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

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Abstract

Background. **Insulin sensitivity and insulin secretion are traits that are both genetically and environmentally determined.**

Aim. **The aim of this study was to describe the distribution of the insulin sensitivity index (Si), the acute insulin response, and glucose effectiveness (Sg) in young healthy Caucasians and to estimate the relative impact of anthropometric and environmental determinants on these variables.**

Methods. **The material included 380 unrelated Caucasian subjects (18–32 yr) with measurement of Si, Sg and insulin secretion during a combined intravenous glucose (0.3 grams/kg body weight) and tolbutamide (3 mg/kg body weight) tolerance test.**

Results. **The distributions of Si and acute insulin response were skewed to the right, whereas the distribution of Sg was Gaussian distributed. Sg was 15% higher in women compared with men ($P < 0.001$). Waist circumference, body mass index, maximal aerobic capacity, and women's use of oral contraceptives were the most important determinants of Si. Approximately one-third of the variation of Si could be explained by these factors. Compared with individuals in the upper four-fifths of the distribution of Si, subjects with Si in the lowest fifth had higher waist circumference, higher blood pressure, lower VO_2max, and lower glucose tolerance and fasting dyslipidemia and dysfibrinolysis. Only 10% of the variation in acute insulin response could be explained by measured determinants.**

Conclusion. **Estimates of body fat, maximal aerobic capacity, and women's use of oral contraceptives explain about one-third of the variation in Si in a population-based sample of young healthy Caucasians. (*J. Clin. Invest.* 1996. 98:1195–1209.) Key words: insulin sensitivity • insulin secretion • glucose effectiveness • body fat • life-style factors**

Introduction

Diabetes and hypertension are common clinical disorders which particularly affect middle-aged and elderly individuals. Both disorders confer an increased risk of premature coronary atherosclerosis (1, 2). The pathogenic mechanisms leading to disease are assumed to begin decades before overt disease is present and several pieces of evidence suggest that impaired insulin sensitivity may be one such factor (1, 3). For example, in prospective studies low insulin sensitivity has been found to be a risk factor for the subsequent development of non–insulin-dependent diabetes mellitus (NIDDM)[1] (4, 5). The clustering in some individuals of NIDDM or impaired glucose tolerance with obesity, hypertension, dyslipidemia, and dysfibrinolysis, all states which separately or in combination are characterized by reduced whole body insulin sensitivity, has been designated the insulin resistance syndrome (1).

Low insulin sensitivity is thought to have a multifactorial basis (6). First degree relatives of subjects with NIDDM or hypertension are in some ethnic groups reported to be insulin resistant (7, 8) pointing to a genetic influence. Life-style factors causing impaired insulin sensitivity like excessive intake of saturated fatty acids, cigarette smoking, or lack of physical activity may alter the degree of and timing of expression of associated disorders like subsets of NIDDM, hypertension, and premature ischemic cardiovascular disorders (9, 10). Each disorder in the insulin resistance syndrome also increases in prevalence as the population ages. In subjects having NIDDM, premature ischemic cardiovascular disorders, or morbid obesity, the level of risk factors, for example maximal aerobic capacity (VO_2max), is also influenced by the disease state. Therefore, studies examining the impact of various factors modulating insulin sensitivity might ideally be undertaken in young healthy subjects.

The interindividual level of insulin sensitivity in the general population varies widely (11, 12). However, insulin sensitivity and environmental factors influencing insulin sensitivity have not been systematically evaluated in any population survey of young adult subjects. Therefore, the objectives of the present investigation were: (*a*) to describe the distribution of the insulin sensitivity index, acute insulin response, and glucose effectiveness in a population-based sample of young healthy Caucasians; (*b*) to identify the potential modulators with high impact

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1. *Abbreviations used in this paper:* AUC, area under the curve; BMI, body mass index; IVGTT, intravenous glucose tolerance test; NIDDM, non–insulin-dependent diabetes mellitus; PAI-1 activity, plasminogen activator inhibitor 1 activity; t-PA antigen, tissue plasminogen activator antigen; VO_2max, maximal aerobic capacity.

on the insulin sensitivity index as well as acute insulin response and glucose effectiveness; and (*c*) to offer an operational definition of insulin resistance, which may be used in prospective studies of the role of a low insulin sensitivity index in the pathogenesis of artherosclerotic disorders and diabetes.

Methods

Subjects. The study participants were randomly recruited from a population of young individuals aged 18–32 yr, who in 1979/80 and again in 1984/85 as children participated in blood pressure surveys in a representative and specified part of Copenhagen city (13, 14). The present examination took place in 1992 and 1993. All subjects from the initial sample except one could be traced in the Danish Central Population Register (n = 1,389). Subjects with insulin-dependent diabetes mellitus, pregnant women, and subjects now living in the western part of Denmark or abroad were excluded from the study (n = 89). A random sample of unrelated subjects in the initial sample was invited to participate in the present examination (n = 684). The participation rate was 56% and altogether 380 nonrelated individuals were included in the study (Table I). As estimated from questionnaires, there was no important difference in anthropometric measures or life-style factors between participants and nonparticipants. All study participants who were Danish Caucasians by self-identification were asked to refrain from physical exercise for 24 h before the investigation. Two lean (body mass index [BMI] < 25 kg/m^2) subjects were treated with inhalation of β-2 adrenergic agonists for their asthma and 50 females were on oral contraceptives. No study participants were taking any other drugs on a regular basis and all were asked not to take aspirin, paracetamol, or nonsteroid antiinflammatory drugs on the day of examination.

Parental history of hypertension or NIDDM was considered present if the subjects reported that one or both of the parents were hypertensives or had NIDDM, respectively. Parental history of premature ischemic cardiovascular disease was present if either of the parents was reported to have experienced a myocardial infarct before age 60 yr. Parental history of obesity was present if the subjects reported that either of the parents at age 40 yr or above had an estimated BMI > 30 kg/m^2. The study was approved by the Ethical Committee of Copenhagen.

Anthropometric measurements, physical fitness, blood pressure, smoking, alcohol, and food intake. Waist circumference was measured midway between the lower rib margin and the iliac crest in the horizontal plane. Hip circumference was measured at the point yielding the maximum circumference over the buttocks. These parameters were measured with the individuals in an upright position and taken to the nearest 0.5 cm. Height was measured to the nearest 0.5 cm with the subjects standing without shoes, the heels together, and the head in the horizontal plane. Body weight was measured to the nearest 0.1 kg with subjects wearing only light clothes. BMI was calculated as weight divided by squared height (kg/m^2). Fat mass was measured with an impedance technique (15). VO_2max was measured by means of a submaximal bicycle exercise test as described by Åstrand (16).

Blood pressure was determined by means of a London School of Hygiene sphygmomanometer (17), making the readings unbiased, as the scale is not visible during deflation of the cuff. Recording of blood pressure took place between noon and 2:00 p.m., when the subjects had participated in the study for a minimum of 4 h and were in a relaxed state. All blood pressure measurements were done in the supine position by the same nurse. Systolic and diastolic blood pressure measurements (read at the disappearance of fifth Korotkoff sound) were recorded. The standard blood pressure cuff was 12 × 35 cm. In subjects having an upper arm circumference > 35 cm, a cuff measuring 15 × 43 cm was used, and in subjects having an upper arm circumference < 20 cm, a cuff measuring 9 × 25 cm was used.

The total daily alcohol consumption was calculated from questionnaire items about average alcohol consumption. Intakes of beer, wine, and spirits were reported separately. Most of the alcohol consumed was in beer. One drink corresponds to 12 grams of ethanol. Current tobacco consumption was calculated from information about the number of cigarettes, cheroots, or cigars or number of grams of pipe tobacco smoked per day. The total use of tobacco was estimated: one cigarette equaled 1 gram, one cheroot equaled 3 grams, and one cigar equaled 4 grams of tobacco. Total food intake was recorded over 4 d and daily intake of saturated fat was calculated from dietary tables (18). 336 subjects (88%) completed their diet recordings.

Biochemical studies. After 12-h overnight fasting, venous blood samples were drawn in the morning for analysis of plasma concentration of glucose and serum levels of triglyceride, total cholesterol, and high-density lipoprotein cholesterol (HDL) (Boehringer Mannheim GmbH Diagnostica, Mannheim, Germany). Serum level of low density lipoprotein cholesterol (LDL) was calculated as serum total cholesterol − serum HDL cholesterol − serum triglyceride/2.2 (19). The concentration of insulin was determined by ELISA with a narrow specificity excluding des(31, 32)- and intact proinsulin, applying the Dako insulin kit with overnight incubation (code No. K6219; Dako Diagnostics Ltd., Ely, United Kingdom) (20). The concentration of C-peptide was determined by RIA (21) using the polyclonal antibody M 1230 (22, 23). The seldom found proinsulin conversion intermedi-

Table I. Clinical Characteristics and Life-Style Profile of Men and Women in a Population-based Sample of 380 Healthy Danish Caucasians

	Quantity	Men	Women	Significance level: men vs. women
n		186	194	
Age	yr	25.5 (3.5)	25.0 (3.5)	
BMI	kg/m^2	24.2 (3.5)	23.0 (3.9)	$P < 0.001$
Waist-hip ratio		0.86 (0.05)	0.77 (0.06)	$P < 0.001$
Waist circumference	cm	82.6 (9.8)	73.0 (9.5)	$P < 0.001$
Body fat	%	20 (6)	26 (7)	$P < 0.001$
VO_2max	ml O_2/(kg × min)	44 (9)	38 (8)	$P < 0.001$
Tobacco consumption	grams/d	5.4 (8.0)	6.4 (8.1)	$P = 0.18$
Proportions of smokers		0.42	0.5	$P = 0.14$
Alcohol consumption	grams/d	15 (15)	6 (7)	$P < 0.001$
Proportions of abstainers		0.07	0.25	$P < 0.001$
Saturated fat intake	energy percent	15 (4) $_{n = 153}$	15 (3) $_{n = 183}$	$P = 0.25$

Mean (standard deviation).

ate form des(64, 65)-proinsulin cross-reacts efficiently (126%), whereas the predominant forms of proinsulin-like immunoreactivity des(31, 32)- and intact proinsulin react 13–15% relative to C-peptide (100%).

Tissue plasminogen activator (t-PA) antigen was measured in plasma with ELISA (product No 101101; Biopool AB, Umeå, Sweden) as devised by Ranby et al. (24). The activity of the fast acting inhibitor against t-PA, normally referred to as plasma PAI-1 activity, was measured by adding a known amount of t-PA to diluted nonacidified plasma and determining t-PA activity as described previously (25) using Biopool reagents spectrolyse/PL, product No. 101102. In this system, one arbitrary unit of PAI-1 activity is the amount inhibiting 1 U of t-PA. Plasma PAI-1 activity is expressed in milliunits per liter.

Measurements of insulin sensitivity index, glucose effectiveness, and acute insulin response and C-peptide response. Each subject underwent an intravenous glucose tolerance test (IVGTT) after the overnight fasting period of 12 h. After insertion of a cannula into the antecubital vein each subject rested in a quiet room for at least 20 min. Baseline values of serum insulin, serum C-peptide, and plasma glucose were taken in duplicate with 5-min intervals. Glucose was injected intravenously in the contralateral antecubital vein over a period of 60 s (0.3 grams/kg body weight of 50% glucose). At 20 min after the end of the glucose injection, a bolus of 3 mg tolbutamide/kg body weight (Rastinon, Hoechst, Germany) was injected during 5 s to elicit a secondary pancreatic β-cell response. Venous blood was sampled at 2, 4, 8, 19, 22, 30, 40, 50, 70, 90, and 180 min, timed from the end of the glucose injection for measurements of plasma glucose, serum insulin and serum C-peptide. All the IVGTTs were done by the same investigator. Insulin sensitivity index and glucose effectiveness were calculated using the Bergman MINIMOD computer program developed specifically for the combined intravenous glucose and tolbutamide tolerance test (26–30). The insulin sensitivity index represents the increase in net fractional glucose clearance rate per unit change in serum insulin concentration after the intravenous glucose load. Glucose effectiveness represents the net fractional glucose clearance rate due to the increase in glucose itself without any increase in circulating insulin concentration above baseline. Furthermore, glucose effectiveness includes a lesser contribution mediated by the preexisting basal insulin status. Importantly, both the insulin sensitivity index and glucose effectiveness involve an inhibition of hepatic glucose output (26, 27). Acute phase insulin and C-peptide responses (0–8 min) were calculated by means of the trapezoidal rule as the incremental values (areas under the curve when expressed above basal values). Glucose disappearance constant (K_g) was calculated as the slope of the line relating the natural logarithm of the glucose concentration to the time between 8 and 19 min after the glucose bolus administered as a part of the IVGTT (31). The disposition index was calculated as the product of insulin sensitivity index and first phase insulin responses (0–8 min) (32, 33).

Validation of the IVGTT with reduced sampling for measurements of insulin sensitivity index and glucose effectiveness. The tolbutamide-boosted protocol for frequently sampled IVGTT with minimal model

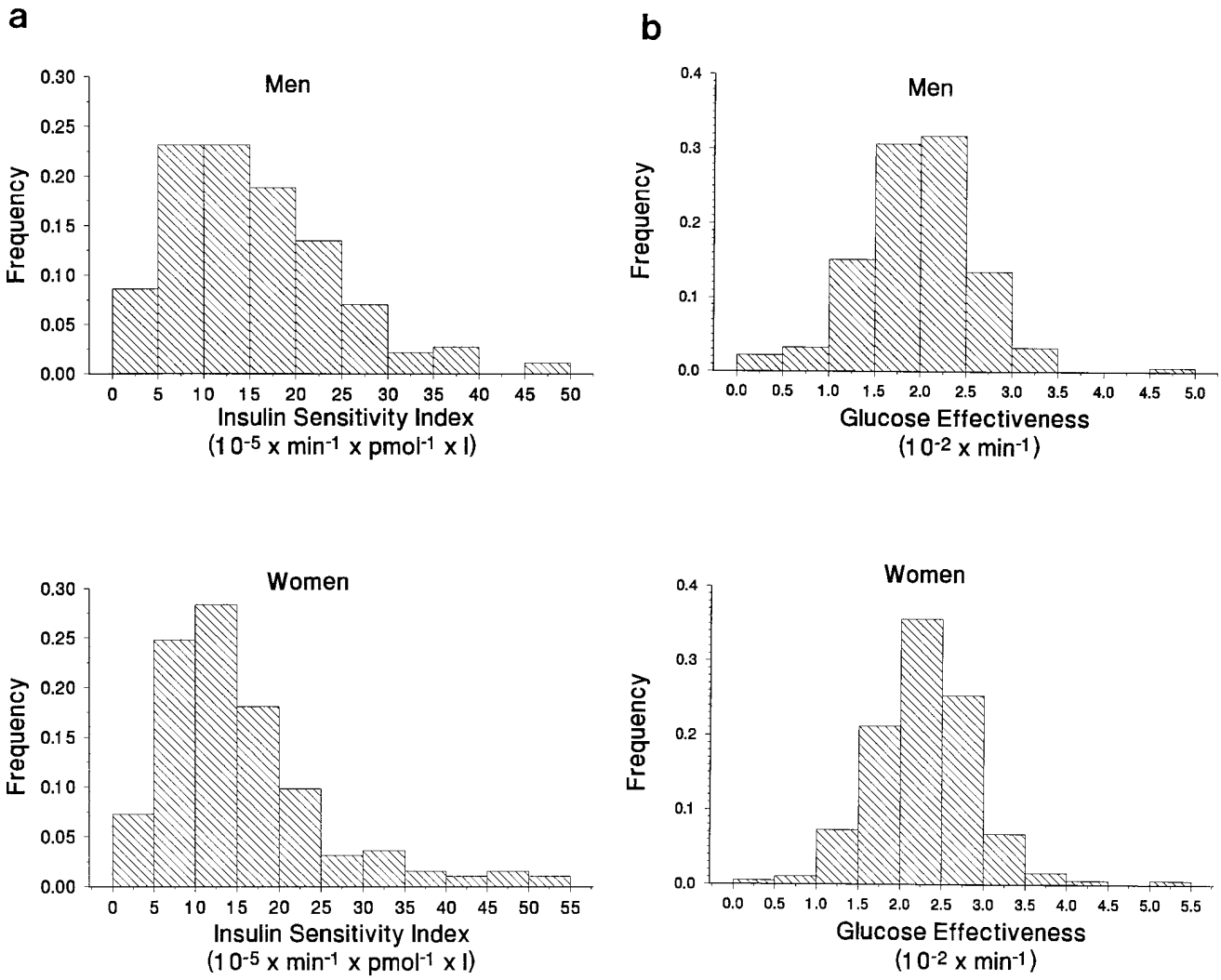

Figure 1. The distribution of the insulin sensitivity index (*a*), glucose effectiveness (*b*), and the acute phase insulin response (*c*).

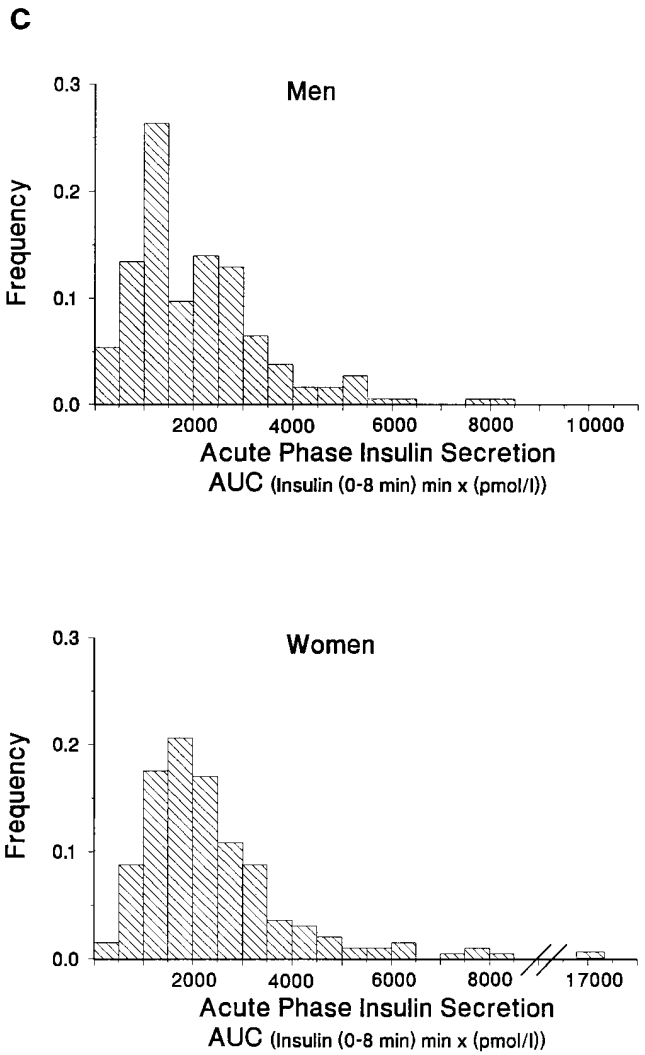

Figure 1 continued.

analysis has been validated previously against the euglycemic, hyperinsulinemic clamp in normal subjects (34, 35). To validate the reduced sampling protocol of the tolbutamide-modified IVGTT, 18 of the study participants volunteered for a study to compare the frequently sampled protocol (33 samples) with the present protocol (12 samples). Highly significant correlations considering insulin sensitivity index ($r = 0.98$, 95% confidence interval 0.95–0.99) and considering glucose effectiveness ($r = 0.93$, 95% confidence interval 0.82–0.97) were found between the IVGTT method using 33 samples and the present method using 12 samples. The difference between the two IVGTT methods was plotted against the average of the two methods for each participant to give an estimate of the agreement between the two methods (Bland-Altman plot) (36). Limits of agreement were calculated as mean difference $\pm 1.96 \times$ SD of the difference. Limits of agreement between the method using 33 samples and the method using 12 samples were from -3.2 to 2.1×10^{-5} (min $\times$ pmol/liter)$^{-1}$ considering insulin sensitivity index and from -0.7 to $0.6 \times 10^{-2} \times$ min^{-1} considering glucose effectiveness. Thus, the 12-sample protocol may estimate insulin sensitivity index 3.2×10^{-5} (min $\times$ pmol/liter)$^{-1}$ below or 2.1×10^{-5} (min $\times$ pmol/liter)$^{-1}$ above the values obtained with the 33-sample schedule. As the limits of agreement are narrower than the variation of both insulin sensitivity index (mean value $= 15.3 \times 10^{-5}$ (min $\times$ pmol/liter)$^{-1}$ and SD $= 9.3$) and glucose effectiveness (mean value $= 2.1 \times 10^{-2} \times$ min^{-1} and SD $= 0.6$), the reduced sampling schedule during the IVGTT as applied here provides an acceptable estimate of both the insulin sensitivity index and the glucose effectiveness in population studies. Similar results have been obtained in a recent comparative study (27).

Statistics. Differences in continuous variables between groups of subjects were tested with Student's *t* test when the distributions of the variables or the logarithmic values of the variables were normal; otherwise the Mann-Whitney test was used. Normality was evaluated by normal distribution plots and histograms for the variable, both untransformed and after logarithm and square root transformations. The relationship between insulin sensitivity index and acute phase insulin response$_{0\text{–}8\ \text{min}}$ was evaluated by the products of the variables, and by various linear regression models, using transformations of the original variables. A parametric oriented measure of normality is skewness, defined at the third central moment divided by the standard deviation cubed. This definition makes it independent of changes in mean and scale. A transformation by the logarithm makes the right tail lower. A square root transformation is intermediate. In fact, it can be mathematically derived to be exactly in the middle of the two others.

An insulin resistance syndrome score was constructed. Factors known or suspected to be associated with a low insulin sensitivity index, i.e., to be part of the insulin resistance syndrome, were included. The resistance score of a given subject was augmented by 1 for each of the following variables if they were above the gender-specific medians: fasting plasma PAI-1 activity, systolic blood pressure, and BMI, and similarly, if one of the following variables was below the gender-specific medians: glucose disappearance constant and fasting serum HDL-cholesterol. An insulin resistance score from 0 to 1 was considered "low," 2 to 3 "intermediate," and 4 to 5 "high."

The insulin sensitivity index was for some analyses stratified into gender-specific fifths to facilitate data description. Multiple linear regression analysis was used to define the relative importance of different determinants of the insulin sensitivity index. Gender, age, BMI, waist circumference, VO_2max, use of tobacco, use of alcohol, and women's use of oral contraceptives were all included in the multiple regression analysis. To evaluate whether waist circumference or waist-hip ratio was the more important determinant of the insulin sensitivity index, a multiple regression analysis with waist-hip ratio instead of waist circumference was done. Interaction variables between gender and age, BMI, waist-hip circumference, VO_2max, use of tobacco, and use of alcohol were constructed and included in a multiple regression analysis. The interaction variables without significant effect were excluded. Multiple regression analysis was also used when comparing the levels of the measured parameters in subjects being in the lowest gender-specific fifth of the insulin sensitivity index compared with all other individuals and controlling for BMI. Subjects with partially missing values (two subjects) were excluded from the multiple regression analyses. Statistical Package of Social Science (SPSS) for Windows, version 6.01, was used for statistical analyses. A P value < 0.05 (two-tailed) was considered significant.

Results

The distribution of insulin sensitivity index, acute phase insulin response, and glucose effectiveness. In Fig. 1, *a–c*, the distributions of insulin sensitivity index, glucose effectiveness, and acute phase insulin responses are shown for men and women. The distributions of insulin sensitivity index and acute phase insulin response were skewed to the right for both genders. In Table II, mean value, standard deviation, and skewness of insulin sensitivity index, acute insulin response, and glucose effectiveness are given. The results suggest that for the insulin sensitivity index and for acute insulin response the square root gives the best fit to a Gaussian distribution, and that for glucose effectiveness the untransformed data are the best fit. The histograms of the insulin sensitivity index, glucose effectiveness, and acute phase in-

Table II. Mean and Standard Deviation, and Skewness for the Insulin Sensitivity Index, and Acute Insulin Response and Glucose Effectiveness in a Population-based Sample of 380 Healthy Danish Caucasians

Variable	Mean	SD	Skewness
Insulin sensitivity index ($10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$)	15.21	9.26	1.31
Insulin sensitivity index, square root	3.73	1.14	0.23
Insulin sensitivity index, log	2.53	0.65	−0.64
Acute phase serum insulin response ($AUC_{\text{Insulin (0–8 min) (min} \times \text{pmol/liter)}}$)	2252	1586	3.09
Acute phase serum insulin response, square root	45	15	0.8
Acute phase serum insulin response, log	7.51	0.73	−1.54
Glucose effectiveness ($10^{-2} \times \text{min}^{-1}$)	2.14	0.64	0.27
Glucose effectiveness, square root	1.44	0.24	−1.07
Glucose effectiveness, log	0.71	0.36	−2.06

sulin response give no indication of there being several modes of distribution.

The median of insulin sensitivity index was $13.1 \times 10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$ and the 10^{th}–90^{th} percentile was $5.7–27.8 \times 10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$. The median of glucose effectiveness was $2.2 \times 10^{-2} \times \text{min}^{-1}$ and the 10^{th}–90^{th} percentiles were $1.4–2.9 \times 10^{-2} \times \text{min}^{-1}$. The median of acute insulin response was 1,962 area under the curve $(AUC)_{\text{Insulin (0–8 min)}}$ (min × pmol/liter) and the 10^{th}–90^{th} percentiles were 889–3,987 $AUC_{\text{Insulin (0–8 min)}}$ (min × pmol/liter).

Gender-related differences of insulin sensitivity index, acute phase insulin response, and glucose effectiveness. The insulin sensitivity index did not differ between men and women. Fasting plasma glucose concentration was 7% lower ($P < 0.001$) in women compared with men. Fasting serum levels of insulin ($P = 0.040$) and C-peptide ($P = 0.011$), glucose disappearance constant ($P < 0.001$), and acute phase insulin $\text{secretion}_{0–8\ \text{min}}$ ($P = 0.006$) were all higher in women compared with men, whereas acute serum C-peptide $\text{secretion}_{0–8\ \text{min}}$ did not differ between men and women (Table III). The disposition index, i.e., the product of the insulin sensitivity index and acute insulin secretion, was higher in women compared with men (increased by 15%, $P = 0.023$), and higher in lean compared with obese (BMI > 25 kg/m^2) subjects (increased by 12%, $P = 0.018$). If women not using oral contraceptives were compared with all men, no significant differences in the insulin sensitivity index ($P = 0.26$), acute insulin response ($P = 0.060$), and fasting levels of serum insulin ($P = 0.24$) and fasting serum C-peptide ($P = 0.12$) were found. However, the glucose disappearance constant ($P < 0.001$), glucose effectiveness ($P < 0.001$), and the disposition index ($P = 0.002$) remained higher in women compared with men.

Insulin sensitivity index, acute insulin response, glucose effectiveness, and body fat. Adiposity was expressed as BMI, body fat percentage (as measured by impedance), waist circumference, and also as waist-hip ratio. The body composition was different in men and women (Table I). BMI ($P < 0.001$), waist circumference ($P < 0.001$), and waist-hip ratio ($P < 0.001$) were all higher in men compared with women, whereas body fat percentage was lower ($P < 0.001$) in men compared with women. In univariate analyses, significantly negative associations with all four measures of body fat and insulin sensitivity index were found in both men and women (Table IV). On the contrary, significantly positive associations with all four measures of body fat and acute insulin response were found in both men and women (Table V). 29 and 12% of the variation in the insulin sensitivity index could be explained by BMI in men and women, respectively. For comparison, BMI explained 16 and 3% of the variation in acute insulin response in men and women, respectively. Glucose effectiveness was not significantly associated with any measure of body fat or body composition.

The variation in the insulin sensitivity index (defined as the

Table III. Insulin and Glucose Dynamics in Men and Women in a Population-based Sample of 380 Healthy Young Danish Caucasians

	Quantity	Men	Women	Significance level: men vs. women
n		186	194	
Insulin sensitivity index	$10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$	15.2 (8.9)	15.2 (9.7)	$P = 0.89$
Glucose effectiveness	$10^{-2} \times \text{min}^{-1}$	2.0 (0.6)	2.3 (0.6)	$P < 0.001$
Glucose disappearance	$10^{-2} \times \text{min}^{-1}$	2.1 (0.9)	2.6 (1.2)	$P < 0.001$
Fasting plasma glucose	mmol/liter	5.2 (0.5)	4.8 (0.4)	$P < 0.001$
Fasting serum insulin	pmol/liter	35 (21)	39 (23)	$P = 0.040$
Fasting serum C-peptide	pmol/liter	456 (159)	492 (160)	$P = 0.011$
Acute serum insulin response	$AUC_{\text{Insulin (0–8 min)(min} \times \text{pmol/liter)}}$	2068 (1372)	2430 (1753)	$P = 0.006$
Acute serum C-peptide response	$AUC_{\text{C-peptide (0–8 min)(min} \times \text{pmol/liter)}}$	6924 (3198)	7277 (3451)	$P = 0.14$
Disposition index	$AUC_{\text{Insulin (0–8 min)}} \times$ insulin sensitivity index	2.68 (1.66)	3.08 (1.78)	$P = 0.023$

Mean (standard deviation).

Table IV. Spearman Correlation Coefficients between the Insulin Sensitivity Index and Modulators of the Insulin Sensitivity Index in Men and Women in a Population-based Sample of 380 Young Healthy Danish Caucasians

	Men			Women		
	r_s	Explained variation	*P* value	r_s	Explained variation	*P* value
n		186			194	
Age (yr)	0.00	0%	($P = 0.96$)	0.10	1%	($P = 0.18$)
BMI (kg/m^2)	−0.54	29%	($P < 0.001$)	−0.34	12%	($P < 0.001$)
Waist-hip ratio	−0.44	19%	($P < 0.001$)	−0.28	8%	($P < 0.001$)
Waist circumference (cm)	−0.52	27%	($P < 0.001$)	−0.36	13%	($P < 0.001$)
Body fat (%)	−0.49	24%	($P < 0.001$)	−0.32	10%	($P < 0.001$)
VO_2max (ml O_2/(kg × min))	0.44	19%	($P < 0.001$)	0.32	10%	($P < 0.001$)
Smoking (yes/no)	0.02	0%	($P = 0.79$)	0.11	1%	($P = 0.12$)
Alcohol consumption (yes/no)	0.09	1%	($P = 0.21$)	0.06	0%	($P = 0.06$)
Saturated fat intake (energy percentage)	−0.19	4%	($P = 0.013$)	−0.01	0%	($P = 0.85$)
Use of oral contraceptives (yes/no)	—	—	—	−0.22	5%	($P = 0.002$)

coefficient of variation) was highest among the leanest subjects. In the obese subjects the variation in the insulin sensitivity index was low partly due to the absolute value of the insulin sensitivity index being lowest in this group and partly due to a lower coefficient of variation in obese subjects compared with lean subjects. Therefore, at BMI > 30 kg/m^2, nearly all subjects had a low insulin sensitivity index (Fig. 2). If subjects with BMI > 25 kg/m^2 were excluded from the analyses, the insulin sensitivity index was independent of BMI, gender, and age, inversely associated with waist-hip ratio, waist circumference, fasting serum levels of triglyceride, and total cholesterol, and positively correlated with glucose disappearance constant. No significant associations were found with systolic or diastolic blood pressure or fasting serum HDL-cholesterol level.

Also to lessen the impact of a high BMI, further analyses including only lean (BMI < 25 kg/m^2) subjects were done. 19 women and 6 men were nonobese (BMI < 25 kg/m^2) and were also insulin resistant as defined by an insulin sensitivity index in the lowest fifth (Fig. 2). In nonobese (BMI < 25 kg/m^2) men and women, the fat percentage and lean body mass were not different between individuals in the lowest fifth of insulin sensitivity index and all other individuals. The lean and insulin-resistant women (insulin sensitivity index in the lowest fifth) had a higher waist-hip ratio ($P = 0.001$), lower fasting serum HDL-cholesterol ($P < 0.001$), higher fasting plasma t-PA antigen ($P = 0.046$), higher fasting plasma fibrinogen ($P = 0.016$), consumed more alcohol ($P = 0.002$), and had a lower VO_2max ($P = 0.024$) when compared with all other lean women ($n = 128$) with an insulin sensitivity index in the four upper fifths. Waist circumference, however, did not differ between the two groups ($P = 0.066$). In the six lean men, the same trends were found although the differences did not attain statistical significance.

Insulin sensitivity index, acute insulin response, glucose effectiveness, VO_2max, and life-style factors. A graded positive association was found between VO_2max and the insulin sensitivity index in both genders and in univariate analyses a positive correlation between VO_2max and the insulin sensitivity index was found in both men and women ($P < 0.001$) (Table IV). 19 and 10% of the variation in the insulin sensitivity index could be explained by VO_2max in men and women, respectively. Consumption of alcohol or smoking was not associated with any significant difference in the insulin sensitivity index in men or women. However, intake of saturated fat was negatively ($P = 0.013$) correlated to the insulin sensitivity index in

Table V. Spearman Correlation Coefficients between the Acute Serum Insulin Response ($AUC_{0-8\ min}$) and Potential Modulators of the Acute Insulin Response in Men and Women in a Population-based Sample of 380 Young Healthy Danish Caucasians

	Men			Women		
	r_s	Explained variation	*P* value	r_s	Explained variation	*P* value
n		186			194	
Age (yr)	−0.07	0%	($P = 0.36$)	−0.05	0%	($P = 0.36$)
BMI (kg/m^2)	0.39	16%	($P < 0.001$)	0.18	3%	($P = 0.030$)
Waist-hip ratio	0.25	6%	($P < 0.001$)	0.27	7%	($P = 0.001$)
Waist circumference (cm)	0.36	13%	($P < 0.001$)	0.28	8%	($P < 0.001$)
Body fat (%)	0.34	11%	($P < 0.001$)	0.18	3%	($P = 0.034$)
VO_2max (ml O_2/(kg × min))	−0.16	3%	($P = 0.028$)	−0.10	1%	($P = 0.22$)
Smoking (yes/no)	0.04	0%	($P = 0.57$)	0.02	0%	($P = 0.83$)
Alcohol consumption (yes/no)	−0.06	0%	($P = 0.44$)	−0.20	4%	($P = 0.015$)
Saturated fat intake (energy percentage)	0.13	2%	($P = 0.097$)	0.03	0%	($P = 0.71$)
Use of oral contraceptives (yes/no)	—	—	—	0.13	2%	($P = 0.069$)

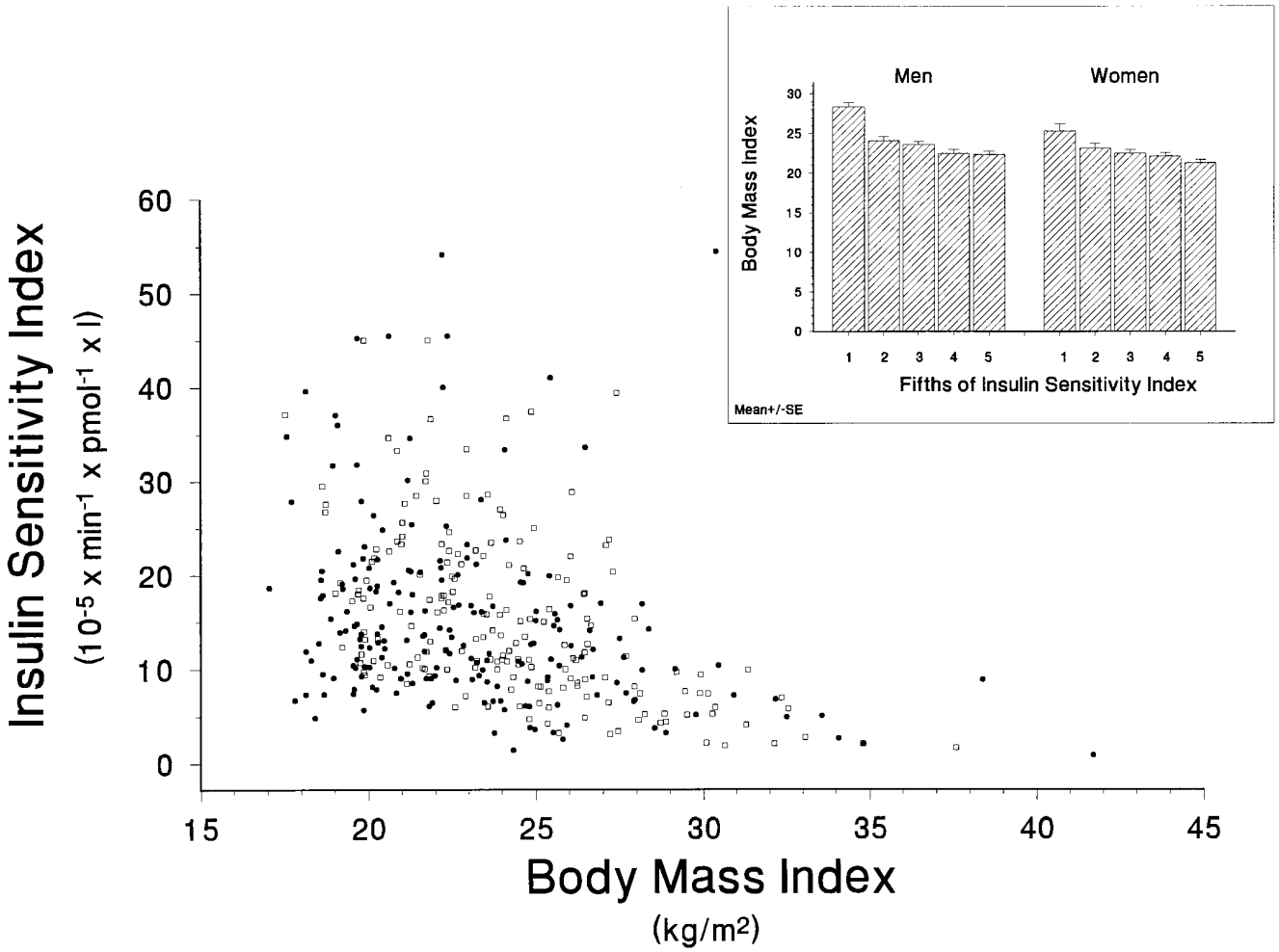

Figure 2. The insulin sensitivity index as a function of the body mass index in 380 young, randomly selected male (*open boxes*) and female (*filled circles*) Caucasians. Fifths of insulin sensitivity index are defined by gender-specific quintiles. The quintiles for men are: 7.9, 11.0, 16.2, and $22.6 \times 10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$. The quintiles for women are 7.9, 11.1, 14.8, and $20.4 \times 10^{-5} \times (\text{min} \times \text{pmol/liter})^{-1}$. Values are given as mean±SE. Values are given as mean±SE.

men, but not in women (Table IV). In women, use of oral contraceptives was associated with a significantly lower insulin sensitivity index (decreased by 27%, $P < 0.001$). Consumption of alcohol was higher ($P < 0.001$) in men compared with women (Table I). Similarly, VO_2max was higher in men. Glucose effectiveness was not found to be significantly associated with life-style factors (alcohol and tobacco consumption and intake of saturated fat) or VO_2max in either men or women. In women, use of oral contraceptives was not associated with any significant difference in glucose effectiveness. Acute insulin response was not significantly associated with any life-style factors except VO_2max in men ($P = 0.028$) and use of alcohol in women ($P = 0.015$) (Table V).

The relationship between the insulin sensitivity index and the pancreatic β-cell function. Figs. 3 and 4 show the values of the insulin sensitivity index and the acute insulin responses, respectively. Apparently there is a negative relationship. This suggests that a person with a low insulin sensitivity index is able to secrete more insulin, and thus potentially compensate for the reduced insulin sensitivity index. A full compensation would require that the relationship was a hyperbola, or, in other words, that the product of the two variables was constant. Also, the coefficient of variation defined should be lesser for the product of the two variables compared with each variable. However, the coefficient of variation is 0.61 for insulin sensitivity index, 0.70 for acute phase serum insulin response, and 0.60 for the product of insulin sensitivity index and acute insulin response. To examine this problem further, we have examined various associations between insulin sensitivity index and acute insulin response in regression analyses. The following plots were made: untransformed values against each other, logarithmic values plotted against each other, and the inverse insulin sensitivity index against acute phase serum insulin response. From these analyses we demonstrated that a standard linear model gives a significantly better description than the other models (data not shown). Furthermore, if a parabolic term was added to the linear model to test for nonlinearity, a significantly better fit than the standard linear model was found (data not shown).

Parental history of hypertension, obesity, NIDDM, and premature cardiovascular disease. The insulin sensitivity index was significantly lower in subjects with a parental history of hypertension ($n = 109$) (decreased by 13%, $P = 0.007$), and in subjects with a parental history of ischemic cardiovascular dis-

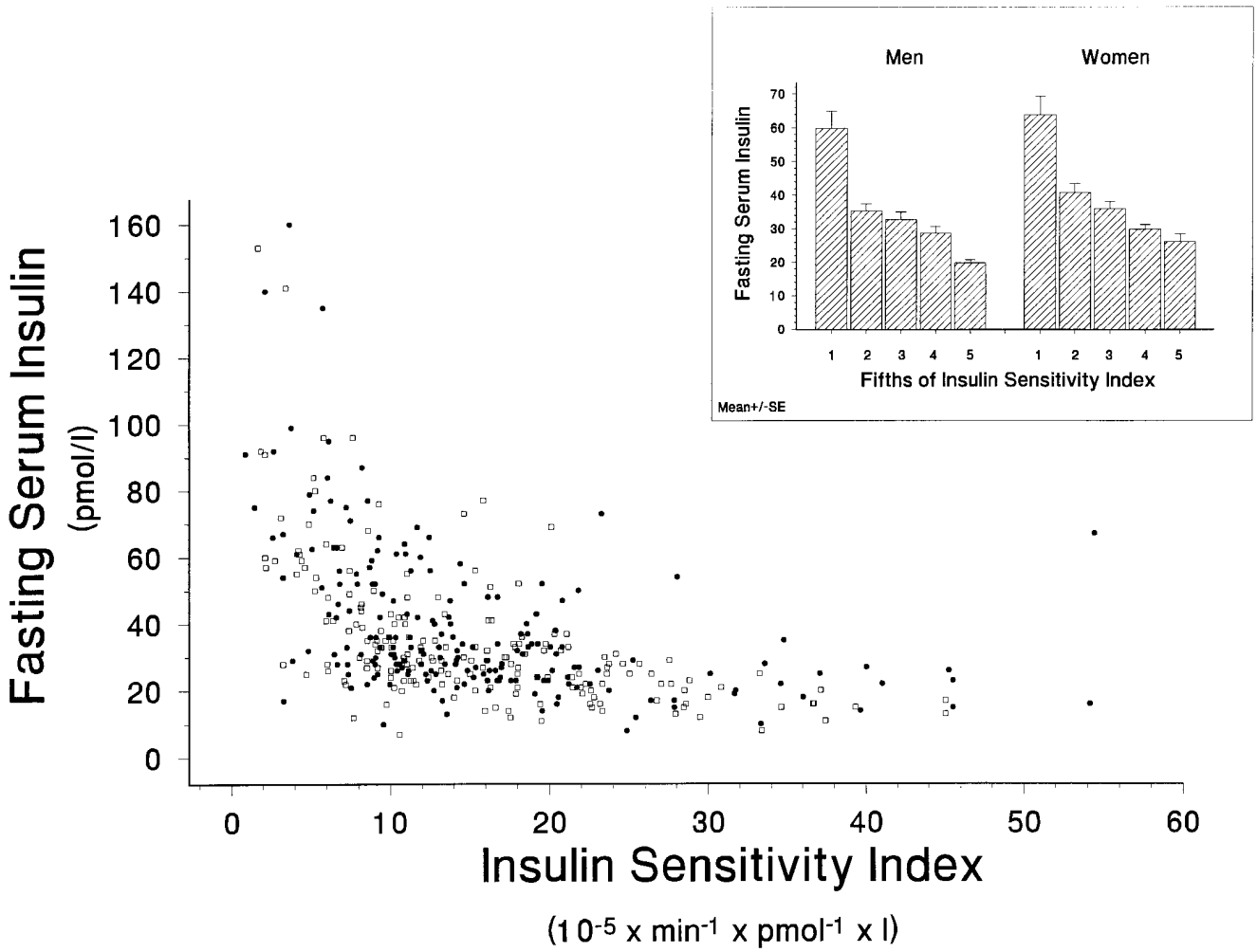

Figure 3. The relationship between the insulin sensitivity index and the fasting serum insulin level in 380 young, randomly selected male (*open boxes*) and female (*filled boxes*) Caucasians. Fifths of the insulin sensitivity index are defined by gender-specific quintiles. The quintiles for men are: 7.9, 11.0, 16.2, and 22.6 $\times 10^{-5} \times$ (min $\times$ pmol/liter)$^{-1}$. Values are given as mean$\pm$SE.

ease before age 60 ($n = 30$) (decreased by 17%, $P = 0.046$) compared with subjects without any parental history of the referred diseases. Compared with subjects without parental history of the referred diseases, subjects with a parental history of obesity ($n = 40$) or NIDDM ($n = 27$) did not have significantly lower insulin sensitivity index (decreased by 15%, $P = 0.095$ and decreased by 15%, $P = 0.066$, respectively). We did not find any difference in subjects with and without a parental history of obesity, NIDDM, cardiovascular disease before age 60, or essential hypertension considering glucose effectiveness, glucose disappearance constant, fasting serum insulin, acute phase serum insulin secretion, acute phase C-peptide secretion, or disposition index.

Importance of known modulators on the insulin sensitivity index, acute insulin response, and glucose effectiveness. In univariate analyses of the total group of subjects, BMI was the most important modulator of the insulin sensitivity index (Table IV). In the multivariate analyses, BMI was negatively associated with the insulin sensitivity index to a lesser degree ($P = 0.014$) (Table VI). Also, waist circumference was negatively associated with the insulin sensitivity index in the multiple regression analysis ($P = 0.0013$). Life-style factors, i.e., consumption of alcohol and smoking did not have any significant impact on the insulin sensitivity index in the multiple regression analysis. Women's use of oral contraceptives was associated with a significantly lower insulin sensitivity index ($P = 0.0001$) (Table VI). If waist circumference was substituted with waist-hip ratio in the multiple regression analysis, and all other explanatory variables in Table V were included, the explained variation, R^2, was the same in the regression analyses including either waist-hip ratio or waist circumference. However, the importance of BMI was higher (regression coefficient -6.6×10^{-2} [95% confidence limits -8.5 to -4.7] $P < 0.0001$) in the analysis including waist-hip ratio than in the analysis including waist circumference. In a multiple regression analysis including daily intake of saturated fat and the above mentioned variables, no significant association between saturated fat intake and the insulin sensitivity index was found. In the multiple regression analyses, the modulators had similar impact on the insulin sensitivity index in men and women as we did not find any interaction between gender and any of the modulators.

In the multivariate analyses with glucose effectiveness as the response variable and including gender, age, BMI, waist circumference, alcohol and tobacco consumption, and women's

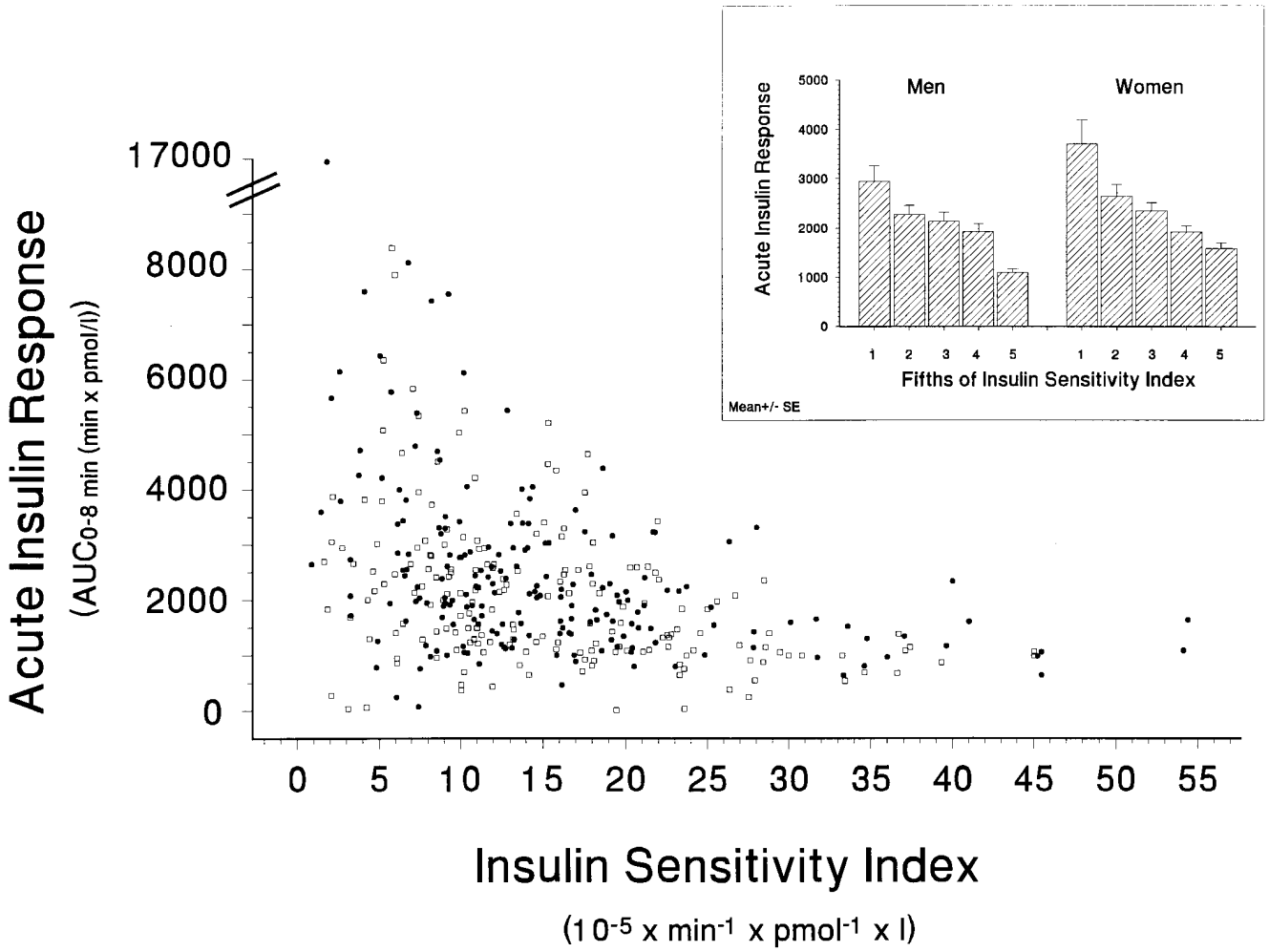

Figure 4. The insulin sensitivity index and β-cell function defined as incremental area under the insulin curve (0–8 min) after an intravenous glucose bolus of 0.3 grams/kg body weight in 380 young, randomly selected male (*open boxes*) and female (*filled circles*) Caucasians. Fifths of the insulin sensitivity index are defined by gender-specific quintiles. Values are given as mean±SE.

use of oral contraceptives as explanatory variables, female gender was the only significant factor, and it was associated with a 36% increase ($P = 0.027$) in glucose effectiveness.

Similarly, in the multivariate analyses with acute insulin response as the response variable and including gender, age, BMI, waist circumference, alcohol and tobacco consumption, and women's use of oral contraceptives as explanatory variables, gender ($P = 0.0075$), age ($P = 0.013$), and waist circum-

Table VI. Multiple Regression Analysis of Modulators of the Insulin Sensitivity Index in a Population-based Sample of 380 Young Healthy Danish Caucasians

Explanatory variable	Response variable: ln (insulin sensitivity index)		*P* value
Gender (0 = men, 1 = women)	-3.6×10^{-2}	(−19.2–12.1)	$P = 0.65$
Age (yr)	2.8×10^{-2}	(1.2–4.3)	$P = 0.0005$
BMI (kg/m^2)	-3.8×10^{-2}	(−6.8–−0.8)	$P = 0.014$
Waist circumference (cm)	-1.9×10^{-2}	(−3.1–−0.8)	$P = 0.0013$
VO_2max (ml O_2/(kg × min))	1.5×10^{-2}	(0.8–2.3)	$P < 0.0001$
Smoking (yes/no)	-1.4×10^{-2}	(−12.2–9.3)	$P = 0.79$
Alcohol consumption (yes/no)	-7.0×10^{-2}	(−21.9–7.8)	$P = 0.35$
Use of oral contraceptives (yes/no)	-3.3×10^{-1}	(−5.0–−1.7)	$P = 0.0001$
R^2	0.37		

Regression coefficients (95% confidence limits). Subjects with partially missing values ($n = 2$) were excluded from the multiple regression analyses.

Table VII. Multiple Regression Analysis of Modulators of Acute Serum Insulin Response in a Population-based Sample of 380 Young Healthy Danish Caucasians

Explanatory variable	Response variable: ln (acute insulin response)		*P* value
Gender (0 = men, 1 = women)	2.9×10^{-1}	(0.8–4.9)	$P = 0.008$
Age (yr)	-2.6×10^{-2}	(−4.7–−0.5)	$P = 0.013$
BMI (kg/m^2)	1.8×10^{-2}	(−2.3–5.8)	$P = 0.39$
Waist circumference (cm)	1.6×10^{-2}	(0.0–3.1)	$P = 0.048$
VO_2max (ml O_2/(kg × min))	0.6×10^{-3}	(−9.2–102.3)	$P = 0.91$
Smoking (yes/no)	1.0×10^{-1}	(−0.42–2.4)	$P = 0.16$
Alcohol consumption (yes/no)	-1.3×10^{-1}	(−3.3–0.6)	$P = 0.18$
Use of oral contraceptives (yes/no)	1.8×10^{-1}	(−0.4–4.1)	$P = 0.11$
R^2	0.10		

Regression coefficients (95% confidence limits). Subjects with partially missing values ($n = 3$) were excluded from the multiple regression analyses.

ference ($P = 0.048$) were significantly associated with acute insulin response (Table VII).

The expression of the insulin resistance syndrome among young healthy Caucasians. Systolic and diastolic blood pressure, and fasting values of serum total-cholesterol, serum triglyceride, plasma PAI-1 activity, and plasma t-PA-antigen were significantly higher in men compared with women. Fasting values of serum HDL-cholesterol and plasma fibrinogen were significantly lower in men compared with women (Table VIII). If women using oral contraception were excluded from the analyses, the same results were found, except that fasting serum LDL-cholesterol level was significantly lower ($P = 0.035$) in the group of women who did not take oral contraceptives.

Compared with individuals in the upper four-fifths of the distribution of insulin sensitivity index, men and women with insulin sensitivity index in the first fifth were more obese, had a higher waist-hip ratio, and had a lower VO_2max (Table IX, second to last column). Men and women in the lowest fifth of the insulin sensitivity index had a lower intravenous glucose tolerance and exhibited features of a relative dyslipidemia since fasting serum total-cholesterol, fasting serum LDL-cholesterol, and fasting serum triglyceride levels were significantly higher and fasting serum HDL-cholesterol concentration was significantly lower compared with all other subjects. Systolic and diastolic blood pressures were both significantly higher in subjects with an insulin sensitivity index in the lowest fifth compared with all other subjects. An increased activation of the fibrinolytic system as reflected by significantly higher levels of fasting plasma t-PA antigen and fasting plasma PAI-1 activity was present in subjects with an insulin sensitivity index in the lowest fifth compared with all other subjects in the sample. Individuals with a low insulin sensitivity index had an excessive risk of having many cardiovascular risk variables, whereas individuals with a high insulin sensitivity index had few cardiovascular risk factors (Fig. 5).

After controlling for BMI the cardiovascular risk factor profile differed less between subjects in the lowest fifth of insulin sensitivity index compared with all other subjects (Table IX, last column). The significant differences in waist circumference, acute phase serum insulin secretion, acute phase C-peptide secretion, fasting plasma t-PA antigen, fasting plasma PAI-1 activity, fasting plasma fibrinogen, and systolic and diastolic blood pressure between subjects having insulin sensitivity index in the lowest fifth compared with all other individuals disappeared when adjusting for the impact of BMI. However, waist-hip ratio, fasting serum total-cholesterol, fasting serum LDL-cholesterol, and fasting serum triglyceride were all still

Table VIII. Blood Pressure, Fasting Serum Lipids, and Fibrinolytic Variables of Men and Women in a Population-based Sample of 380 Young Danes

	Quantity	Men	Women	Significance level: men vs. women
n		186	194	
Systolic blood pressure	mmHg	121 (12)	109 (9)	$P < 0.001$
Diastolic blood pressure	mmHg	67 (8)	62 (8)	$P < 0.001$
Fasting serum total-cholesterol	mmol/liter	4.6 (0.9)	4.4 (0.8)	$P = 0.31$
Fasting serum HDL-cholesterol	mmol/liter	1.1 (0.2)	1.3 (0.3)	$P < 0.001$
Fasting serum LDL-cholesterol	mmol/liter	2.9 (0.9)	2.7 (0.7)	$P = 0.20$
Fasting serum triglyceride	mmol/liter	1.2 (0.9)	1.0 (0.5)	$P < 0.001$
Fasting plasma t-PA antigen	ng/ml	4.9 (2.2)	3.4 (1.5)	$P < 0.001$
Fasting plasma PAI-1 activity	mU/liter	10.3 (8.9)	7.0 (7.7)	$P < 0.001$
Fasting plasma fibrinogen	grams/liter	2.1 (0.5)	2.5 (0.6)	$P < 0.001$

Mean (standard deviation).

Table IX. Clinical and Biochemical Data of 380 Young Healthy Danish Caucasians when Stratified According to One-fifth or Two- to Five-fifths of the Insulin Sensitivity Index

	Quantity	One-fifth of insulin sensitivity index	Two- to Five- fifths of insulin sensitivity index	Significance level*, univariate	Significance level controlled for BMI‡
n (male/female)		37/37	149/157		
Age	yr	25.5 (3.7)	25.2 (3.5)	—	—
BMI	kg/m^2	27.1 (4.6)	22.7 (2.9)	$P < 0.001$	—
Insulin sensitivity index	$10^{-5} \times (min \times pmol/liter)^{-1}$	5.2 (1.9)	17.6 (8.8)	$P < 0.001$	—
Acute phase serum insulin secretion	$AUC_{Insulin\ (0–8\ min)\ min}$	3324 (2519)	1994 (1123)	$P = 0.020$	$P = 0.12$
Acute phase C-peptide secretion	$AUC_{C\text{-}peptide\ (0–8\ min)}$	8947 (4663)	6659 (2748)	$P = 0.013$	$P = 0.11$
Glucose disappearance constant	$10^{-2} \times min^{-1}$	1.9 (0.9)	2.4 (1.1)	$P < 0.001$	$P < 0.001$
Waist-hip ratio		0.86 (0.08)	0.81 (0.06)	$P < 0.001$	$P = 0.040$
Waist circumference	cm	88 (11)	75 (9)	$P < 0.001$	$P = 0.36$
Systolic blood pressure	mmHg	120 (15)	114 (11)	$P < 0.001$	$P = 0.35$
Diastolic blood pressure	mmHg	69 (10)	64 (8)	$P < 0.001$	$P = 0.32$
Fasting serum total-cholesterol	mmol/liter	4.9 (1.0)	4.4 (0.8)	$P < 0.001$	$P = 0.018$
Fasting serum HDL-cholesterol	mmol/liter	1.0 (0.2)	1.2 (0.3)	$P < 0.001$	$P = 0.024$
Fasting serum LDL-cholesterol	mmol/liter	3.1 (1.0)	2.7 (0.7)	$P < 0.001$	$P = 0.029$
Fasting serum triglyceride	mmol/liter	1.5 (1.0)	1.0 (0.5)	$P < 0.001$	$P = 0.006$
Fasting plasma t-PA antigen	ng/ml	5.3 (2.3)	3.9 (1.8)	$P = 0.001$	$P = 0.29$
Fasting plasma PAI-1 activity	mU/liter	13.1 (11.6)	7.5 (7.1)	$P = 0.002$	$P = 0.25$
Fasting plasma fibrinogen	grams/liter	2.5 (0.7)	2.2 (0.5)	$P < 0.001$	$P = 0.16$

Mean (standard deviation). *Significance between one-fifth of insulin sensitivity index and two- to five-fifths of insulin sensitivity index. ‡Significance between one-fifth of insulin sensitivity index and two- to five-fifths of insulin sensitivity index adjusted for BMI.

higher in subjects in the lowest gender-specific fifth of the insulin sensitivity index compared with all other individuals. Furthermore, fasting serum HDL-cholesterol and the glucose disappearance constant were significantly lower in subjects in the lowest gender-specific fifth of the insulin sensitivity index compared with all other individuals.

Discussion

In this paper the insulin sensitivity in a population-based sample of 380 young healthy individuals has been estimated by means of the insulin sensitivity index in accordance with Bergman's minimal model. The insulin sensitivity index is a trait

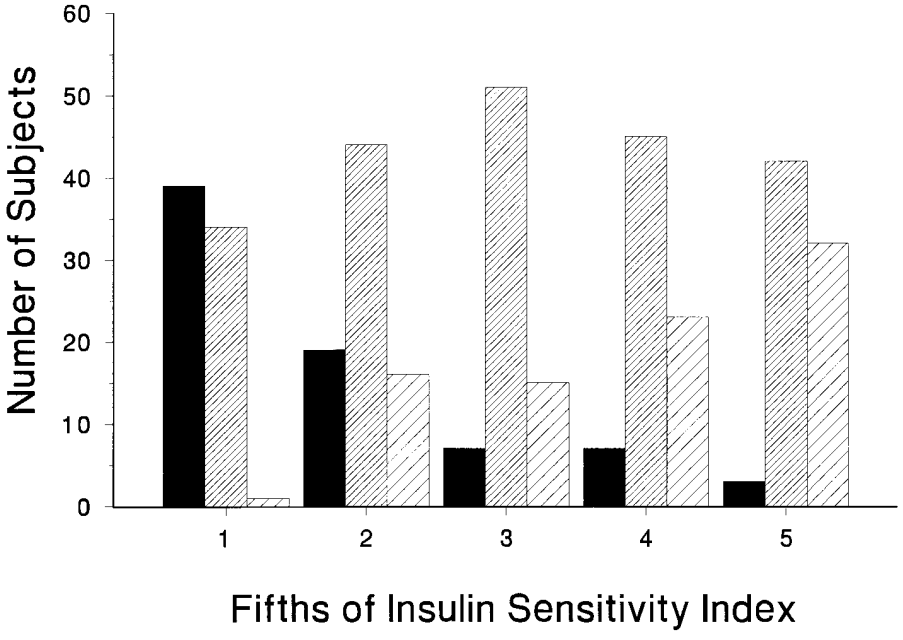

Figure 5. A histomer of the insulin resistance syndrome score (see Methods) among the 380 study participants when stratified according to fifths of insulin sensitivity index. The insulin resistance syndrome score of each subjects was augmented by 1 for each of the following variables if they were above the gender-specific medians: PAI activity, systolic blood pressure, and BMI. Similarly, the insulin resistance syndrome score was augmented by 1 for each of the following variables being below the gender-specific medians: glucose disappearance, constant and fasting serum HDL-cholesterol. An insulin resistance syndrome score from 0 to 1 was considered "low" (*striped bars*), 2 to 3 "intermediate" (*densely striped bars*), and 4 to 5 "high" (*filled bars*). Most subjects with a low insulin sensitivity index (first fifth of insulin sensitivity index) have a high insulin resistance syndrome score and most subjects with a high insulin sensitivity index (last fifth of insulin sensitivity index) have a low insulin resistance syndrome score.

that varies widely in the normal population of young Danes. It is a major goal to explain the variation. The distributions of insulin sensitivity index and acute phase serum insulin secretion were skewed to the right in both men and women, whereas the distribution of glucose effectiveness was Gaussian distributed. In univariate analyses, BMI, body fat percentage, waist circumference, and waist-hip ratio were all negatively associated with the insulin sensitivity index whereas VO_2max was positively associated with this variable. In women, use of oral contraceptives was negatively associated with the insulin sensitivity index. In multiple regression analysis including gender, age, VO_2max, BMI, waist circumference, intake of alcohol, intake of saturated fat, smoking, and use of oral contraceptives, variables measuring obesity (BMI, waist circumference, or waist-hip ratio), VO_2max, and use of oral contraceptives were the most important determinants of the insulin sensitivity index. Only 37% of the variation in insulin sensitivity index can be explained by the variables measured in this study. This leaves open a large component for unmeasured variables including genetic effects on the overall variance in the insulin sensitivity index. However, to what extent the unexplained variation can be attributed to genetic or environmental factors cannot be solved by this study. Compared with individuals in the upper four-fifths of the distribution of the insulin sensitivity index both men and women with an insulin sensitivity index in the first fifth had higher waist circumference and higher blood pressure but lower VO_2max and they exhibited a relative glucose intolerance, fasting dyslipidemia, and dysfibrinolysis.

Recently, it has been shown that young adult women have an enhanced muscle insulin sensitivity (37). In older studies, the results considering the effect of gender on whole body insulin sensitivity have been conflicting, with some studies finding no gender difference and another finding a lower insulin sensitivity in women compared with men (12, 38, 39). Some studies adjust for VO_2max, while other studies do not adjust, and this may explain the different findings. Sex steroids influence insulin sensitivity evidenced both by the lower insulin sensitivity found in women using contraceptive pills and also by the negative association between insulin sensitivity and free serum testosterone level in women with abdominal adiposity (40, 41). Animal studies show that a high level of serum testosterone in female rats may be associated with a decreased number of insulin-sensitive type 1 muscle fibers, a reduced capillary density, and an increased number of insulin-resistant type 2 fibers (42). In male rats both low and high levels of serum testosterone may be associated with a low insulin sensitivity (43). However, due to the lack in difference of the insulin sensitivity index between men and women the more detrimental cardiovascular profile found in men compared with women cannot be explained by differences in the insulin sensitivity index in young healthy individuals.

Several other studies (4, 5, 11, 44–46) have measured the insulin sensitivity index in large groups of individuals, but the present study is the first to measure the insulin sensitivity index and glucose effectiveness in a population-based sample. In studies using frequently sampled IVGTT with minimal modeling, the mean value of estimates of the insulin sensitivity index varies considerably (4, 44–46). Our mean value and median for the insulin sensitivity index are $\sim$ 50% higher than the values from studies by Kahn et al. (46) and Allemann et al. (44). This is an expected finding because we used an insulin assay, which has no cross-reactivity to intact proinsulin, or des(31, 32 proinsulin) (20). Our mean value of the fasting serum insulin was 50% lower than the values estimated in the study by Kahn et al. (46), for example. If the measured insulin values were 50% lower for all the measured insulin values during the IVGTT, then the calculated insulin sensitivity index would be 50% higher compared with the insulin sensitivity index value measured, if a nonspecific insulin assay was used (47). However, the higher values for the insulin sensitivity index in the present study compared with previous reports may also be related to the fact that our study population was young and relatively lean.

Obesity, abdominal fat distribution, and weight gain are important risk factors for the development of NIDDM (48–50). Also, obesity has been shown in prospective studies to be associated with increased risk of hypertension and mortality from cardiovascular disease (51–54). In the present study, obesity measured as BMI was the strongest determinant of the insulin sensitivity index explaining 29% of the variance of the insulin sensitivity index in men, which agrees with other studies (55). The lesser impact of BMI on the insulin sensitivity index in multiple regression analysis including waist circumference suggests that BMI is only a surrogate measure for another parameter, which we have not measured. A good candidate for such a variable is the amount of abdominal fat, which somewhat is reflected by waist circumference. Abdominal fat and especially visceral fat is supposed to be more metabolically active and more pathogenic than its counterpart in the buttocks (56, 57).

Obesity and low insulin sensitivity are certainly closely associated (58, 59). However, the relationship is complex. Obesity is associated with low insulin sensitivity, but high insulin sensitivity may predict weight gain (60). With increasing obesity, the variation in insulin sensitivity decreases. In our analysis of subjects with a BMI > 30 kg/m^2, nearly all subjects were insulin resistant. Therefore, in obese subjects the insulin sensitivity index may not be an appropriate measure of the interaction between insulin and glucose, when evaluating the influence of other determinants, i.e., genetic factors. Low insulin sensitivity index and obesity are both related to high blood pressure, dyslipidemia, and risk of NIDDM (4, 5, 7, 8, 50). The strong association between obesity and a low insulin sensitivity index raises the fundamental question of whether the clustering of cardiovascular risk factors in subjects with a low insulin sensitivity index is caused by obesity. Actually, in these young and healthy subjects the only prevalent disease state is obesity. If separate analyses including only subjects with either a BMI < 30, < 27, < 26, or< 25 kg/m^2 were done, the insulin sensitivity index was still negatively associated with waist-hip ratio, fasting serum triglyceride and total fasting serum cholesterol, independent of BMI, gender, and age, but no significant association was found between the insulin sensitivity index and systolic or diastolic blood pressure. Therefore, abdominal fatness is an important determinant of the insulin sensitivity index and knowledge of an individual being lean or obese as estimated from BMI is not sufficient to predict whether the subject will be insulin sensitive or insulin resistant.

A physically active life-style may diminish the risk of acquiring NIDDM and physical activity is reported to be positively associated with glucose tolerance independent of obesity and fat distribution (2, 61). VO_2max and insulin sensitivity are positively associated (62–64), and in our study VO_2max was the second strongest (defined as explained variation of the insulin sensitivity index) determinant of the insulin sensitivity in-

dex in both men and women (R^2 = 17%). However, controlling for BMI did diminish the strength of the association between VO_2max and the insulin sensitivity index as the partial correlation coefficient fell from 0.41 to 0.25. In a study including only nonobese subjects, the association between VO_2max and the insulin sensitivity index was influenced by BMI to a lesser degree than in our study (63). Most obese subjects have a low insulin sensitivity, and this may explain the various findings.

A high intake of saturated fat and smoking may be associated with a reduction in insulin sensitivity (65, 66). In the multiple regression analysis, no significant association of these lifestyle factors with the insulin sensitivity index was found. The lack of an association between the insulin sensitivity index and intake of saturated fat and tobacco consumption may reflect that these factors are of minor importance compared with body fatness and VO_2max.

In previous publications, the relationship between the insulin sensitivity index and insulin secretion has been expressed as a hyperbola (32, 33, 46), in which insulin sensitivity × acute insulin response$_{0–8\ min}$ = disposition index. This disposition index has been considered a characteristic constant for the population. In the present study, we were not able to demonstrate from a statistical perspective that the hyperbola was the best analytic function to account for the data in our population. In fact, it can be shown that an equal or better nonlinear regression can be obtained with a straight line relationship (with a negative slope) between acute insulin response$_{0–8\ min}$ and the insulin sensitivity index (data not shown). A parabolic relationship also provides an equal or better representation of the data than the previously suggested hyperbola. However, in the present study, we have chosen to continue to use the hyperbola since it can account for the data over the entire possible range of values of insulin secretion and sensitivity. The straight line relationship must be limited to positive values of the insulin sensitivity index and acute insulin response$_{0–8\ min}$ and has no meaning when these values are negative. Similar but more bizarre results would occur with a parabola; this function would predict that as the insulin sensitivity index increase, the acute insulin response$_{0–8\ min}$ would tend to infinity. An additional difficulty with the alternative functions is that, by design, our data set is limited to young, healthy volunteers. We did not have a large number of very insulin-resistant individuals. We know from previous studies that as the insulin sensitivity index is reduced below 10×10^{-5} (min × pmol/liter)$^{-1}$, one would expect a precipitous rise in acute insulin response$_{0–8\ min}$, assuming the subjects are nondiabetic. Because our cohort includes only young subjects, the "rising limb" of a hyperbola (low insulin sensitivity index, high acute insulin response$_{0–8\ min}$) was not observed. It is likely that if such data were included (i.e., if older, more insulin-resistant subjects had been examined) that a hyperbola would be the function of choice to fit the data. Taken together, these considerations suggest that we do not have a broad enough population base in this study to have power to determine the best function to use to fit the acute insulin response$_{0–8\ min}$ versus the insulin sensitivity index data.

The product of the insulin sensitivity index and insulin secretion is different in men and women. The higher insulin secretion observed in all women compared with men is probably explained by use of oral contraceptives as the difference disappears, when women using oral contraceptives are excluded from the analysis. The higher disposition index and the higher glucose effectiveness observed in women compared with men is reflected by a lower fasting plasma glucose level and a higher glucose tolerance in women.

Glucose effectiveness is a measure of the insulin-independent glucose uptake and is an important factor determining glucose tolerance. Glucose effectiveness has not been extensively validated, as has the insulin sensitivity index. The definition of glucose effectiveness, from the minimal model, is quite clear: it is the relative effect of glucose, at basal insulin, to increase net glucose disappearance (i.e., to enhance glucose utilization and suppress hepatic glucose output). The other factors determining glucose tolerance are insulin secretion and insulin sensitivity (12, 67). In a prospective study a low level of glucose effectiveness has been shown to precede the development of NIDDM (4). Normoglycemic relatives of patients with NIDDM have been found to have an increased glucose effectiveness compared with normoglycemic controls (67). Subjects with impaired glucose tolerance have a lower glucose effectiveness than normoglycemic controls (68). Therefore, in subjects having a low insulin sensitivity, i.e., some relatives of NIDDM patients, a high level of glucose effectiveness may compensate for the low insulin sensitivity (67). No other study has measured glucose effectiveness at the population level, and no gender difference in glucose effectiveness has been reported. The higher glucose effectiveness and glucose disappearance constant found in women compared with men did not disappear, when controlling for BMI, waist circumference, VO_2max, use of oral contraceptives, smoking, and alcohol consumption in a multiple regression analysis. Whether the higher glucose effectiveness in women compared with men may add to the explanation of the low morbidity from cardiovascular disease in premenopausal women compared with age-matched men remains unsettled.

Consistent with the results from previous studies (69, 70) in normal subjects, the acute insulin response to intravenous glucose in the subjects of the present cohort also showed a considerable interindividual variation. Together the measured environmental and anthropometric factors could account for 10% of the variation in the acute insulin response with the female gender being the major determinant.

Evidence does not exist that proves insulin sensitivity to be an independent risk factor for hypertension and dyslipidemia. However, ongoing prospective studies examine whether impaired insulin sensitivity may join dyslipidemia, hypertension, and glucose intolerance as a major risk factor for atherosclerosis and subsets of NIDDM. But how is impaired insulin sensitivity defined in the literature? Often insulin resistance is referred to qualitatively as impaired sensitivity to the effects of insulin on whole body glucose turnover rate and there is no accepted consensus on a reference limit. Like blood pressure, fasting serum lipids, and fasting and 2-hour post–oral glucose tolerance test blood glucose, insulin sensitivity is a continuous variable. To have rationale platforms for a treatment of hypertension, dyslipidemia, and diabetes quantitative clinical criteria have been established based on long-term monitoring on the clinical outcome of alterations in blood pressure, serum lipids, and blood glucose. If insulin resistance is to be more than a mere taxonomic convention, similar longitudinal studies are needed to define the possible prognostic significance of impaired insulin sensitivity in the risk profile of cardiovascular disorders and subsets of pre-NIDDM. As a starting point the present cross-sectional investigation uses a statistical definition

of insulin resistance. By applying the lowest gender-specific fifth of the insulin sensitivity index as an arbitrary cutoff value, subjects within this fifth were characterized by being more obese and less glucose tolerant, having elevated fasting serum levels of lipids and a dysfunction of the fibrinolytic system, and having higher blood pressure compared with the other subjects in the population sample. Whether this operational definition is useful to identify subjects at increased risk of developing premature cardiovascular events and some forms of NIDDM awaits to be elucidated in prospective studies.

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