Long-Term Predictors of Insulin Resistance

Role of lifestyle and metabolic factors in middle-aged men

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OBJECTIVE — Predictors of insulin resistance have hitherto only been examined in cross-sectional studies without information on lifestyle factors. Few researchers have measured insulin sensitivity directly and compared different metabolic and lifestyle predictors in a large population.

RESEARCH DESIGN AND METHODS — Our aim was to investigate independent long-term predictors of insulin sensitivity in a large population-based sample (the Uppsala Longitudinal Study of Adult Men cohort) of 50-year-old men who underwent a euglycemic clamp 20 years later ($n = 770$). Subjects with diabetes and treatment of cardiovascular disease at baseline were excluded. In linear regression models, metabolic (BMI, triglycerides, HDL cholesterol, glucose, and blood pressure) and lifestyle factors (physical activity, smoking, saturated fat biomarkers, and socioeconomic status) were independent variables at baseline (age 50 years) and insulin sensitivity–dependent variables at follow-up (age 70 years). A subsample of only normal-weight men from the initial population was also examined ($n = 440$).

RESULTS — BMI was the strongest predictor of insulin sensitivity even after addition of metabolic factors. One SD (±2.8) increase in BMI corresponded to a mean 19% decrease in insulin sensitivity. After addition of lifestyle factors, all factors except triglycerides and smoking were significant predictors. BMI remained the strongest predictor ($\beta = -0.67$ [95% CI -0.83 to -0.51], $P < 0.0001$) followed by physical activity, HDL cholesterol, saturated fat, and socioeconomic status (all $P < 0.05$). BMI remained the strongest predictor in normal-weight subjects also ($P < 0.001$). In addition, after adjustment for baseline insulin concentrations, BMI remained the strongest predictor ($P < 0.001$).

CONCLUSIONS — Multiple factors, including novel factors such as saturated fat and socioeconomic status, independently predict insulin sensitivity after 20 years. BMI is, however, the single strongest predictor, even in normal-weight subjects.

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Insulin resistance, i.e., low insulin sensitivity, precedes type 2 diabetes and is an emerging risk factor for cardiovascular disease (1). Approximately 25% of the U.S. population has clinically significant insulin resistance (2). It is therefore important to identify predictors of insulin sensitivity to help optimize prevention. The etiology of insulin resistance is complex as both metabolic/genetic and lifestyle factors contribute. Cross-sectional studies suggest that insulin resistance is more prevalent in obese subjects (3) with hypertriglyceridemia, low HDL cholesterol (2,4,5), hypertension (6), and other metabolic aberrations (4). Lyssenko et al. (7) assessed longitudinal (6 year-follow-up) predictors for type 2 diabetes but not for insulin sensitivity per se. No researchers have, however, adjusted for lifestyle factors or other metabolic syndrome components. Examining which factors predict insulin sensitivity independently from the others could be informative. Socioeconomic status is a factor related to diabetes, but its association with insulin sensitivity per se is unknown. In addition, in only one of the above-mentioned cross-sectional studies (3) was insulin sensitivity assessed by a gold standard technique, i.e., the euglycemic clamp.

Despite the importance of insulin resistance in metabolic diseases, there are no longitudinal data on predictors of insulin sensitivity. To study these, a large longitudinal cohort study including direct assessments (e.g., euglycemic clamp) of insulin sensitivity is required. In addition, such direct measurement must be available at the end of the follow-up time rather than at baseline (or preferably at both occasions). Finally, a long follow-up period is required to allow for impairment of insulin sensitivity over time, with available lifestyle factors in addition to metabolic factors. The Uppsala Longitudinal Study of Adult Men (ULSAM) is a cohort study that may be suitable for addressing this issue as it fulfills two of these criteria. Furthermore, most studies have used insulin resistance as a dichotomous variable defined arbitrarily despite the fact that insulin sensitivity is a continuum. Using the ULSAM cohort, we addressed our current aim: to identify and compare long-term predictors of insulin sensitivity after adjusting for lifestyle factors and socioeconomic status. This is the first multivariate analyses of long-term predictors of clamp-derived insulin sensitivity in a large population-based sample of nondiabetic men followed for 20 years. This study could add new knowledge regarding the role of lifestyle factors in insulin resistance.

RESEARCH DESIGN AND METHODS — ULSAM is a longitudinal population-based cohort study (www.pubcare.uu.se/ULSAM/). In 1970–1973, all 50-year-old men living in Uppsala, Sweden, were invited to participate in a health survey, and of the men invited,

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Table 1—*Baseline characteristics before and after exclusions and insulin sensitivity at follow-up*

		Study samples with longitudinal data	
	Original sample	All study samples	BMI $\leq$25 kg/m^2
n	2,322	770	440
BMI (kg/m^2)	25.0 ± 3.2	24.7 ± 2.8	22.7 ± 1.5
Plasma glucose (mg/dl)	90.1 ± 10.8	88.3 ± 9.0	86.5 ± 9.0
Triglycerides (mg/dl)	168.1 ± 115.0	159.3 ± 79.6	141.6 ± 61.9
HDL cholesterol (mg/dl)	52.7 ± 15.5	53.1 ± 14.6	55.7 ± 15.2
Systolic blood pressure (mmHg)	133 ± 18	130 ± 15	128 ± 15
Diastolic blood pressure (mmHg)	84 ± 11	82 ± 10	80 ± 10
Fasting insulin (μU/ml)	13.0 ± 7.7	12.0 ± 6.3	10.6 ± 5.4
M at age 70 years (mg · kg^{-1} · min^{-1})*	—	5.2 ± 2.0	5.8 ± 1.9
Smoking status (% yes/no)	49/51	55/45	50/50
Physical activity (%)			
Sedentary	15	12	10
Moderate	36	36	35
Regular	44	46	48
Athletic	5	6	7
Saturated fat index (16:1n-7/16:0)	0.33 ± 0.11	0.32 ± 0.09	0.30 ± 0.09
Socioeconomic status (%)			
1 (low)	15	16	18
2 (medium)	39	38	34
3 (high)	46	46	48

Data are means ± SD. *M determined at follow-up defines insulin sensitivity from clamp. To convert values for glucose to millimoles per liter, multiply by 0.0555. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. To convert values for cholesterol to millimoles per liter, multiply by 0.02586.

2,322 (82%) participated in the baseline investigation. At a reexamination 20 years later in 1991–1995 (at age 70 years), 1,221 men (73% of surviving men still living in the Uppsala region) participated. At baseline, we excluded 124 subjects who were taking glucose-lowering medication or who had diabetes and subjects treated with drugs for cardiovascular disease that may affect insulin sensitivity, i.e., glucocorticoids (n = 64), antihypertensive agents (n = 130), and lipid lowering drugs (n = 57). For the follow-up, 422 men died, 219 moved, and another 460 did not participate. We also excluded subjects with incomplete data for variables at baseline and follow-up (n = 76). Thus, after all exclusions the present study included all men with baseline data on all included variables who also had follow-up data on insulin sensitivity (n = 770) (Table 1). In addition, of the 770 subjects, we also examined a subsample of 440 normal-weight men (excluding subjects with BMI >25). All men gave informed consent, and the Ethics Committee of Uppsala University approved the study.

Baseline examinations
We selected specific variables that have been associated with insulin sensitivity in cross-sectional studies, i.e., metabolic factors (BMI, HDL cholesterol, triglycerides, glucose, and blood pressure) and lifestyle factors that were available at baseline (physical activity, smoking, and estimated saturated fat intake). In addition, socioeconomic status was regarded as a lifestyle factor and was included in the lifestyle model. In the baseline examination (at age 50 years), blood samples were drawn in the morning after an overnight fast. Blood glucose was measured by spectrophotometry using the glucose oxidase method. BMI was calculated as the weight in kilograms divided by the square of height in meters. Serum insulin concentrations were determined with the Phadebas Insulin Test (Pharmacia, Uppsala, Sweden), using a radioimmunosorbent technique. Serum triglyceride concentrations and HDL cholesterol were assayed by enzymatic techniques. Supine blood pressure was measured twice in the right arm after a 10-min rest, and means were calculated. Fatty acid composition was analyzed in serum cholesterol esters by gas chromatography as described previously (8). As a biomarker of saturated fat intake ("saturated fat index"), the 16:1n-7–to–16:0 ratio was calculated; a high ratio reflects a high intake of saturated fat in a western diet as shown in controlled studies (9). Leisure-time physical activity was assessed using a validated questionnaire providing four activity levels: sedentary, moderate, regular, and athletic. Coding of smoking was based on interview reports and defined as smoking (1) or nonsmoking (0). Socioeconomic status was based on interview and defined as three conventional social classes according to the Central Bureau of Statistics.

Follow-up
Insulin sensitivity was determined at age 70 years using a hyperinsulinemic-euglycemic clamp, according to the method of DeFronzo et al. (10), slightly modified [insulin was infused at a constant rate of 56 mU/(min per m^2)]. Insulin sensitivity (M) was calculated as glucose infusion rate (mg · kg body wt^{-1} · min^{-1}) during the last 60 min of the 2-h clamp.

Statistical analysis
All analyses were defined a priori. All variables except smoking were treated as continuous variables. Triglycerides, saturated fat index, insulin, glucose, and diastolic blood pressure were skewed, but all variables were normally distributed after log transformation. The intraclass coefficients of variation (representing the biological variation and measurement error) were as follows: BMI, 1.0; triglycerides, 0.96; glucose, 0.95; HDL cholesterol, 0.84; diastolic blood pressure, 0.73; and

insulin, 0.80. Initially, univariate linear regression was performed between metabolic factors at baseline and insulin sensitivity at follow-up. Then multivariate regression models were used to identify independent predictors (assessed at baseline) of insulin sensitivity. All metabolic independent variables were standardized to 1 SD. Three multivariate models were used. First, we included all metabolic factors (metabolic model: BMI, HDL cholesterol, triglycerides, glucose, and diastolic blood pressure). Because diastolic blood pressure was slightly better correlated to insulin sensitivity than to systolic blood pressure in univariate analyses ($r = 0.23$ vs. $r = 0.21$, both $P < 0.0001$), we only included diastolic blood pressure in multivariate models to avoid colinearity. Second, we added lifestyle factors (smoking status, saturated fat index, physical activity level, and socioeconomic status) to the metabolic model (lifestyle model). Finally, to adjust for "subclinical insulin resistance" we added fasting insulin levels to the lifestyle model (insulin model). We used insulin instead of homeostasis model assessment of insulin resistance (HOMA-IR) because these measures are equally good predictors of directly measured insulin sensitivity (5), and if we had used HOMA-IR instead of insulin, we would not have been able to keep glucose in the model because of colinearity. JMP software (SAS Institute, Cary, NC) was used for statistical analyses.

RESULTS — All relationships between the independent variables and insulin sensitivity were linear. Baseline data for the total original cohort and the study sample did not differ to any major degree, although subjects in the study sample were slightly healthier than those in the original population as a consequence of the exclusions (Table 1).

Unadjusted analyses

Univariate correlation coefficients for all predictors are shown in Table 2. All metabolic and lifestyle factors except smoking significantly predicted insulin sensitivity (Tables 2 and 3). BMI was the strongest predictor. For every 1 SD increase of BMI ($\sim$3 units), insulin sensitivity (M) decreased by nearly 1 unit, corresponding to a decrease in insulin sensitivity by 19% of the mean.

Metabolic model

In the metabolic model, all variables were significant independent predictors of insulin sensitivity (overall $R^2 = 0.21$). BMI was the strongest predictor followed by triglycerides, HDL cholesterol, diastolic blood pressure, and glucose (Table 3). The R^2 for BMI was 0.18, indicating that BMI was the sole most important factor explaining the variation in insulin sensitivity.

Lifestyle model

All metabolic and lifestyle variables significantly predicted insulin sensitivity independently of each other except for triglycerides and smoking (overall $R^2 = 0.25$). BMI was the strongest predictor followed by physical activity, HDL cholesterol, saturated fat index, socioeconomic status, diastolic blood pressure, and glucose (Table 3). These results remained similar, if we also excluded men who developed diabetes ($n = 106$) or cardiovascular disease ($n = 211$) during follow-up. The ranking among predictors persisted with statistically significant regression coefficients, with only one exception: HDL cholesterol became a stronger predictor than physical activity ($\beta = 0.37$, $P < 0.0001$, and $\beta = 0.27$, $P = 0.004$, respectively). Furthermore, the results remained after subjects with malignant diseases at age 50 or 70 years were excluded. Because results were similar after these additional exclusions and to maintain a high statistical power ($n = 453$ vs. $n = 770$ for the lifestyle model), these data are not shown in the tables.

Adjustment for baseline insulin resistance (insulin model)

After baseline fasting insulin was added to the lifestyle model, insulin was, as expected, an independent predictor ($\beta = 0.57$ [95% CI -0.72 to -0.41], $P < 0.0001$, $n = 770$; overall $R^2 = 0.31$) (data not shown in the tables). BMI, however, remained a strong predictor followed by socioeconomic status, HDL cholesterol, physical activity, and saturated fat. Smoking, triglycerides, diastolic blood pressure, and glucose levels were not significant predictors. In unadjusted analyses, BMI was a slightly stronger predictor (Table 2) than insulin (-0.85 [-1.0 to -0.70], $P < 0.0001$). If Δ BMI (BMI at age 70 $-$ BMI at age 50) was calculated and this variable was used instead of baseline BMI in the model, the results were similar, but the predictive capacity of Δ BMI was stronger (-0.84 [-0.96 to -0.71], $P < 0.0001$, $R^2 = 0.42$) than that for BMI alone. Further, the overall results remained similar, and the strong predictive capacity of BMI remained in all multivariate models after adjustment for Δ BMI (data not shown).

Another approach to adjust for subclinical insulin resistance at baseline is to exclude all insulin-resistant subjects, defined as the highest quartile of HOMA-IR. Results were strikingly similar to those presented in Table 2.

HOMA-IR at age 50 and 70 years

To replicate the results from the clamp data (only available at follow-up), we also assessed HOMA-IR both at baseline and 20 years later in the study population. There was a 19% mean decrease in insulin sensitivity over 20 years. Using HOMA-IR as the outcome variable at follow-up, BMI was again the strongest predictor even after inclusion of baseline HOMA-IR in the multivariate model ($\beta = 0.13$ [95%CI $0.08–0.19$], $P < 0.0001$), followed by baseline HOMA-IR (0.11 [$0.08–0.15$],

Table 2—*Univariate associations between metabolic and lifestyle factors at baseline (age 50 years) and* M *at follow-up (age 70 years)*

Independent variables	Correlation coefficient (r)	P value
BMI	-0.43	<0.0001
Plasma glucose	-0.12	<0.001
Triglycerides	-0.27	<0.0001
HDL cholesterol	0.22	<0.0001
Systolic blood pressure	-0.21	<0.0001
Diastolic blood pressure	-0.23	<0.0001
Fasting insulin	-0.39	<0.0001
HOMA-IR	-0.36	<0.0001
Physical activity	0.16	<0.0001
Smoking	-0.05	0.17
Saturated fat index*	-0.20	<0.0001
Socioeconomic status	-80.11	<0.01

$n = 770$. *The 16:1n-7–to–16:0 ratio determined in serum cholesterol esters.

Table 3—*Associations of metabolic and lifestyle factors with insulin sensitivity in univariate and multivariate regression analyses*

Independent variables	All subjects		Normal weight	
	β (95% CI)	*P*	β (95% CI)	*P*
n	770		440	
BMI				
Unadjusted	−0.99 (−1.13 to −0.85)	<0.0001	−1.04 (−1.38 to −0.69)	<0.0001
Metabolic model	−0.77 (−0.92 to −0.62)	<0.0001	−0.78 (−1.14 to −0.43)	<0.0001
Lifestyle model	−0.67 (−0.83 to −0.51)	<0.0001	−0.68 (−1.03 to −0.32)	<0.001
Insulin model	−0.51 (−0.68 to −0.34)	<0.0001	−0.54 (−0.90 to −0.18)	<0.01
Fasting glucose				
Unadjusted	−0.29 (−0.46 to −0.13)	<0.001	−0.24 (−0.44 to −0.04)	0.02
Metabolic model	−0.17 (−0.32 to −0.02)	<0.05	−0.16 (−0.35 to 0.03)	0.10
Lifestyle model	−0.18 (−0.33 to −0.03)	<0.05	−0.21 (−0.38 to −0.01)	<0.05
Insulin model	−0.10 (−0.25 to 0.06)	0.22	−0.09 (−0.29 to 0.11)	0.39
Triglycerides				
Unadjusted	−0.59 (−1.73 to −0.45)	<0.0001	−0.51 (−0.71 to −0.30)	<0.0001
Metabolic model	−0.21 (−0.37 to −0.06)	0.006	−0.30 (−0.52 to −0.09)	0.005
Lifestyle model	−0.12 (−0.28 to 0.04)	0.15	−0.17 (−0.39 to 0.05)	0.12
Insulin model	−0.03 (−0.20 to 0.13)	0.69	−0.12 (−0.35 to 0.11)	0.30
HDL cholesterol				
Unadjusted	0.47 (0.33 to 0.61)	<0.0001	0.33 (0.15 to 0.50)	<0.001
Metabolic model	0.21 (0.07 to 0.35)	<0.01	0.19 (0.01 to 0.37)	<0.05
Lifestyle model	0.27 (0.12 to 0.43)	<0.001	0.22 (0.03 to 0.41)	<0.05
Insulin model	0.27 (0.11 to 0.44)	<0.01	0.22 (0.01 to 0.44)	<0.05
Diastolic blood pressure				
Unadjusted	−0.50 (−0.65 to −0.36)	<0.0001	−0.29 (−0.47 to −0.1)	<0.01
Metabolic model	−0.18 (−0.32 to −0.04)	<0.05	−0.12 (−0.31 to 0.07)	0.20
Lifestyle model	−0.21 (−0.36 to −0.06)	<0.01	−0.19 (−0.38 to 0.02)	0.05
Insulin model	−0.15 (−0.31 to 0.01)	0.05	−0.17 (−0.37 to 0.03)	0.10
Physical activity				
Unadjusted	0.41 (3.75 to 4.66)	<0.0001	0.21 (4.68 to 5.87)	0.06
Metabolic model	—	—	—	—
Lifestyle model	0.29 (0.12 to 0.45)	<0.001	0.20 (−0.02 to 0.41)	0.08
Insulin model	0.25 (0.08 to 0.42)	<0.01	0.15 (−0.07 to 0.38)	0.19
Smoking				
Unadjusted	−0.09 (−0.04 to 0.23)	0.18	−0.26 (0.09 to 0.43)	<0.01
Metabolic model	—	—	—	—
Lifestyle model	−0.12 (−0.01 to 0.25)	0.07	−0.24 (0.07 to 0.41)	<0.01
Insulin model	−0.08 (−0.06 to 0.22)	0.26	0.20 (0.02 to 0.38)	<0.05
Saturated fat index*				
Unadjusted	−0.45 (−0.59 to −0.30)	<0.0001	−0.29 (−0.48 to −0.10)	<0.01
Metabolic model	—	—	—	—
Lifestyle model	−0.24 (−0.39 to −0.10)	<0.001	−0.23 (−0.41 to −0.05)	<0.05
Insulin model	−0.21 (−0.36 to −0.06)	<0.01	−0.20 (−0.39 to −0.01)	<0.05
Socioeconomic status				
Unadjusted	−0.30 (−0.49 to −0.11)	<0.01	−0.34 (−0.56 to −0.11)	<0.01
Metabolic model	—	—	—	—
Lifestyle model	−0.22 (0.12 to 0.45)	<0.05	−0.29 (−0.51 to −0.06)	<0.05
Insulin model	−0.32 (−0.50 to −0.13)	<0.001	−0.36 (−0.60 to −0.13)	<0.01

Data are regression coefficients (β, change in *M* per 1 SD change in the predictor), 95% CI, and *P* values. Metabolic model is the regression model including BMI, glucose, diastolic blood pressure, triglycerides, and HDL cholesterol. For the lifestyle model, physical activity, smoking, saturated fat, and socioeconomic status were added to the metabolic model. For the insulin model, baseline fasting insulin was added to the lifestyle model. *Saturated fat index is defined as the 16:1n-7–to–16:0 ratio in serum cholesterol esters.

$P < 0.0001$) and HDL cholesterol (−0.08 [−0.14 to −0.03], $P = 0.004$).

Normal-weight sample
Of the study population, 43% (330 of 770) were overweight or obese at base-line, yielding a subsample of 440 normal-weight men. Despite the lower sample size, the results from multivariate models were similar to those of the study sample (Table 3), with the exception that smoking, but not physical activity, was an in-dependent predictor (lifestyle model, Table 3). BMI, however, remained the strongest independent predictor in all models. In the insulin model, BMI (β = −0.56) (Table 3) was even a stronger pre-dictor than insulin (β = −0.53 [95% CI

−0.74 to −0.33], $P < 0.0001$, $n = 440$) (data not shown in the tables).

CONCLUSIONS — Although insulin resistance is an important disorder, there are no data concerning metabolic longitudinal predictors of insulin sensitivity in which various predictors have been ranked. Furthermore, the independent and additional role of different lifestyle factors has been unclear. This is the first analysis including both metabolic and lifestyle predictors in long-term prediction of insulin sensitivity assessed by a gold standard technique. Several conclusions can be drawn from this study: *1*) multiple factors including metabolic, lifestyle, and socioeconomic factors independently contribute to predict insulin sensitivity, supporting a complex background of insulin resistance; *2*) saturated fat intake and socioeconomic status are independent predictors that seem to be as important as physical activity; *3*) BMI is still the strongest predictor of insulin sensitivity after adjustment for lifestyle factors and HOMA-IR, even in men with normal BMI; and *4*) in fact, BMI was a stronger predictor of clamp-derived insulin sensitivity than either fasting insulin or HOMA-IR in univariate analyses. The present results suggest that predictors of insulin resistance are similar, but not identical, to those reported to predict type 2 diabetes (7), the metabolic syndrome (11), and hyperinsulinemia (12).

There are limited data on the association between lifestyle factors including dietary fat, smoking, and socioeconomic status and insulin sensitivity per se. Interestingly, saturated fat intake, as assessed by the serum 16:1n-7–to–16:0 ratio, was an independent predictor in all models. A high 16:1n-7–to–16:0 ratio in a western diet mirrors a relatively high intake of saturated fat (9). It should, however, be noted that the 16:1n-7–to–16:0 ratio may also be influenced by factors other than diet, i.e., genetic factors and drugs. In line with our finding, a high intake of saturated fat impairs insulin action in intervention studies (13), whereas reduced intake is related to decreased diabetes risk (14), probably by affecting cell membrane function. Our results also fit with a previous cross-sectional substudy of the present 70-year-old men, in whom palmitic acid in skeletal muscle ($n = 39$) and serum ($n = 215$), in particular, was closely associated with insulin sensitivity (8). An independent link between saturated fat (assessed by a 24-h dietary recall)

and fasting insulin levels was previously reported by Marshall et al. (15). Importantly, our results accord with those of primary prevention trials, which indicated that improving multiple lifestyle factors, factors that were independently related to decreased risk of type 2 diabetes (14), including reducing saturated fat and enhancing physical activity improves insulin sensitivity (16,17). These effects were likely to be mediated in part by improving insulin sensitivity (17), and lifestyle changes had beneficial long-term effects (18), in line with the present observational data. In the present study, it would have been valuable to have data on other dietary factors such as alcohol, coffee, or fiber intake. Another novel finding was the fact that socioeconomic status predicted insulin sensitivity independently of lifestyle factors that have been closely related to socioeconomic status.

BMI was the strongest predictor, explaining the majority of the variation in insulin sensitivity 20 years later. This finding fits well with previous weight loss studies (19), and in the Finnish Diabetes prevention study, there was a strong correlation between the 4-year changes in insulin sensitivity and weight (17). The strong predictive effect of BMI also accords with previous cross-sectional observational studies reporting a close link between insulin resistance and overweight (2,3,20,21), dyslipidemia (2,4,5), and hypertension (6). However, in general, these studies have not compared different predictors using multivariate analyses.

Interestingly, BMI was a better marker for insulin sensitivity than either insulin or HOMA-IR (Table 2). To our knowledge this is the first time this finding has been described. Thus, BMI is an excellent noninvasive marker that may even be preferable to HOMA-IR and insulin, which are commonly used as surrogate markers of insulin resistance. BMI alone explained 18% of the variation in insulin sensitivity 20 years later, a result not far from the 22–25% found cross-sectionally (3,21). Other metabolic factors explained another 2%, and adding lifestyle factors explained an additional 4%. A fully adjusted model including insulin explained 31% of the variation in insulin sensitivity, suggesting that other genetic and/or nongenetic factors are also involved. If Δ BMI (the change of BMI during follow-up) was substituted for baseline BMI, the R^2 value increased to 42%.

When the data are interpreted, it should be remembered that BMI may have a higher precision than other metabolic and lifestyle factors, thus explaining the stronger association with BMI. However, reproducibility data from this cohort indicated that although BMI had a higher intraclass correlation coefficient than, for example, diastolic blood pressure and HDL cholesterol, it was virtually the same as that for triglycerides and glucose.

Despite the fact that physical activity is a powerful predictor of insulin sensitivity, the predictive capacity of BMI persisted after adjustment for lifestyle factors including physical activity, possibly supporting a role of adiposity per se as shown previously (19). Notably, even in normal-weight men, BMI was the strongest predictor, implying that even modest excess body fat within the normal-weight range might deteriorate insulin sensitivity.

Both triglycerides and HDL cholesterol closely correlate with insulin resistance (22). In our prospective analyses, they were strong predictors independent of each other. The strong correlation with triglycerides, also described cross-sectionally (2), however, disappeared after adjustment for saturated fat in particular. In contrast, HDL cholesterol remained a predictor in all models.

There are several limitations of this study. First, the lack of clamp measurements at baseline limits the interpretation regarding the direction of the effects. To address this limitation, we adjusted for insulin concentrations (reflecting subclinical insulin resistance at baseline), which did not alter the results. We also excluded subjects in the highest quartile of HOMA-IR to obtain an "insulin-sensitive" sample at baseline. In this analysis, the results remained the same. Nevertheless, HOMA-IR is only a surrogate marker of insulin sensitivity, and it would have been optimal to have clamp data at baseline and follow-up, which are not available in any cohort we are aware of. It is thus possible that associations between predictors at baseline and insulin sensitivity at follow-up might be a result of cross-sectional associations at baseline that are due to tracking of insulin resistance over time. There is a risk of survival bias, as the men with the most insulin resistance might have died during the follow-up. Such bias would, however, decrease the chance of finding associations. We did not have data on lean body mass, and, therefore, we adjusted the clamp glu-

cose infusion rate for body weight, which might have overestimated insulin resistance (3), nor did we have measurements of abdominal obesity, which would have relevant. The ranking among predictors may not have been affected, however. Unfortunately, we did not have waist measurements for all men. Cross-sectional data suggest, however, that waist and BMI are equally good predictors of insulin sensitivity (3,20). It should be noted that in this 50-year-old Swedish population, the mean BMI at baseline was 24.7 kg/m^2, which may be lower than that in many other countries. On the other hand, one should remember that BMI was assessed >35 years ago, before the pronounced increase in the prevalence of obesity seen worldwide during the last few decades. It would also have been interesting to study other age-groups, especially younger subjects, to investigate further early predictors of insulin resistance. Finally, we only studied Caucasian middle-aged men, lacking data for women and other ethnic groups. The strengths of the study include the large sample of clamp measurements, the longitudinal design, assessments of insulin sensitivity, and availability of data for several lifestyle factors.

In summary, this large study investigating long-term predictors of insulin sensitivity per se demonstrated that multiple factors contribute independently from each other. Our findings accord with and partly confirm previous data on predictors of type 2 diabetes and the metabolic syndrome. Lifestyle factors including a high proportion of saturated fat in the diet, low physical activity, and socioeconomic status all contribute to the variation in insulin sensitivity, but adiposity is the most important single factor, even in individuals with "normal" BMI.

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