the predictive value of the factors with regard to the risk of CHD and stroke. Table 4 shows the age-adjusted hazard ratios and their 95% CIs for the 3 factors during 5-, 10-, 15, and 22-year follow-up periods. Factor 1, insulin

resistance factor, was a statistically significant predictor of CHD risk during all follow-up periods, with some attenuation of the hazard ratio with lengthening follow-up time. With regard to the risk of stroke, the predictive value of insulin resistance factor was significant during 15 and 22 years of follow-up. Factor 2, lipid factor, was a significant predictor of CHD risk during all follow-up periods, with some attenuation of the hazard ratio with lengthening follow-up time. Lipid

TABLE 4. Age-Adjusted Hazard Ratios and 95% CIs for 3 Factors Obtained by Using 10 Variables With Regard to Risk of CHD and Stroke During Different Follow-Up Periods

	Follow-Up Time			
	5 y	10 y	15 y	22 y
CHD	n=28	n=68	n=105	n=164
Factor 1	1.56 (1.08–2.26)	1.45 (1.14–1.84)	1.39 (1.14–1.69)	1.28 (1.10–1.50)
Factor 2	1.70 (1.19–2.44)	1.66 (1.32–2.10)	1.56 (1.29–1.88)	1.47 (1.26–1.71)
Factor 3	0.94 (0.64–1.38)	0.76 (0.59–0.98)	0.81 (0.66–0.99)	0.87 (0.74–1.01)
Stroke	n=7	n=21	n=33	n=70
Factor 1	1.62 (0.79–3.35)	1.44 (0.94–2.23)	1.64 (1.16–2.31)	1.64 (1.29–2.08)
Factor 2	0.89 (0.41–1.93)	1.21 (0.78–1.86)	1.08 (0.77–1.54)	1.18 (0.93–1.49)
Factor 3	1.01 (0.46–2.22)	0.66 (0.41–1.06)	0.76 (0.52–1.10)	0.85 (0.66–1.09)

n indicates number of events. 95% CIs are in parentheses.



Kaplan-Meier curves for remaining free of CHD and stroke during 22-year follow-up by tertiles (T1 through T3) of insulin resistance factor score.

factor showed no significant relation to the risk of stroke. Factor 3, lifestyle factor, was a statistically significant predictor of reduced CHD risk during 10 and 15 years of follow-up.

The association of insulin resistance factor with the risk of CHD and stroke was further explored by calculating Kaplan-Meier survival curves for remaining free of CHD and stroke during the 22-year follow-up by tertiles of insulin resistance factor score (Figure). The proportion of men remaining free of CHD and stroke was significantly smaller in the highest insulin resistance factor tertile than in the 2 lower tertiles.

The single insulin resistance factor obtained from the factor analysis with only 6 variables predicted significantly both the risk of CHD and stroke over the 22-year follow-up in the Cox model analyses, adjusting for age, cholesterol, smoking, physical activity, and maximal O_2 uptake. The hazard ratios for the 22-year follow-up were 1.48 (95% CI 1.23 to 1.77) with regard to CHD risk and 2.02 (95% CI 1.54 to 2.66) with regard to stroke risk.

Repeating all the analyses after the exclusion of 23 men taking diuretics did not change the results (data not shown).

Because our study population included men with mild abnormalities of glucose tolerance, we also carried out factor analyses in the subset of 891 men who were strictly normoglycemic according to combined World Health Organization and American Diabetes Association criteria.^{16,23} The factors obtained were virtually similar to those obtained in the entire study population. For insulin resistance factor, obtained from factor analysis with 10 variables, the age-adjusted hazard ratios over 22 years were 1.24 (95% CI 1.05 to 1.46) with regard to CHD risk and 1.75 (95% CI 1.36 to 2.26) with regard to stroke risk.

Discussion

Our 22-year prospective study on healthy middle-aged Helsinki policemen demonstrated that insulin resistance factor, either obtained from a factor analysis including 10 potential risk factors for CHD and stroke or from a factor analysis including only 6 core risk factor variables of IRS, was a statistically significant predictor of the risk of both CHD and stroke. With regard to CHD risk, our findings accord with those recently reported from a prospective study involving elderly nondiabetic Finnish subjects; insulin resistance factor identified by factor analysis predicted the 7-year risk of CHD events in men but not in women.²⁶

One of the starting points of the present study was that the results of conventional multivariate analyses of the 22-year follow-up data from the Helsinki Policemen Study concern-

ing the association of hyperinsulinemia with the risk of CHD and stroke were different: hyperinsulinemia predicted the risk of CHD independently of other risk factors,² whereas the association between hyperinsulinemia and the risk of stroke became nonsignificant after adjustment for other risk factors, particularly indices of obesity.⁵ The aim of factor analysis is to identify common factors underlying the intercorrelations between risk factor variables. The resulting factors, after orthogonal rotation, are uncorrelated. The use of insulin resistance factor score in the prediction of CHD and stroke risk avoids the problem of overadjustment arising in conventional multivariate analyses. Thus, the findings of the present study are compatible with the view that the associations of hyperinsulinemia and the associated risk factor cluster to the risk of CHD and stroke are largely similar. Analysis of the 22-year CHD and stroke risk by tertiles of the insulin resistance factor score showed that the excess risk of both CHD and stroke was confined to the highest tertile.

Our factor analysis including 10 potential risk factors for CHD and stroke produced 3 factors. The principal factor was insulin resistance factor, with strong loadings for BMI, subscapular skinfold, composite insulin and glucose variables (AUC insulin and AUC glucose), and maximal O_2 uptake (inverse loading) and somewhat lesser loadings for mean blood pressure and triglycerides. The 2 subsidiary factors were lipid factor, with strong loadings for cholesterol and triglycerides, and lifestyle factor, with a strong positive loading for leisure time physical activity and a strong inverse loading for smoking. Factor analyses reducing the number of risk factor variables stepwise toward core components of IRS yielded only 1 factor, insulin resistance factor, which was very similar to the corresponding factor obtained with 10 risk factor variables.

Maximal O_2 uptake measured in an exercise test showed a strong inverse correlation with AUC insulin and a strong loading on the insulin resistance factor. These findings are in accordance with studies demonstrating a strong relation between maximal O_2 uptake and insulin sensitivity measured by the euglycemic clamp or the minimal model method.^{27,28} Interestingly, in factor analysis, exclusion or inclusion of maximal O_2 uptake had no substantial impact on the loadings of other variables on insulin resistance factor.

Several other studies have applied factor analysis to examine risk factor clustering in IRS in nondiabetic subjects.^{26,29–34} These studies have included men and women of different ages and from different ethnic groups. Some studies have used only risk factor variables proposed to be components of IRS,^{29–31,33,34} whereas other studies,^{26,32} like the present study, have also used a wider set of risk factor variables. Despite these differences, in all studies except one,³⁰ the principal factor explaining the largest amount of the total variance in the data has been a factor with strong loadings for obesity and insulin variables. With 2 exceptions,^{31,34} glucose variables have also shown significant loadings on this principal factor. With regard to the 2 lipid variables (triglycerides and HDL cholesterol) associated with insulin, the results have not been uniform: both triglycerides and HDL cholesterol showed loadings on the principal factor in 2 studies^{26,31}; triglycerides but not HDL cholesterol showed loadings on the principal factor in another study³²; and these lipid variables failed to load on the principal factor

in other studies.^{29,30,33,34} Although elevated blood pressure belongs to the original concept of IRS, none of the previous studies found a significant loading for blood pressure on the principal factor.

Previous studies examining the putative risk factors variables of IRS have resulted in the identification of 2 to 4 separate factors.^{29–34} The factors identified, in addition to the principal factor, have been named according to the variables characterizing them as follows: insulin/glucose (impaired glucose tolerance) factor, lipid (dyslipidemia) factor, and blood pressure factor. In 3 of the 4 studies producing a separate insulin/glucose or impaired glucose tolerance factor, both fasting and postload glucose and insulin values were included in the factor analysis.^{29–31} When we performed factor analyses of our baseline risk factor data by entering fasting and 2-hour postload glucose and insulin variables instead of AUC glucose and AUC insulin, fasting and 2-hour insulin remained loaded on the principal factor, but a separate insulin/glucose factor emerged, characterized by strongest loadings for 2-hour glucose and insulin and somewhat lesser loadings for fasting glucose and insulin. In all the 4 studies producing a separate blood pressure factor, highly intercorrelated systolic and diastolic blood pressure values were both entered in factor analyses.^{30,31,33,34} In our factor analyses, we used a single blood pressure variable, mean blood pressure, which combines information from both systolic and diastolic blood pressure, and found that this blood pressure variable showed loading on the principal factor. We also carried out factor analyses entering both systolic and diastolic blood pressure, and these analyses produced a separate blood pressure factor. The results of our analyses with different sets of glucose, insulin, and blood pressure variables emphasize that one of the limitations of factor analysis is its sensitivity to the variables included.

With one exception,³¹ previous factor analyses including putative IRS risk factor variables produced a separate lipid factor with strong loadings for triglycerides and HDL cholesterol. In the present study, triglycerides showed a moderately strong loading on the single factor that was obtained by using the 6 putative variables of IRS. Our baseline study protocol did not include HDL cholesterol measurement; therefore, the possible contribution of HDL cholesterol to IRS in our study population remains unknown.

Because our study population included only men, our findings cannot be generalized to women. In the only other prospective study that used factor analysis, the study on elderly nondiabetic Finnish subjects,²⁶ insulin resistance factor predicted CHD risk in men but not in women. Further prospective studies that use factor analysis and in which both sexes are included will be of interest, because studies of the relation between hyperinsulinemia and the risk of atherosclerotic disease have suggested that hyperinsulinemia may be a less important risk factor in women than in men.²

The identification of several underlying factors in previous factor analyses of IRS has been interpreted to mean that the etiology of IRS may be heterogeneous; ie, insulin resistance, reflected by hyperinsulinemia, alone may not underlie all features of the syndrome.^{29,31} However, the unifying feature of the results of all factor analyses of IRS, including ours, is the characterization of the principal factor by obesity, its central distribution, and hyperinsulinemia, implying that

these characteristics belong to the core of the syndrome. In contrast to other studies, our factor analysis including proposed components of IRS yielded only 1 factor; thus, our results would even be compatible with the possibility that there would be a single underlying cause for this cluster of risk factors. This underlying cause could be insulin resistance itself.

Insulin resistance and the associated cluster of risk factors have been shown to predict the development of non-insulin-dependent diabetes³⁵; therefore, it could be argued that impaired glucose tolerance would be the mechanism explaining the association we found between the clustering of IRS and the risk of CHD and stroke. Our findings, however, do not support this hypothesis; the results of factor analyses in strictly normoglycemic men were similar to those obtained in the entire study population, and the predictive value of the factors with regard to CHD and stroke remained essentially unchanged.

Our finding that risk factor clustering of IRS predicts both CHD and stroke is compatible with at least 2 different interpretations. First, the increased risk of these 2 manifestations of atherosclerotic disease in subjects with high insulin resistance factor scores may reflect a combined effect of different risk factors forming this cluster. Second, it is possible that insulin resistance itself or some unidentified factor leading to insulin resistance and hyperinsulinemia may enhance the development of atherosclerosis. Indeed, there is cross-sectional evidence that insulin resistance measured by direct methods is associated with ultrasonographically assessed thickening of arterial walls,^{36–39} angiographically documented coronary atherosclerosis,⁴⁰ or a composite score for systemic atherosclerosis.⁴¹ In those studies, the association between insulin resistance and atherosclerosis has appeared to be, at least in part, independent of risk factors belonging to IRS. Furthermore, a small prospective study in healthy nonobese subjects has demonstrated a marked increase of clinical cardiovascular disease events in subjects belonging to the most insulin-resistant tertile.⁴²

In conclusion, factor analyses of the baseline data of healthy middle-aged Helsinki policemen resulted in the identification of a distinct factor characterized by core components of IRS. This factor predicted the risk of both CHD and stroke during the 22-year follow-up.

Acknowledgments

This study was supported by grants from the Academy of Finland, the Finnish Heart Research Foundation, and the University of Kuopio.

References

1. Ruige JB, Assendelft WJJ, Dekker JM, Kostense PJ, Heine RJ, Bouter LM. Insulin and risk of cardiovascular disease: a meta-analysis. *Circulation*. 1998;97:996–1001.
2. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia predicts coronary heart disease risk in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Circulation*. 1998;98:398–404.
3. Kuusisto J, Mykkänen L, Pyörälä K, Laakso M. Non-insulin-dependent diabetes and its metabolic control are important predictors of stroke in elderly subjects. *Stroke*. 1994;25:1157–1164.
4. Burchfiel CM, Rodriguez BL, Abbott RD, Sharp DS, Curb JD. Insulin levels and risk of stroke. *Circulation*. 1998;97:824. Abstract.

5. Pyörälä M, Miettinen H, Laakso M, Pyörälä K. Hyperinsulinemia and the risk of stroke in healthy middle-aged men: the 22-year follow-up results of the Helsinki Policemen Study. *Stroke*. 1998;29:1860–1866.
6. Folsom AR, Rasmussen ML, Chambles LE, Howard G, Cooper LS, Schmidt MI, Heiss G, for the Atherosclerosis Risk in Communities (ARIC) Study Investigators. Prospective association of fasting insulin, body fat distribution, and diabetes with risk of ischemic stroke. *Diabetes Care*. 1999;22:1077–1083.
7. Stout RW. Insulin and atheroma: 20-yr perspective. *Diabetes Care*. 1990;13:631–654.
8. Laakso M. Insulin resistance and coronary heart disease. *Curr Opin Lipidol*. 1996;7:217–226.
9. Reaven GM. Role of insulin resistance in human disease. *Diabetes*. 1988;37:1595–1607.
10. Juhani-Vague I, Alessi MC. PAI-1, obesity, insulin resistance and risk of cardiovascular events. *Thromb Haemost*. 1997;78:656–660.
11. Imperatore G, Riccardi G, Iovine C, Rivellese AA, Vaccaro O. Plasma fibrinogen: a new factor of the metabolic syndrome: a population based study. *Diabetes Care*. 1998;21:649–654.
12. Kario K, Nago N, Kayaba K, Saegusa T, Matsuo H, Goto T, Tsutsumi A, Ishikawa S, Kuroda T, Miyamoto T, Matsuo T, Shimada K, on the behalf of the Jichi Medical School Cohort Study Group. Characteristics of the insulin resistance syndrome in a Japanese population: the Jichi Medical School Cohort Study. *Arterioscler Thromb Vasc Biol*. 1996;16:269–274.
13. Schmidt MI, Watson RL, Duncan BB, Metcalf P, Brancati FL, Sharrett AR, Davis CE, Heiss G. Clustering of dyslipidemia, hyperuricemia, diabetes, and hypertension and its association with fasting insulin and central and overall obesity in a general population. *Metabolism*. 1996;45:699–706.
14. Yarnell JW, Patterson CC, Bainton D, Sweetnam PM. Is metabolic syndrome a discrete entity in the general population?: evidence from the Caerphilly and Speedwell population studies. *Heart*. 1998;79:248–252.
15. Liese AD, Mayer-Davis EJ, Haffner SM. Development of the multiple metabolic syndrome: an epidemiologic perspective. *Epidemiol Rev*. 1998;20:157–172.
16. Diabetes Mellitus. *Report of a WHO Study Group*. Geneva, Switzerland: World Health Organization; 1985. Technical Report Series No. 727.
17. Saltin B, Grimby G. Physiological analysis of middle-aged and old former athletes. *Circulation*. 1968;38:1104–1115.
18. Åstrand PO, Ryhming I. A nomogram for calculation of aerobic capacity (physical fitness) from pulse rate during submaximal work. *J Appl Physiol*. 1954;7:218–221.
19. Hyvärinen A, Nikkilä E. Specific determination of blood glucose with *o*-toluidine. *Clin Chim Acta*. 1962;7:140–143.
20. Herbert V, Lau KS, Gotlieb CW, Bleicher SJ. Coated charcoal immunoassay of insulin. *J Clin Endocrinol*. 1965;25:1375–1384.
21. Abell LL, Levy BB, Brodie BB, Kendall FE. A simplified method for the estimation of total cholesterol in serum and demonstration of its specificity. *J Biol Chem*. 1952;195:357–366.
22. Björkstén F. Determination of plasma and serum triglycerides with a fully automated method. *Clin Chim Acta*. 1972;40:143–152.
23. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care*. 1997;20:1183–1197.
24. Walker AE, Robins M, Weinfeld FD. The national survey of stroke: clinical findings. *Stroke*. 1981;12(suppl 1, pt 2):I-13–I-44.
25. Stevens J. Principal components. In: Stevens J, ed. *Applied Multivariate Statistics for the Social Sciences*. Hillsdale, NJ: Lawrence Erlbaum Associates; 1986:337–350.
26. Lempiäinen P, Mykkänen L, Pyörälä K, Laakso M, Kuusisto J. Insulin resistance syndrome predicts coronary heart disease events in elderly nondiabetic men. *Circulation*. 1999;100:123–128.
27. Yki-Järvinen H, Koivisto V. Effects of body composition on insulin sensitivity. *Diabetes*. 1983;32:965–969.
28. Clausen JO, Borch-Johnsen K, Ibsen H, Bergman RN, Hougaard P, Winther K. Insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of 380 young healthy Caucasians: analysis of the impact of gender, body fat, physical fitness, and life-style factors. *J Clin Invest*. 1996;98:1195–1209.
29. Edwards KL, Austin MA, Newman B, Mayer E, Krauss RM, Selby JV. Multivariate analysis of the insulin resistance syndrome in women. *Arterioscler Thromb*. 1994;14:1940–1945.
30. Wingard D, Von Muhlen D, Barrett-Connor E, Kritiz-Silverstein D. Factor analysis of proposed components of the insulin resistance syndrome. *Diabetes*. 1996;45(suppl 2):137A. Abstract.
31. Meigs JB, D'Agostino RB, Wilson PWF, Cupples A, Nathan DM, Singer DE. Risk variable clustering in the insulin resistance syndrome: the Framingham Offspring Study. *Diabetes*. 1997;46:1594–1600.
32. Leyva F, Godsland IF, Worthington M, Walton C, Stevenson JC. Factors of the metabolic syndrome: baseline interrelationships in the first follow-up cohort of the HDDRISC Study (HDDRISC-1). *Arterioscler Thromb Vasc Biol*. 1998;18:208–214.
33. Gray RS, Fabsitz RR, Cowan LD, Lee ET, Howard BV, Savage PJ. Risk factor clustering in the insulin resistance syndrome: the Strong Heart Study. *Am J Epidemiol*. 1998;148:869–878.
34. Edwards KL, Burchfiel CM, Sharp DS, Curb JD, Rodriguez BL, Fujimoto WY, LaCroix AZ, Vitiello MV, Austin MA. Factors of the insulin resistance syndrome in nondiabetic and diabetic elderly Japanese-American men. *Am J Epidemiol*. 1998;147:441–447.
35. Kekäläinen P, Sarlund H, Pyörälä K, Laakso M. Hyperinsulinemia cluster predicts the development of type 2 diabetes independently of family history of diabetes. *Diabetes Care*. 1999;22:86–92.
36. Laakso M, Sarlund H, Salonen R, Pyörälä K, Salonen JT, Karhapää P. Asymptomatic atherosclerosis and insulin resistance. *Arterioscler Thromb*. 1991;11:1068–1076.
37. Agewall S, Fagerberg B, Attwall S, Wendelhag I, Urbanovicus V, Wikstrand A. Carotid artery wall thickness is associated with insulin-mediated glucose disposal in men at high and low coronary risk. *Stroke*. 1995;26:956–960.
38. Howard G, O'Leary DH, Zaccaro D, Haffner S, Rewers M, Hamman R, Selby JV, Saad MF, Savage P, Bergman R, for the IRAS Investigators. Insulin sensitivity and atherosclerosis. *Circulation*. 1996;93:1809–1817.
39. Suzuki M, Shinozaki K, Kanazawa A, Hara Y, Hattori Y, Tsushima M, Harano Y. Insulin resistance as an independent risk factor for carotid wall thickening. *Hypertension*. 1996;28:593–598.
40. Bressler P, Bailey SR, Matsuda M, DeFronzo RA. Insulin resistance and coronary artery disease. *Diabetologia*. 1996;39:1345–1350.
41. Howard G, Hamman RF, Rewers M, Hiatt W, Haffner S, for the IRAS Investigators. Insulin sensitivity and systemic atherosclerosis. *Circulation*. 1999;99:1115. Abstract.
42. Yip J, Facchini FS, Reaven GM. Resistance to insulin-mediated glucose disposal as a predictor of cardiovascular disease. *J Clin Endocrinol Metab*. 1998;83:2773–2776.

Arteriosclerosis, Thrombosis, and Vascular Biology



JOURNAL OF THE AMERICAN HEART ASSOCIATION

Insulin Resistance Syndrome Predicts the Risk of Coronary Heart Disease and Stroke in Healthy Middle-Aged Men: The 22-Year Follow-Up Results of the Helsinki Policemen Study

Marja Pyörälä, Heikki Miettinen, Pirjo Halonen, Markku Laakso and Kalevi Pyörälä

Arterioscler Thromb Vasc Biol. 2000;20:538-544

doi: 10.1161/01.ATV.20.2.538

Arteriosclerosis, Thrombosis, and Vascular Biology is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Copyright © 2000 American Heart Association, Inc. All rights reserved.

Print ISSN: 1079-5642. Online ISSN: 1524-4636

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://atvb.ahajournals.org/content/20/2/538>

Data Supplement (unedited) at:

<http://atvb.ahajournals.org/content/suppl/2000/01/12/20.2.538.DC1>

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in *Arteriosclerosis, Thrombosis, and Vascular Biology* can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the [Permissions and Rights Question and Answer](#) document.

Reprints: Information about reprints can be found online at:

<http://www.lww.com/reprints>

Subscriptions: Information about subscribing to *Arteriosclerosis, Thrombosis, and Vascular Biology* is online at:

<http://atvb.ahajournals.org/subscriptions/>