# Relation of Direct and Surrogate Measures of Insulin Resistance to Cardiovascular Risk Factors in Nondiabetic Finnish Offspring of Type 2 Diabetic Individuals

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**Context:** Methods to directly measure insulin resistance are invasive, complex, and costly. Surrogate indexes derived from the oral glucose tolerance test (OGTT) have been developed, but few studies have systematically analyzed these indexes.

**Objective:** We examined the relation of surrogate and direct measures of insulin resistance to metabolic variables.

**Design and Setting:** We conducted a cross-sectional analysis of the validation cohort of the Metabolic Syndrome in Men study.

**Participants:** Participants included 272 nondiabetic Finnish offspring of type 2 diabetic individuals (age, 24–50 yr; 55% female).

**Intervention:** Surrogate indexes of insulin resistance were computed according to published formulas. Insulin sensitivity was also directly measured by the euglycemic-hyperinsulinemic clamp.

**Results:** The strength of the correlation of the Matsuda index with directly measured insulin sensitivity ($r = 0.77$) was similar to that of Avignon's insulin sensitivity index ($r = 0.76$; $P = 0.581$) and simple index assessing insulin sensitivity using OGTT measurements ($r = 0.74$; $P = 0.060$) and stronger than that of indexes derived from fasting measurements [*e.g.* fasting insulin ($r = 0.72$; $P = 0.011$) and homeostasis model assessment of insulin resistance ($r = 0.71$; $P = 0.001$)]. Surrogate indexes were similar to directly measured insulin sensitivity in their relationships with metabolic abnormalities including definitive measures of fat distribution. Some indexes, however, had distinctive correlations: McAuley index with lipoproteins and Avignon insulin sensitivity and Stumvoll indexes with adiposity and fibrinogen.

**Conclusions:** Surrogate indexes are valid measures of insulin resistance. Multiple sampling times during an OGTT may not be mandatory to adequately estimate insulin resistance in clinical and epidemiological studies. **(*J Clin Endocrinol Metab* 95: 5082–5090, 2010)**

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Abbreviations: AUC, Area under the receiver operating characteristic curve; BMI, body mass index; HOMA IR, homeostasis model assessment of insulin resistance; IFG, impaired fasting glucose; IGR, insulin-to-glucose ratio; IGT, impaired glucose tolerance; ISI, insulin sensitivity index; $ISI(gly)_{area}$, ISI using areas under the glucose and insulin curves; $MCR_{OGTT}$, Stumvoll's metabolic clearance rate of glucose using OGTT measurements; $ISI_{OGTT}$, Stumvoll's ISI using OGTT measurements; $M_{LBM}/I$, whole-body glucose uptake expressed as steady-state glucose disposal per kilogram lean body mass divided by steady state insulin concentrations; OGTT, oral glucose tolerance test; QUICKI, quantitative insulin sensitivity check index; $SI_{IS}OGTT$, simple index assessing insulin sensitivity using OGTT measurements; Avignon's SiM, Avignon's insulin sensitivity index.

Insulin resistance is an important risk factor for cardiovascular disease and diabetes and a key determinant of clustering of cardiovascular risk factors (1–3). Methods to directly measure insulin resistance are invasive, complex, and costly. Therefore, surrogate indexes have been developed using insulin and/or glucose levels in the fasted state alone (4–12) or in combination with insulin and glucose levels at various oral glucose tolerance test (OGTT) sampling times as well as with other metabolic variables (4, 8, 9, 13–19). Few studies, however, have systematically compared these indexes using as reference a direct measure of insulin resistance (2, 8). Thus, this study had a 2-fold objective: 1) to compare surrogate indexes with the gold standard, directly measured insulin sensitivity by the euglycemic-hyperinsulinemic clamp, and 2) to examine the relationship of surrogate and direct measures of insulin resistance with cardiovascular risk factors.

## Subjects and Methods

A total of 348 Finnish offspring of type 2 diabetic individuals aged 25–50 yr living in Kuopio, Finland, were enrolled in the validation study cohort of the Metabolic Syndrome in Men study (20). The validation study was designed to compare OGTT-derived indexes of insulin secretion and insulin sensitivity with parameters measured by the iv glucose tolerance test and euglycemic-hyperinsulinemic clamp. Validated OGTT-derived indexes were used in the analysis of Metabolic Syndrome in Men study data, an ongoing population-based cross-sectional study among men aged 45–70 yr randomly selected from the population register of the town of Kuopio in Eastern Finland (20). The study was approved by the ethics committee of the University of Kuopio and Kuopio University Hospital and was in accordance with the Helsinki Declaration. Study methods have been described elsewhere (20). Briefly, an OGTT (75 g glucose) was administered, and venous blood samples were drawn at 0, 30, 60, 90, and 120 min. We used the trapezoidal method to calculate the area under the glucose and insulin curves. Definitive measures of fat distribution were obtained by computed tomography (Siemens Volume Zoom, Forchheim, Germany) at the level of the fourth lumbar vertebra (21). Subcutaneous and intraabdominal fat areas were calculated as previously described (22).

We assessed glucose tolerance status using the 2003 American Diabetes Association criteria. Diabetes was defined as fasting plasma glucose concentration of at least 7.0 mmol/liter and/or 2-h plasma glucose concentration of at least 11.1 mmol/liter, impaired fasting glucose (IFG) as fasting glucose concentration of 5.6 to less than 7.0 mmol/liter, and impaired glucose tolerance (IGT) as 2-h glucose concentration of 7.8 to less than 11.1 mmol/liter (23). Individuals treated with glucose-lowering medications were considered to have diabetes. The 10-yr risk of coronary heart disease was estimated by Framingham risk equations (24). The metabolic syndrome was defined according to the 2005 American Heart Association/National Heart, Lung, and Blood Institute Scientific Statement (25).

In 287 nondiabetic participants, insulin sensitivity was directly measured by euglycemic-hyperinsulinemic clamp for 120 min. Using clamp data from the last 60 min, whole-body glucose uptake was expressed as steady-state glucose disposal per kilogram lean body mass divided by steady-state insulin concentrations ($M_{LBM}/I$). Relevant information was missing in 15 participants. Therefore, this study presents information on 272 nondiabetic individuals. Surrogate indexes of insulin sensitivity were calculated according to published formulas (Table 1 and Supplemental Material, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org) (4–19).

### Statistical analysis

Statistical analyses were performed using SAS statistical software (version 9.1; SAS Institute Inc., Cary, NC). Continuous and dichotomous variables were compared using one-way analysis of covariance and logistic regression analysis, respectively. Spearman correlation coefficients were used to analyze the strength of

**TABLE 1.** Formulas for surrogate indexes of insulin resistance

| | Formula |
|---|---|
| Based on fasting measurements | |
| Fasting glucose | $G_0$ |
| Fasting insulin (4) | $I_0$ |
| Raynaud (5) | $40/I_0$ |
| HOMA IR (6) | $(I_0 \times G_0)/22.5$ |
| FIRI (7) | $(I_0 \times G_0)/25$ |
| IGR (8) | $I_0/G_0$ |
| $ISI_{basal}$ (9) | $10^4 / (I_0 \times G_0)$ |
| QUICKI (10) | $1/[\log I_0 + \log G_0]$ |
| Bennett's $S_I$ (11) | $1/(\log I_0 \times \log G_0)$ |
| Belfiore's $ISI(gly)_{basal}$ (12) | $2/[(I_{0/N} \times G_{0/N}) + 1]$ |
| McAuley (13) | $e^x$, where $x = 2.63 - 0.28 \ln(I_0) - 0.31 \ln(Tg_0)$ |
| Based on OGTT measurements | |
| 2-h glucose | $G_{120}$ |
| 2-h insulin (4) | $I_{120}$ |
| $IGR_{2h}$ (8) | $I_{120}/G_{120}$ |
| $ISI_{2h}$ (9) | $10^4/(I_{120} \times G_{120})$ |
| Gutt's $ISI_{0,120}$ (14) | $(m/[(G_0 + G_{120})/2])/\log[(I_0 + I_{120})/2]$[a] |
| Avignon's SiM (15) | $[(w \times Sib) + Si2h]/2$[b] |
| $Stumvoll_{(0,120)}$ (16) | $0.156 - 0.0000459 \times I_{120} - 0.000321 \times I_0 - 0.00541 \times G_{120}$ |
| Stumvoll with demographics (16) | $0.222 - 0.00333 \times BMI - 0.0000779 \times I_{120} - 0.000422 \times age$ |
| Stumvoll $MCR_{OGTT}$ (17) | $18.8 - 0.271 \times BMI - 0.0052 \times I_{120} - 0.27 \times G_{90}$ |
| Stumvoll $ISI_{OGTT}$ (17) | $0.226 - 0.0032 \times BMI - 0.0000645 \times I_{120} - 0.00375 \times G_{90}$ |
| Belfiore's $ISI(gly)_{area}$ (12) | $2/[(I_a \text{ mean } I_a \times G_a/\text{mean } G_a) + 1]$[c] |
| $SI_{IS}OGTT$ (18) | $1/[\log(G_0 + G_{30} + G_{90} + G_{120}) + \log(I_0 + I_{30} + I_{90} + I_{120})]$ |
| Matsuda (19) | $10^4/(G_0 \times I_0 \times \text{mean } G_{OGTT} \times \text{mean } I_{OGTT})^{0.5}$ |

FIRI, Fasting insulin resistance index; $ISI(gly)_{basal}$, ISI using fasting values of glucose and insulin; Si2h, insulin sensitivity index derived from insulin and glucose concentrations at the second hour of an OGTT; Sib, insulin sensitivity index derived from insulin and glucose concentrations in the basal state; VD, glucose distribution volume (monocompartment model).

[a] m = (75,000 mg + (fasting glucose − 2-h glucose) × 0.19 × body weight)/120 min (glucose in mg/dl; insulin in μIU/ml).

[b] w = mean Si2h / mean Sib, Sib = $10^8$ / (fasting insulin (μIU/ml) × fasting glucose (mg/dl) × VD), Si2 h = $10^8$ / (2-h insulin (μIU/ml) × 2-h glucose (mg/dl) × VD), where VD = 150 ml/kg body weight.

[c] $G_a$, Area under the glucose curve; $I_a$, area under the insulin curve.

**TABLE 2.** Age-adjusted characteristics by sex

| | Men | Women | *P* value |
|---|---|---|---|
| n | 127 | 145 | |
| Age (yr)[a] | 35.5 ± 0.6 | 35.2 ± 0.5 | 0.704 |
| BMI (kg/m$^2$) | 26.5 ± 0.4 | 25.9 ± 0.4 | 0.305 |
| Waist circumference (cm) | 94.2 ± 1.1 | 84.0 ± 1.0 | <0.001 |
| Subcutaneous fat (cm$^2$) | 211.3 ± 11.1 | 281.9 ± 10.7 | <0.001 |
| Intraabdominal fat (cm$^2$) | 117.6 ± 4.9 | 82.6 ± 4.8 | <0.001 |
| Lean body mass (kg) | 64.9 ± 0.6 | 46.7 ± 0.6 | <0.001 |
| Systolic blood pressure (mm Hg) | 131.4 ± 1.1 | 123.2 ± 1.0 | <0.001 |
| Diastolic blood pressure (mm Hg) | 85.7 ± 0.8 | 80.8 ± 0.8 | <0.001 |
| Total cholesterol (mmol/liter) | 5.12 ± 0.08 | 4.74 ± 0.07 | <0.001 |
| LDL cholesterol (mmol/liter) | 3.38 ± 0.07 | 2.91 ± 0.07 | <0.001 |
| HDL cholesterol (mmol/liter) | 1.14 ± 0.02 | 1.39 ± 0.02 | <0.001 |
| Triglycerides (mmol/liter)[b] | 1.25 ± 0.06 | 0.93 ± 0.04 | <0.001 |
| Fasting glucose (mmol/liter) | 5.41 ± 0.03 | 5.02 ± 0.03 | <0.001 |
| 2-h glucose (mmol/liter) | 6.12 ± 0.12 | 6.27 ± 0.11 | 0.353 |
| Fasting insulin (pmol/liter)[b] | 51.4 ± 2.1 | 49.9 ± 2.0 | 0.533 |
| 2-h insulin (pmol/liter)[b] | 196.4 ± 12.1 | 237.5 ± 14.7 | 0.018 |
| HOMA IR | 2.31 ± 0.10 | 2.08 ± 0.10 | 0.100 |
| Matsuda index | 5.26 ± 0.24 | 5.91 ± 0.22 | 0.047 |
| $M_{LBM}$/I ($\mu$mol/kg · min · mU/liter) | 0.78 ± 0.03 | 0.87 ± 0.7 | 0.056 |
| C-reactive protein ($\mu$g/ml)[b] | 1.15 ± 0.17 | 1.13 ± 0.16 | 0.929 |
| Fibrinogen (mg/ml) | 3.02 ± 0.06 | 3.23 ± 0.06 | 0.014 |
| Adiponectin ($\mu$g/ml) | 7.8 ± 0.4 | 10.7 ± 0.4 | <0.001 |
| Metabolic syndrome (%) | 18.7 (13.1–25.9) | 27.3 (20.3–35.8) | 0.091 |
| Framingham score (%)[c] | 5.15 (4.93–5.42) | 0.87 (0.83–0.92) | <0.001 |

Data are shown as n, mean ± SE, and percentage and 95% confidence interval. HDL, High-density lipoprotein; LDL, low-density lipoprotein.

[a] Unadjusted results.

[b] Log-transformed variables. These variables were then back-transformed to their units for presentation in the table.

[c] Logit transformation of Framingham risk estimates and then back-transformed.

the relationship between indices of insulin resistance. Correlation coefficients were compared by the T2 method (26). The ability of each index to detect individuals with the metabolic syndrome or $M_{LBM}$/I-defined insulin resistance was assessed by the area under the receiver operating characteristic curve (AUC). Statistical differences between AUC were determined by the method developed by DeLong *et al.* (27). The impact of sex, body mass index (BMI), and glucose tolerance status on the relation of $M_{LBM}$/I, Matsuda index, and homeostasis model assessment of insulin resistance (HOMA IR) to selected metabolic variables was assessed by linear regression analysis.

## Results

Men had more central adiposity and dyslipidemia than women (Table 2). Men also had higher Matsuda index, fasting glucose concentration, blood pressure, and Framingham risk score. Conversely, women had more sc fat and higher levels of 2-h insulin, adiponectin, and fibrinogen. No significant differences according to sex were observed for age, BMI, fasting insulin, 2-h glucose, C-reactive protein, $M_{LBM}$/I, and prevalent metabolic syndrome.

### Correlations of surrogate indexes of insulin resistance with $M_{LBM}$/I

Indices derived from fasting values had strong correlations with $M_{LBM}$/I across sex, glucose tolerance, and BMI categories (Table 3). Matsuda index had a stronger correlation with $M_{LBM}$/I than did the other indexes except for simple index assessing insulin sensitivity using OGTT measurements ($SI_{IS}$OGTT) and Avignon's insulin sensitivity index (Avignon's SiM).

### Ability of indexes to detect individuals with metabolic syndrome or low $M_{LBM}$/I

The AUC of McAuley, Avignon's SiM, Stumvoll's metabolic clearance rate of glucose using OGTT measurements ($MCR_{OGTT}$), and Stumvoll's insulin sensitivity index using OGTT measurements ($ISI_{OGTT}$) for identifying individuals with the metabolic syndrome were greater than the AUC of $M_{LBM}$/I (Table 4). The AUC of the other indexes were comparable to that of $M_{LBM}$/I except for the 2-h insulin-to-glucose ratio ($IGR_{2h}$). Most surrogate indexes (excluding fasting and 2-h glucose, $IGR_{2h}$, and $ISI_{2h}$) were similar to Matsuda index in their ability to detect subjects in the lower $M_{LBM}$/I quartile.

### Relation of measures of obesity and fasting and 2-h insulin and glucose levels to $M_{LBM}$/I

Directly measured intraabdominal fat was no more strongly correlated with $M_{LBM}$/I than was waist circumference (r = −0.49 *vs.* −0.51; $P = 0.607$) and BMI (r =

**TABLE 3.** Spearman correlation coefficients relating surrogate indexes of insulin resistance to $M_{LBM}/I$

| Surrogate indexes | All | Men | Women | Normal glucose tolerance status | IFG and/or IGT | BMI <30 kg/m² | BMI ≥30 kg/m² |
|---|---|---|---|---|---|---|---|
| Based on fasting measurements | | | | | | | |
| Fasting glucose | −0.32[c] | −0.33[c] | −0.29[c] | −0.24[c] | −0.18[c] | −0.28[c] | −0.39[b] |
| Fasting insulin | −0.72[a] | −0.70[a] | −0.73 | −0.68 | −0.74 | −0.62[a] | −0.68[b] |
| Raynaud | 0.72[a] | 0.70[a] | 0.73 | 0.68 | 0.74 | 0.62[a] | 0.68[b] |
| HOMA IR | −0.71[b] | −0.70[a] | −0.71[a] | −0.66[a] | −0.72[b] | −0.61[b] | −0.69[b] |
| FIRI | −0.71[b] | −0.70[a] | −0.71[a] | −0.66[a] | −0.72[b] | −0.61[b] | −0.69[b] |
| IGR | −0.70[b] | −0.69[a] | −0.74 | −0.67 | −0.73[a] | −0.60[b] | −0.64[c] |
| $ISI_{basal}$ | 0.71[b] | 0.70[a] | 0.71[a] | 0.66[a] | 0.72[b] | 0.61[b] | 0.69[b] |
| QUICKI | 0.71[b] | 0.70[a] | 0.71[a] | 0.66[a] | 0.72[b] | 0.61[b] | 0.69[b] |
| Bennett's $S_I$ | 0.71[b] | 0.70[a] | 0.72 | 0.67 | 0.73[a] | 0.62[a] | 0.70[b] |
| Belfiore's $ISI(gly)_{basal}$ | 0.71[b] | 0.70[a] | 0.71[a] | 0.66[a] | 0.72[b] | 0.61[b] | 0.69[b] |
| McAuley | 0.67[c] | 0.57[c] | 0.73 | 0.62[b] | 0.67[b] | 0.59[c] | 0.62[b] |
| Based on OGTT measurements | | | | | | | |
| 2-h glucose | −0.37[c] | −0.46[c] | −0.29[c] | −0.25[c] | −0.26[c] | −0.25[c] | −0.39[c] |
| 2-h insulin | −0.66[c] | −0.65[b] | −0.72 | −0.60[b] | −0.65[b] | −0.59[b] | −0.64[a] |
| $IGR_{2h}$ | −0.65[c] | −0.63[b] | −0.72 | −0.61[b] | −0.67[a] | −0.59[b] | −0.63[a] |
| $ISI_{2h}$ | 0.64[c] | 0.65[b] | 0.68[a] | 0.57[c] | 0.60[b] | 0.56[c] | 0.57[b] |
| Gutt's $ISI_{0,120}$ | 0.66[c] | 0.66[b] | 0.66[b] | 0.58[c] | 0.60[b] | 0.56[c] | 0.61[b] |
| Avignon's SiM | 0.76 | 0.73 | 0.75 | 0.69 | 0.80 | 0.68 | 0.70[b] |
| $Stumvoll_{(0,120)}$ | 0.69[c] | 0.71 | 0.68[b] | 0.61[c] | 0.70[a] | 0.59[b] | 0.67[b] |
| Stumvoll with demographics | 0.65[c] | 0.66[a] | 0.64[b] | 0.55[c] | 0.78 | 0.57[b] | 0.60[b] |
| Stumvoll $MCR_{OGTT}$ | 0.65[c] | 0.65[b] | 0.62[b] | 0.53[c] | 0.75 | 0.56[b] | 0.61[b] |
| Stumvoll $ISI_{OGTT}$ | 0.65[c] | 0.65[b] | 0.62[b] | 0.53[c] | 0.74 | 0.56[b] | 0.61[b] |
| Belfiore's $ISI(gly)_{area}$ | 0.73[b] | 0.75 | 0.70[c] | 0.67[a] | 0.74[a] | 0.64[b] | 0.79 |
| $SI_{IS}OGTT$ | 0.74 | 0.76 | 0.72[a] | 0.69 | 0.74 | 0.66 | 0.73[a] |
| Matsuda | 0.77 | 0.77 | 0.76 | 0.72 | 0.80 | 0.69 | 0.79 |

FIRI, Fasting insulin resistance index; $ISI(gly)_{basal}$, ISI using fasting values of glucose and insulin. *P* values are for the test of difference in the correlation of each surrogate index with $M_{LBM}/I$ relative to that of Matsuda index with $M_{LBM}/I$.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

**TABLE 4.** AUC of indexes of insulin resistance for detecting subjects with the metabolic syndrome or $M_{LBM}/I$ in the lower quartile

| | Metabolic syndrome | $M_{LBM}/I$ lower quartile |
|---|---|---|
| $M_{LBM}/I$ | 0.802 | |
| Indexes based on fasting values | | |
| Fasting glucose | 0.740[d] | 0.644[f] |
| Fasting insulin | 0.820 | 0.875 |
| Raynaud | 0.820 | 0.876 |
| HOMA IR | 0.835 | 0.869 |
| FIRI | 0.835 | 0.869 |
| IGR | 0.793[d] | 0.875 |
| $ISI_{basal}$ | 0.836 | 0.868 |
| QUICKI | 0.836 | 0.869 |
| Bennett's $S_I$ | 0.829 | 0.873 |
| Belfiore's $ISI(gly)_{basal}$ | 0.835 | 0.869 |
| McAuley | 0.895[c,d] | 0.859 |
| Indexes based on OGTT measurements | | |
| 2-h glucose | 0.762[d] | 0.717[f] |
| 2-h insulin | 0.784[d] | 0.841 |
| $IGR_{2\ h}$ | 0.738[a,f] | 0.829[d] |
| $ISI_{2\ h}$ | 0.801 | 0.835[d] |
| Gutt's $ISI_{0,120}$ | 0.835 | 0.845 |
| Avignon's SiM | 0.869[b,d] | 0.880 |
| Stumvoll (0,120 min) | 0.846 | 0.875 |
| Stumvoll with demographics | 0.834 | 0.850 |
| Stumvoll $MCR_{OGTT}$ | 0.848[a] | 0.853 |
| Stumvoll $ISI_{OGTT}$ | 0.848[a] | 0.853 |
| Belfiore's $ISI(gly)_{area}$ | 0.801 | 0.877 |
| $SI_{IS}$OGTT | 0.818 | 0.876 |
| Matsuda index | 0.839 | 0.891 |

$ISI(gly)_{basal}$, ISI using fasting values of glucose and insulin. *P* values are for test of difference in AUC between indices of insulin resistance.

[a–c] The statistical difference relative to $M_{LBM}/I$: [a] $P < 0.05$; [b] $P < 0.01$; [c] $P < 0.001$.

[d–f] The statistical difference relative to Matsuda index: [d] $P < 0.05$; [e] $P < 0.01$; [f] $P < 0.001$.

$-0.51$; $P = 0.410$) (Table 5). Subcutaneous fat had a weaker correlation with $M_{LBM}/I$ than did BMI ($r = -0.41$ *vs.* $-0.51$; $P = 0.012$). Fasting and 2-h insulin levels were similarly related to $M_{LBM}/I$ ($r = -0.72$ *vs.* $-0.66$; $P = 0.088$), and so were fasting and 2-h glucose levels ($r = -0.32$ *vs.* $-0.37$; $P = 0.487$).

### Surrogate indices as compared with $M_{LBM}/I$ in their relation to metabolic variables

Indexes based on fasting measurements were mostly similar to $M_{LBM}/I$ in their relationships with metabolic variables (Table 5). However, the correlation of McAuley index with lipoproteins and Framingham risk score was particularly strong. In general, fasting-derived indexes had more robust correlations with fasting insulin and glucose concentrations than did $M_{LBM}/I$. Indexes based on OGTT sampling times were also largely similar to $M_{LBM}/I$ but were more strongly related to 2-h insulin and glucose levels. In addition, some OGTT-derived indexes had distinctive correlations relative to those of $M_{LBM}/I$. Matsuda index had more robust relationships with blood pressure and fasting insulin and glucose levels. Indexes with a measure of adiposity in their formula, such as Avignon's SiM, Stumvoll with demographics, and Stumvoll $MCR_{OGTT}$, had stronger correlations with adiposity, blood pressure, fasting insulin concentration, fibrinogen, and Framingham risk score.

There was no interaction effect of sex, glucose tolerance, and BMI on the relation of $M_{LBM}/I$, Matsuda index, and HOMA IR to selected metabolic variables and Framingham risk score (Fig. 1).

## Discussion

In nondiabetic Finnish offspring of type 2 diabetic individuals, indexes derived from either fasting values or OGTT sampling times are valid measures of insulin resistance across sex, glucose tolerance, and BMI categories. However, Matsuda index along with $SI_{IS}$OGTT and Avignon's SiM correlate better with directly measured insulin sensitivity by euglycemic-hyperinsulinemic clamp than do the other surrogate indexes. In addition, the strength by which most surrogate indexes correlate with cardiovascular risk factors is similar to the corresponding correlation of directly measured insulin sensitivity.

Studies that compare surrogate and direct indexes have suggested that surrogate indexes are adequate measures of insulin resistance (4, 8, 18, 19, 28). Nevertheless, few studies have carried out systematic comparisons in large datasets to determine which index is best (2, 8). In a previous analysis of three epidemiological studies, we reported that Avignon's SiM, Belfiore's $ISI(gly)_{area}$, $ISI_{2h}$, and Stumvoll with demographics had the most robust correlations with ISI measured by the frequently sampled iv glucose tolerance test with minimal model analysis, but Gutt's $ISI_{0,120}$ consistently showed the strongest prediction of future diabetes (2). $SI_{IS}$OGTT and Matsuda were not examined because of the OGTT sampling time requirements by their formulas. In the original description of the Matsuda index, Matsuda index was superior to Gutt's $ISI_{0,120}$ and Belfiore's indexes in their correlation with $M_{LBM}/I$ (19). Conversely, Piché *et al.* (29) described stronger correlations for surrogate indexes based on OGTT sampling times and a measure of adiposity (such as Gutt's $ISI_{0,120}$ and Stumvoll's $MCR_{OGTT}$ and $ISI_{OGTT}$) than for indexes derived form fasting measurements alone or lacking a measure of adiposity (such as HOMA IR and Matsuda index). In these last two studies, however, comparisons between indexes were not sustained by statistical analyses. Our present re-

**TABLE 5.** Spearman correlation coefficients relating $M_{LBM}/I$ and selected surrogates indexes of insulin resistance to age, metabolic variables, and Framingham risk

| | $M_{LBM}/I$ | McAuley | Fasting insulin | HOMA IR | QUICKI | Belfiore $ISI(gly)_{basal}$ | Matsuda | Gutt $ISI_{0,120}$ | Avignon SiM | Stumvoll with demo | Stumvoll $MCR_{OGTT}$ | Belfiore $ISI(gly)_{area}$ | $SI_{IS}OGTT$ |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Age | 0.01 | −0.05 | 0.01 | 0.03 | −0.03 | −0.03 | −0.04 | −0.07 | −0.06 | **−0.20**[c] | −0.10 | −0.03 | −0.04 |
| BMI | −0.51 | −0.49 | 0.49 | 0.50 | −0.50 | −0.49 | −0.52 | −0.46 | **−0.67**[c] | **−0.87**[c] | **−0.85**[c] | −0.47 | −0.48 |
| Waist circumference | −0.51 | −0.52 | 0.47 | 0.50 | −0.50 | −0.50 | −0.53 | **−0.42**[a] | **−0.65**[c] | **−0.74**[c] | **−0.74**[c] | −0.48 | −0.48 |
| Subcutaneous fat | −0.41 | −0.32 | 0.42 | 0.38 | −0.38 | −0.38 | −0.41 | −0.43 | **−0.56**[c] | **−0.73**[c] | **−0.70**[c] | −0.37 | −0.41 |
| Intraabdominal fat | −0.49 | −0.52 | 0.45 | 0.48 | −0.48 | −0.48 | −0.53 | −0.47 | **−0.64**[c] | **−0.66**[c] | **−0.64**[c] | −0.48 | −0.48 |
| Systolic blood pressure | −0.23 | −0.32 | 0.28 | 0.31 | −0.31 | −0.31 | **−0.33**[a] | −0.27 | **−0.33**[a] | −0.30 | −0.31 | −0.31 | −0.29 |
| Diastolic blood pressure | −0.24 | **−0.34**[a] | 0.29 | 0.32 | −0.32 | −0.32 | **−0.35**[b] | −0.33 | **−0.38**[c] | **−0.37**[b] | **−0.38**[b] | **−0.33**[a] | −0.32 |
| Total cholesterol | −0.20 | **−0.35**[b] | 0.15 | 0.19 | −0.19 | −0.19 | −0.26 | −0.22 | −0.24 | −0.26 | −0.29 | −0.28 | −0.27 |
| LDL cholesterol | −0.20 | −0.29 | 0.12 | 0.17 | −0.17 | −0.17 | −0.24 | −0.18 | −0.24 | −0.28 | **−0.31**[a] | −0.26 | −0.25 |
| HDL cholesterol | 0.36 | 0.44 | −0.30 | −0.33 | 0.33 | 0.33 | 0.34 | 0.30 | 0.42 | 0.35 | 0.36 | 0.30 | 0.30 |
| Triglycerides | −0.48 | **−0.89**[c] | 0.42 | 0.44 | −0.44 | −0.44 | −0.52 | −0.53 | **−0.55**[a] | −0.48 | −0.50 | −0.52 | −0.52 |
| Fasting glucose | −0.32 | −0.40 | 0.40 | **0.54**[c] | **−0.54**[c] | **−0.54**[c] | **−0.45**[c] | −0.33 | **−0.44**[b] | −0.25 | −0.28 | −0.34 | −0.32 |
| Fasting insulin | −0.72 | −0.77 | **1.00**[c] | **0.98**[c] | **−0.98**[c] | **−0.98**[c] | **−0.88**[c] | −0.66 | **−0.84**[c] | **−0.64**[a] | **−0.60**[b] | −0.70 | −0.73 |
| 2-h glucose | −0.37 | −0.44 | 0.30 | 0.31 | −0.31 | −0.31 | −0.43 | **−0.82**[c] | **−0.59**[c] | **−0.50**[b] | **−0.62**[c] | **−0.49**[b] | **−0.55**[c] |
| 2-h insulin | −0.66 | −0.64 | 0.65 | 0.63 | −0.63 | −0.63 | **−0.80**[c] | **−0.92**[c] | **−0.85**[c] | **−0.77**[b] | **−0.75**[b] | **−0.82**[c] | **−0.89**[c] |
| C-reactive protein | −0.39 | −0.32 | 0.30 | 0.28 | −0.28 | −0.28 | −0.32 | −0.28 | −0.33 | −0.34 | −0.38 | −0.32 | −0.32 |
| Fibrinogen | −0.22 | −0.25 | 0.26 | 0.25 | −0.25 | −0.25 | −0.27 | −0.27 | **−0.32**[a] | **−0.41**[c] | **−0.40**[c] | −0.26 | −0.28 |
| Adiponectin | 0.49 | 0.50 | −0.45 | −0.48 | 0.48 | 0.48 | 0.51 | 0.38 | 0.48 | **0.33**[b] | **0.36**[a] | 0.45 | 0.44 |
| Framingham risk score | −0.21 | **−0.39**[c] | 0.18 | 0.26 | −0.26 | −0.26 | −0.28 | −0.22 | **−0.33**[b] | **−0.34**[b] | **−0.33**[a] | −0.25 | −0.24 |

HDL, High-density lipoprotein; LDL, low-density lipoprotein. *P* values are for the test of difference in the correlation between single metabolic variables and surrogate indexes of insulin resistance relative to the correlation between the same metabolic variable and $M_{LBM}/I$. Values in *bold* represent correlation coefficients relating surrogate indexes to metabolic variables that are statistically different from the corresponding coefficient of $M_{LBM}/L$.

[a] $P < 0.05$.

[b] $P < 0.01$.

[c] $P < 0.001$.

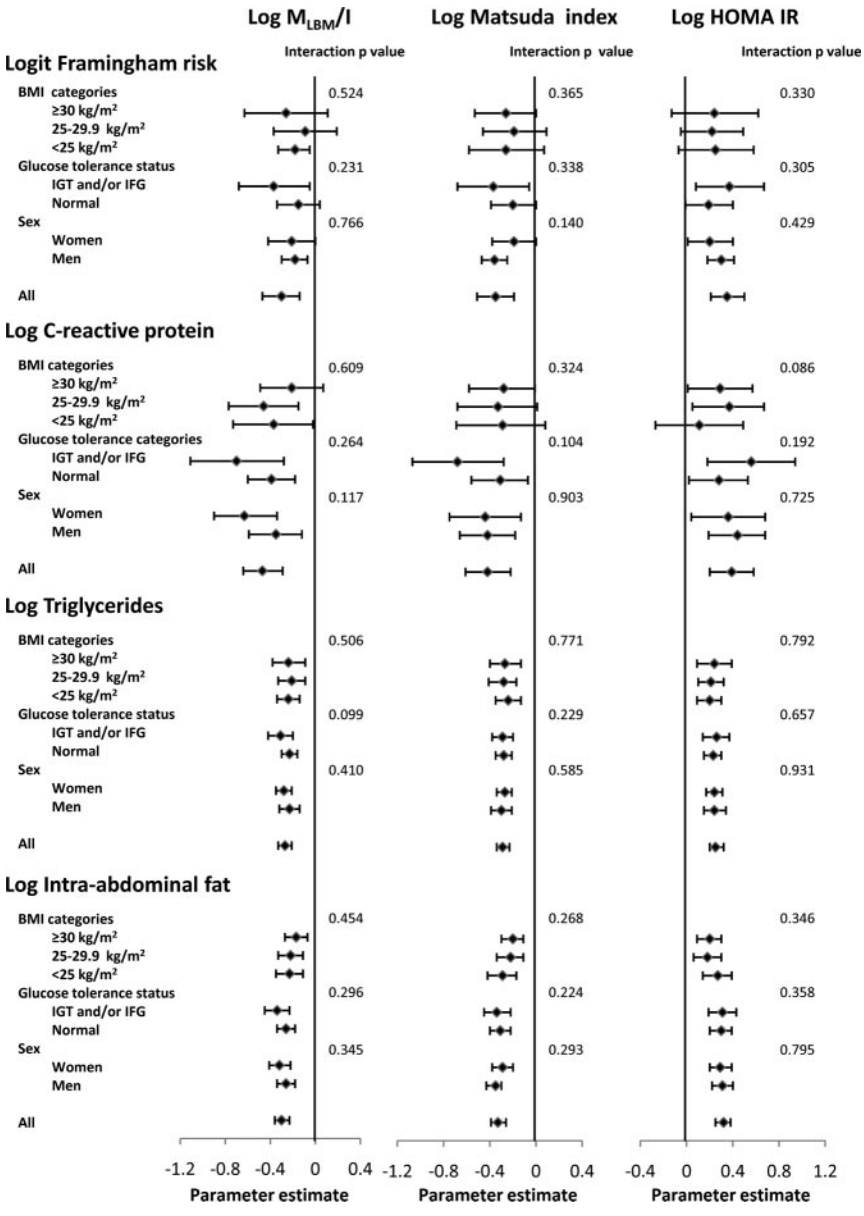


**FIG. 1.** Heterogeneity analysis on the relation of $M_{LBM}$/I, Matsuda index, and HOMA IR to selected metabolic variables and Framingham risk score. Estimates are expressed for a 1 SD unit change. Interaction *P* value is for the effect of sex, glucose tolerance, and BMI categories on the relation of $M_{LBM}$/I, Matsuda index, and HOMA IR to selected metabolic variables and Framingham risk score.

sults indicate that Matsuda, $SI_{IS}$OGTT, and Avignon's SiM are the strongest correlates of directly measured insulin sensitivity by euglycemic-hyperinsulinemic clamp.

Although inferior to the Matsuda index, all indexes have strong correlations with directly measured insulin sensitivity. Earlier studies differ on the optimal surrogate index of insulin resistance (2, 18, 19, 29). Reasons for the discrepancies may be multiple: inadequate suppression of endogenous glucose production of the liver by some euglycemic-hyperinsulinemic clamp protocols or other methods to directly measure insulin resistance, characteristics of the study population particularly glucose tolerance abnormalities and obesity, sample size, and selection of surrogate indexes. Despite the disagreement, consensus exists on the validity of surrogate indexes as adequate measures of insulin resistance for clinical and epidemiological studies (2, 4, 8, 18, 19, 28). Furthermore, indexes derived from fasting measurements including fasting insulin concentration and HOMA IR display robust correlations with directly measured insulin sensitivity (4, 18, 28).

Most surrogate indexes are comparable to $M_{LBM}$/I in their relationship with cardiovascular risk factors, Framingham risk score, and prevalent metabolic syndrome. Malita *et al.* (28) reported similar results examining simple indexes [fasting insulin, quantitative insulin sensitivity check index (QUICKI), and HOMA IR] and glucose uptake measured by euglycemic-hyperinsulinemic clamp. In our study, several indexes display some distinctive correlations with cardiovascular risk factors. These correlations may reflect the use of particular metabolic variables in the formulas. Triglyceride concentration explains the stronger relationship of McAuley index with lipoproteins and metabolic syndrome. Adiposity accounts for the stronger relationship of Avignon's SiM and Stumvoll indexes with adiposity, blood pressure, Framingham risk score, and metabolic syndrome. On the other hand, Gutt's $ISI_{0,120}$, which also includes a measure of adiposity in its formula, has a pattern of associations largely similar to that of $M_{LBM}$/I. Consequently, some indexes may signal not only insulin resistance but also other important domains for diabetes and cardiovascular disease such as β-cell dysfunction, hepatic glucose production, dyslipidemia, and adiposity (2). Whether this is relevant for predicting future cardiovascular disease is not known, but it appears not essential for predicting conversion to diabetes. In our previous report, Gutt's $ISI_{0,120}$, Belfiore's $ISI(gly)_{area}$, Avignon's SiM, and QUICKI had the best overall ability to predict the development of diabetes (2).

Limitations of the present study include analysis of a Caucasian study sample (lean, relatively young nondiabetic offspring of type 2 diabetic individuals), which limits

applicability to other groups of individuals. Many of these groups differ in terms of diabetic and cardiovascular risks as well as sociodemographic, lifestyle, anthropometric, and metabolic characteristics. Therefore, additional studies are needed to validate our findings particularly in high-risk populations such as South Asians, Hispanics, and Blacks. Another significant limitation is the lack of prospective data, which precludes any speculation about cause and temporal relationships.

In summary, surrogate indexes are valid measures of insulin resistance, although Matsuda index, $SI_{IS}OGTT$, and Avignon's SiM display the strongest correlations with directly measured insulin sensitivity. Thus, multiple sampling times during an OGTT may not be mandatory to adequately estimate insulin resistance in clinical and epidemiological studies. Similarly, most surrogate indexes including those derived from fasting measurements are comparable to directly measured insulin sensitivity in their relation to cardiovascular risk factors and definitive measures of fat distribution. Further studies are needed to compare surrogate and direct indexes in their ability to predict diabetes and cardiovascular disease.

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