Insulin Resistance
- Simple Index -

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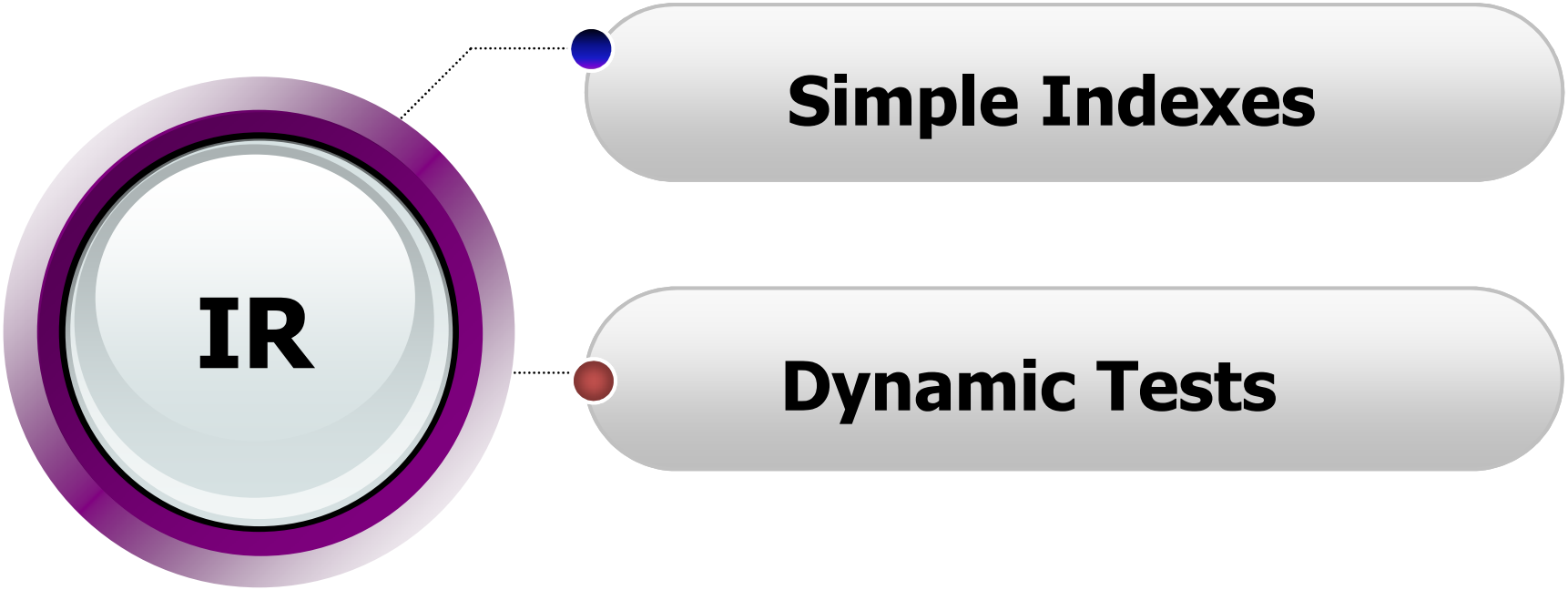
Consider

whether the IR index is

the primary endpoint or

secondary interest.

Methods of assessing IR



- Hyperinsulinemic euglycemic clamp test
- Frequently sampled intravenous glucose tolerance test

General considerations for choosing the appropriate technique

- Reference techniques

  - Hyperinsulinemic Euglycemic Clamp (HEC): gold standard

  - Frequently sampled intravenous glucose tolerance (FSIVGTT): silver

- Number of subjects

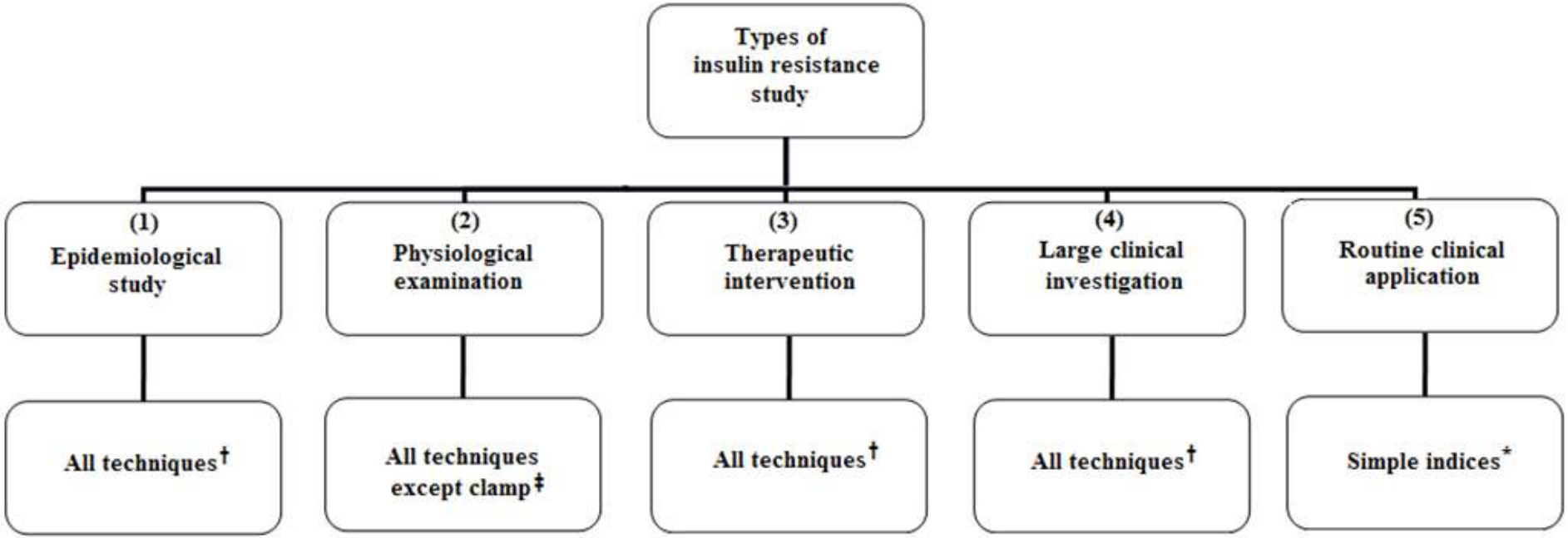
  - reference techniques: generally unsuitable for epidemiological studies involving large numbers of subjects.

- Glycemic status of subjects

  - subjects with diabetes: HEC or insulin-modified FSIVGTT

- Budget, Materials and Equipment

Different types of insulin resistance studies



†The priority is for the clamp technique followed by the alternative technique of FSIVGTT then simple indices.
‡The clamp technique which utilises supraphysiological insulin levels at steady state does not accurately estimate the natural conditions of insulin and glucose dynamics.
*It is not possible to apply the three hours technique of clamp or its alternative FSIVGTT in a routine clinical trial.

Indexes of Insulin Resistance

- Studies in which simple indexes of insulin resistance may be used

  - Large clinical practice and epidemiological investigations
  - Where the assessment of direct IR is not required
  - Where the outcome of IR is of secondary interest
  - Where the requirement of reference techniques are not available (e.g. equipment, trained staff, enough budget)
  - Where a new simple index is under evaluation
  - Investigating validity and pitfalls of simple indices in specific clinical conditions

Simple Surrogate Indexes

Fasting sample derived

- Most commonly used indexes
- Simple, cost-effective
- Assess hepatic IR more than peripheral insulin sensitivity
- Reliable : subjects with sufficient insulin secretion
- Unreliable: elderly, uncontrolled diabetes or type 1 diabetes

OGTT derived

- Correlate with the clamp study
- Validated in different populations
- Evaluate several parameters
- Potentially be confounded by physiological factors
  - Rate of glucose absorption
  - Endogenous insulin secretion in response to glucose and incretins

Indexes derived from fasting values

Index	Formula
HOMA-IR	$(I_0 \text{ X } G_0)/22.5$
QUICKI	$1/[\log I_0 + \log G_0]$
Raynaud	$40/ I_0$
IGR	I_0/ G_0
ISI_{basal}	$10^4/ (I_0 \text{ X } G_0)$
Bennett's	$1/(\log I_0 \times \log G_0)$

Indexes derived from OGTT

Index	Formula
Matsuda	$10^4/(G_0 x\ I_0 x \text{ mean } G_{OGTT} \text{ x mean } I_{OGTT})^{0.5}$
$\text{Stumvoll}_{(0,120)}$	$0.156 - 0.0000459\times I_{120} - 0.000321\times I_0 - 0.00541\times G_{120}$
Stumvoll with demographics	$0.222 - 0.00333\times \text{BMI} - 0.0000779\times I_{120} - 0.000422\times \text{age}$
Stumvoll MCR_{OGTT}	$18.8 - 0.271\times \text{BMI} - 0.0052\times I_{120} - 0.27\times G_{90}$
Stumvoll ISI_{OGTT}	$0.226 - 0.0032\times \text{BMI} - 0.0000645\times I_{120} - 0.00375\times G_{90}$
IGR_{2h}	I_{120}/G_{120}
ISI_{2h}	$10^4/(I_{120} \times G_{120})$
$\text{SI}_{is}\text{OGTT}$	$1/[\log(G_0 + G_{30} + G_{90} + G_{120}) + \log(I_0 + I_{30} + I_{90} + I_{120})]$

Who is being assessed?

- General population
- High risk group
- Diabetics
- Other specific population

General Population

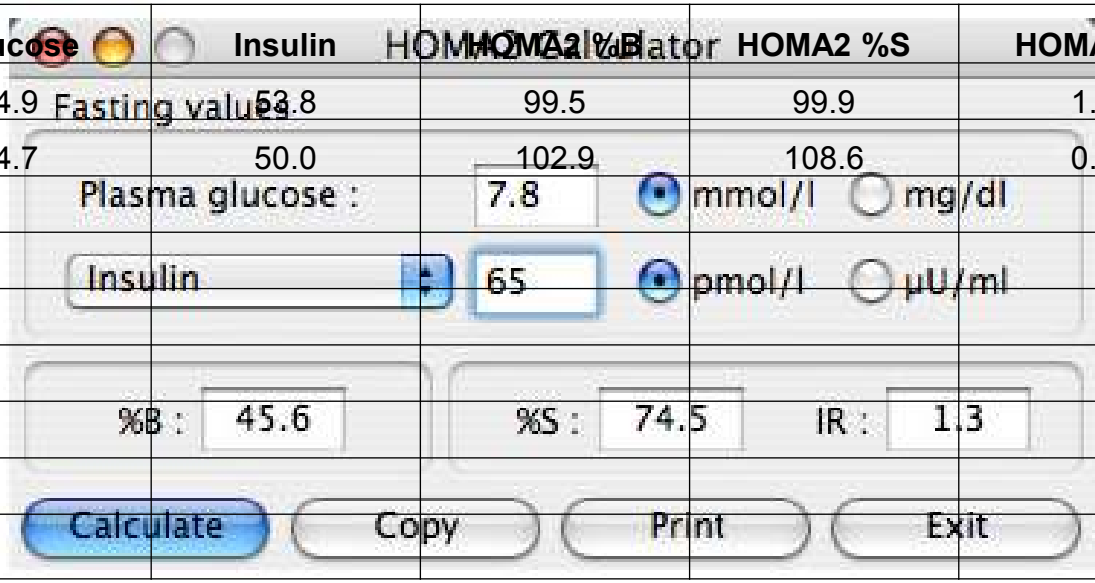
HOMA index

- HOMA: useful in large epidemiological studies by demonstrating good correlations with clamp results in several populations.

- HOMA2 on the Oxford University website, now allows the estimation of steady-state beta-cell function (%B) and insulin sensitivity (%S) as percentages of a normal reference population.

  (http://www.dtu.ox.ac.uk/homacalculator/index.php)

Glucose	Insulin	HOMA2 %B	HOMA2 %S	HOMA2 IR
4.9	53.8	99.5	99.9	1.0
4.7	50.0	102.9	108.6	0.9



Insulin Resistance and Risk of Incident Cardiovascular Events in Adults without Diabetes: Meta-Analysis

- Meta analysis: 65 studies (involving 516,325 participants)

		Number of Studies	Participants	Pooled relative risk per 1 SD (95% CI)	I^2
CHD	Glucose	23	140,721	1.21 (1.13, 1.30)	64.9%
	Insulin	9	32, 104	1.04 (0.96, 1.12)	43.0%
	HOMA-IR	7	17,452	1.46 (1.26, 1.69)	0.0%
CVD	Glucose	44	450, 487	1.19 (1.14, 1.23)	66.8%
	Insulin	16	46,236	1.13 (1.05, 1.22)	58.3%
	HOMA-IR	17	51,161	1.25 (1.16, 1.35)	52.4%

The relative risk of CHD, CVD was higher in HOMA-IR compared to fasting glucose or fasting insulin concentration.

The HOMA-IR could be useful to predict the CV risk.

PLoS One 2012;7(12)

HOMA and CV risk factors

- 605 Iranian subjects aged 25–79 yrs
- With normal fasting glucose and normal glucose tolerance

Partial correlation coefficients between HOMA-IR and other variables

Parameters	Male			Female		
	Model 1	Model 2	Model 3	Model 1	Model 2	Model 3
SBP (mmHg)	0.179**	0.100 Ns	0.060 NS	0.202**	0.048 NS	0.027 NS
DBP (mmHg)	0.239***	0.134*	0.109 NS	0.224**	0.76 NS	0.062 NS
BMI (kg/m^2)	0.503***	–	–	0.549***	–	–
Waist circumference (cm)	0.492***	0.200**	–	0.499***	0.162**	
Fasting glucose (mmol/l)	0.480***	0.460***	0.442***	0.374***	0.376***	0.376***
2 h glucose (mmol/l)	0.137 NS	0.178 NS	0.191 NS	0.146 NS	0.060 NS	0.066 NS
Fasting insulin (μU/ml)	0.969***	0.956***	0.955***	0.976***	0.966***	0.966***
Total cholesterol (mmol/l)	0.256***	0.114 NS	0.105 NS	0.196**	0.056 NS	0.031 NS
Triglyceride (mmol/l)	0.339***	0.219*	0.193*	0.319***	0.159**	0.134*
HDL-cholesterol (mmol/l)	−0.316***	−.249***	−0.252**	−0.340***	−0.269***	−0.245**
LDL-cholesterol (mmol)	0.271***	0.135 NS	0.131 NS	0.216**	0.075 NS	0.046 NS
Apolipoprotein B (mmol)	0.272*	0.113 NS	0.048 NS	0.334***	0.129 NS	0.102 NS

SBP: systolic blood pressure; DBP: diastolic blood pressure. Model 1 is adjusted for age; Model 2 is adjusted for age and BMI; Model 3 is adjusted for age, BMI, WC and physical activity. *$p<0.05$; **$p<0.01$; ***$p<0.001$.

- HOMA-IR is associated with the features of metabolic syndrome

Clin Chim Acta. 2006 371(1-2)

Insulin resistance and risk of ischemic stroke

- Cohort of 1,509 non-diabetic participants from the Northern Manhattan Study, follow-up of 8.5 years

Table 3. Relation Between HOMA-IR Quartiles and Risk of Ischemic Stroke, Myocardial Infarction, Vascular Death, and Combined Vascular Events

	Hazard Ratio (95% CI)			
Adjusted for	Model 1: Age	Model 2: Sociodemographics[a]	Model 3: Sociodemographics and Metabolic Syndrome	Model 4: Multivariate Adjusted[b]
Ischemic stroke				
HOMA	Trend $P = .04$	Trend $P = .06$	Trend $P = .07$	Trend $P = .08$
Q1	1 [Reference]	1 [Reference]	1 [Reference]	1 [Reference]
Q2	1.88 (0.72-4.87)	1.87 (0.71-4.89)	1.87 (0.71-4.91)	1.59 (0.58-4.33)
Q3	0.93 (0.29-2.95)	0.87 (0.27-2.81)	0.88 (0.27-2.86)	0.65 (0.18-2.36)
Q4	3.11 (1.25-7.76)	2.98 (1.16-7.62)	3.01 (1.13-8.04)	2.97 (1.05-8.35)
HOMA Q4 vs Q1-Q3	2.47 (1.28-4.77)	2.40 (1.23-4.67)	2.43 (1.21-4.91)	2.83 (1.34-5.99)
Myocardial infarction				
HOMA Q4 vs Q1-Q3	1.87 (1.00-3.48)	1.79 (0.94-3.39)	1.48 (0.76-2.88)	1.77 (0.88-3.58)
Vascular death				
HOMA Q4 vs Q1-Q3	1.27 (0.84-1.93)	1.34 (0.87-2.05)	1.25 (0.80-1.96)	1.10 (0.69-1.74)
Combined vascular events				
HOMA Q4 vs Q1-Q3	1.45 (1.04-2.03)	1.52 (1.08-2.14)	1.37 (0.96-1.96)	1.25 (0.86-1.82)

Insulin resistance estimated using the HOMA is a marker of increased risk of incident stroke in non-diabetic individuals.

Arch Neurol. 2010 67(10)

Multiethnic Cohort of Women

- The Women's Health Initiative Observational Study
- 82,069 women (50-79 yrs), free of CV disease or diabetes
- Median f/u 5.9 yrs (1,584 diabetic vs. 2,198 matched controls)

Table 4—*RRs of diabetes according to different levels of HOMA-IR and HOMA-B*

- High HOMA-IR and low HOMA-B were independently and consistently associated with an increased diabetes risk in a multiethnic cohort of U.S. postmenopausal women.
- These data suggest the value of HOMA indexes for diabetes risk in epidemiologic studies.

Data a[illegible] and low levels of HOMA-IR and HOMA-B were based on a median split among controls; the median cut points were 1.459 for HOMA-IR and 81.7 for HOMA-B. *Matching factors included age, race/ethnicity, clinical center, and time of blood draw. †Model 1 was adjusted for matching factors, BMI, alcohol intake, level of physical activity, cigarette smoking status, the use or nonuse of postmenopausal hormone therapy, and family history of diabetes. ‡Model 2 additionally adjusted for waist-to-hip ratio in model 1.

Diabetes Care. 2007 30(7)

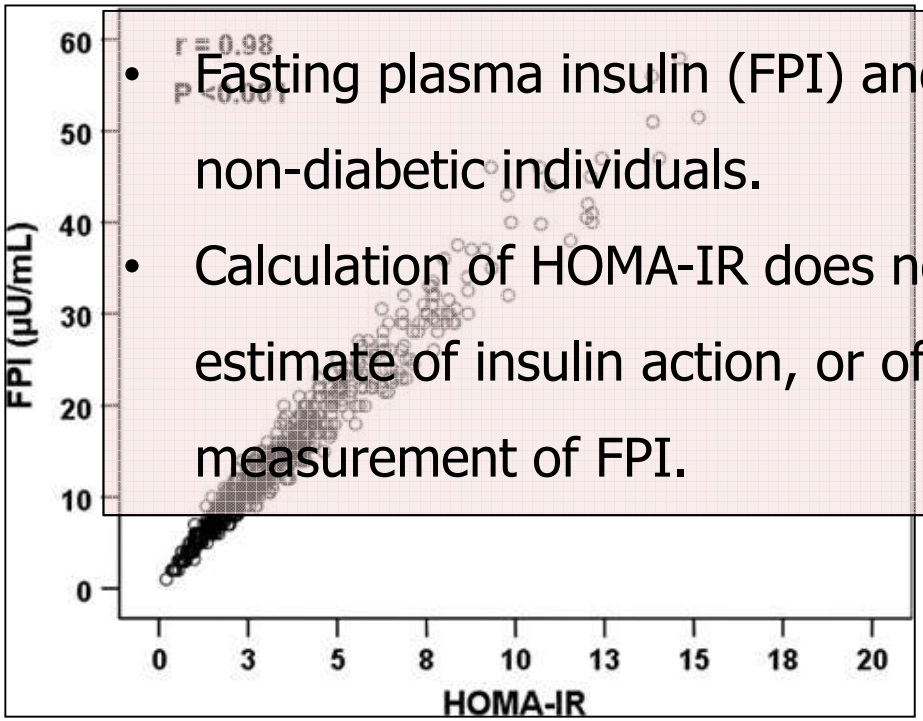
Fasting Insulin

1) healthy subjects
   - increased fasting insulin levels correspond to insulin resistance
   - 1/fasting insulin: insulin sensitivity

2) diabetic or glucose-intolerant subjects
   - not cover inappropriately low insulin secretion in the face of hyperglycemia

Fasting plasma insulin

- 758 healthy individuals. (83% Hispanic Whites)



Surrogate marker	Metabolic/clinical variable			
	SSPG	TG	HDL-C	BMI
FPI	0.60	0.35	−0.40	0.53
HOMA-IR	0.64	0.39	−0.41	0.56

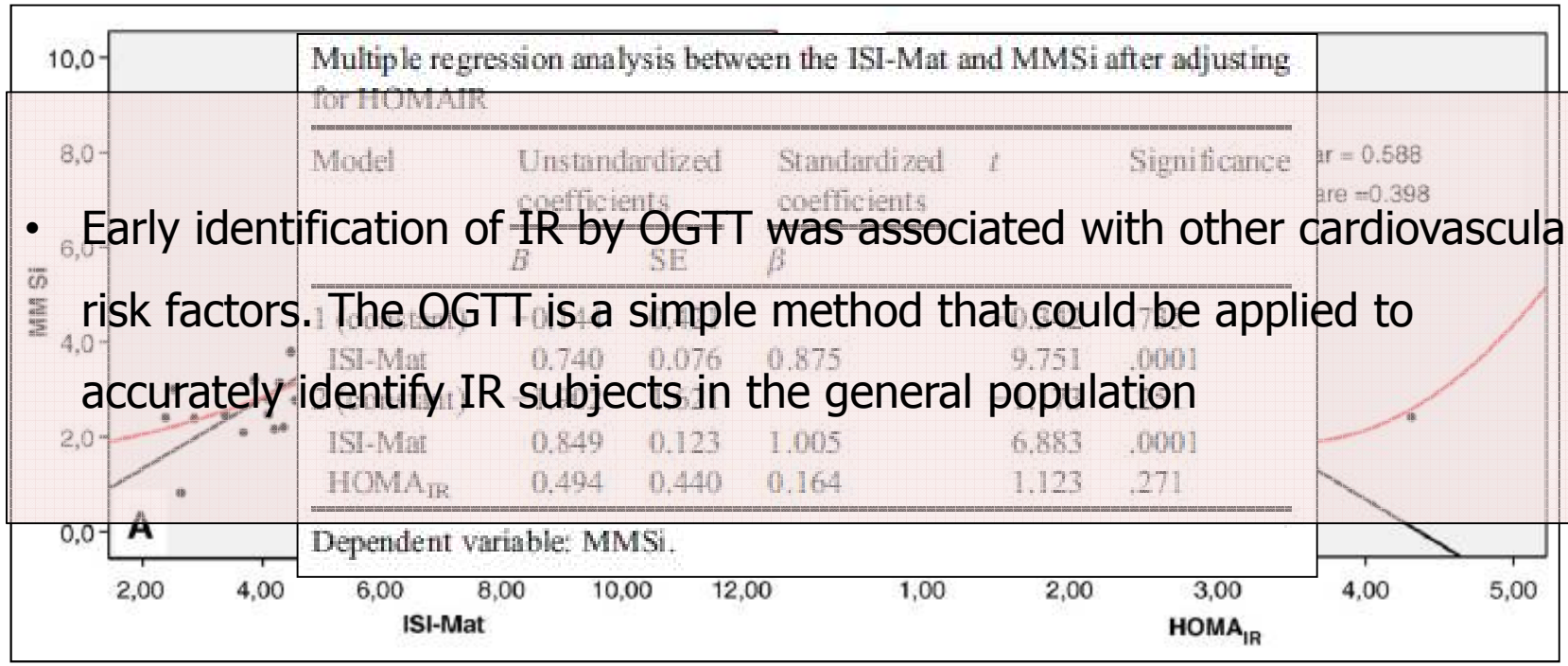
[illegible] each corre-
lation was significant at $P < 0.001$

- Fasting plasma insulin (FPI) and HOMA-IR are highly correlated in non-diabetic individuals.
- Calculation of HOMA-IR does not provide a better surrogate estimate of insulin action, or of its associated dyslipidemia, than measurement of FPI.

Acta Diabetol 2013

Postprandial method based on OGTT

- 90 nonobese, nondiabetic, and nonsmoker individuals



Multiple regression analysis between the ISI-Mat and MMSi after adjusting for HOMAIR

Model	Unstandardized coefficients		Standardized coefficients	t	Significance
	B	SE	β		
ISI-Mat	0.740	0.076	0.875	9.751	.0001
ISI-Mat	0.849	0.123	1.005	6.883	.0001
HOMA$_{IR}$	0.494	0.440	0.164	1.123	.271

Dependent variable: MMSi.

- Early identification of IR by OGTT was associated with other cardiovascular risk factors. The OGTT is a simple method that could be applied to accurately identify IR subjects in the general population

Metabolism. 2011, 60(5)

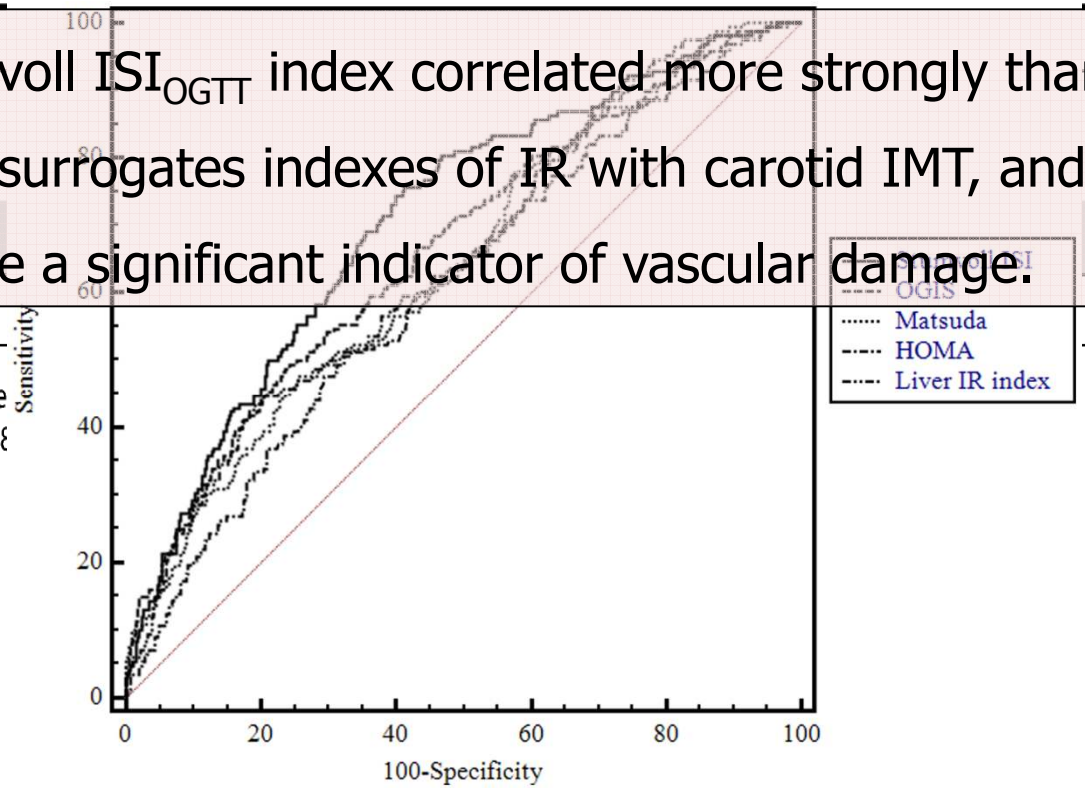
Association of Insulin Resistance Indexes to Carotid Intima–Media Thickness

- 847 non-diabetic Caucasians

The Stumvoll ISI_{OGTT} index correlated more strongly than other validated surrogates indexes of IR with carotid IMT, and, therefore, it might be a significant indicator of vascular damage.

HOMA		Stumvoll ISI	
β coefficient	P	β coefficient	P
0.13	<0.0001	−0.22	<0.0001

HOMA = homeostasis model asse
doi:10.1371/journal.pone.0053968



PLoS One. 2013;8(1)

High Risk Group

Diabetes Risk in Mexican-Americans

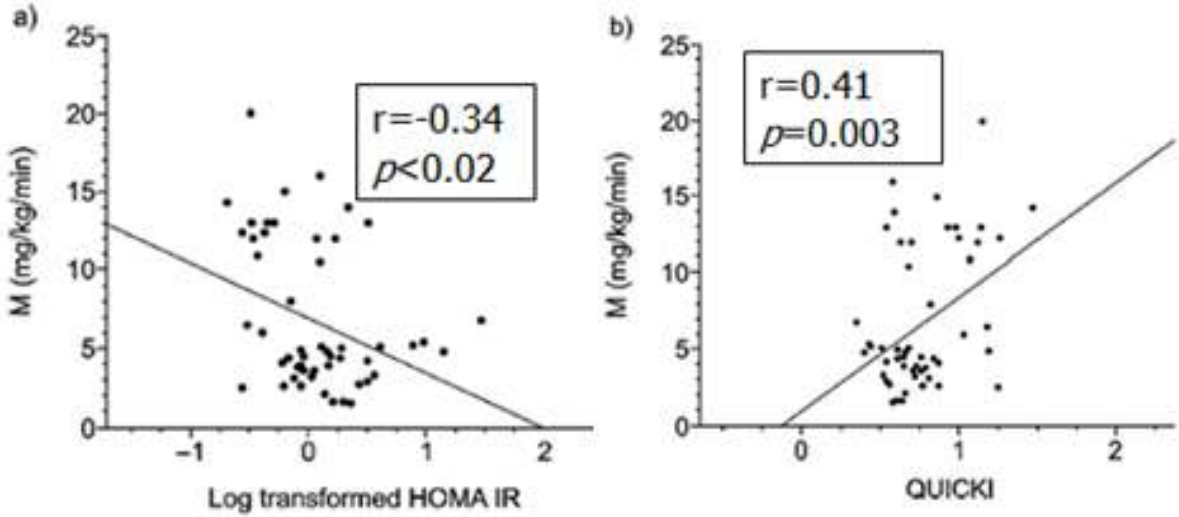
	Model	Adjustment models	Ethnic difference OR (95% CI)[a]	Percentage reduction[b]	*P* value[c]	*P* value[d]
Adding individual variables to a basic model	1	Basic model (age and sex)	2.26 (1.53–3.34)	Referent	Referent	<0.001
Family history of diabetes, measures of adiposity, or plasma glucose	2	Age, sex, and family history of diabetes	1.84 (1.33–2.56)	33.3%	<0.001	0.022
	3	Age, sex, and BMI	1.75 (1.17–2.61)	40.5%	<0.001	0.352
	4	Age, sex, and waist circumference	2.03 (1.36–3.04)	18.3%	0.024	0.006
	5	Age, sex, and fasting glucose	2.23 (1.48–3.38)	2.4%	0.888	<0.001
	6	Age, sex, and IGT	1.91 (1.26–2.89)	27.8%	0.014	0.062
Measures of insulin resistance/sensitivity	7	Age, sex, and fasting insulin	1.88 (1.25–2.83)	30.2%	0.004	<0.001
	8	Age, sex, and HOMA1R	[illegible]	[illegible]	[illegible]	<0.001
	9	Age, sex, and HOMA2S	1.87 (1.24–2.81)	31.0%	0.002	<0.001
	10	Age, sex, and Matsuda index	1.64 (1.08–2.48)	49.2%	<0.001	Referent
Measures of insulin secretion	11	Age, sex, and HOMA β-cell	2.71 (1.45–3.13)	11.9%	<0.001	<0.001
	12	Age, sex, and HOMA2B	2.08 (1.40–3.08)	12.7%	0.004	<0.001
	13	Age, sex, and $\Delta I_{0-30}/\Delta G_{0-30}$	2.66 (1.78–3.97)	−31.7%	<0.001	<0.001
	14	Age, sex, and $\Delta I_{0-120}/\Delta G_{0-120}$	2.18 (1.42–3.33)	6.3%	0.708	0.018
More complex models	15	Age, sex, Matsuda index, and HOMA β-cell	1.70 (1.11–2.60)	44.4%	<0.001	0.332
	16	Age, sex, Matsuda index, and HOMA2B	1.69 (1.10–2.58)	45.2%	<0.001	0.516
	17	Age, sex, Matsuda index, and $\Delta I_{0-30}/\Delta G_{0-30}$	2.07 (1.33–3.24)	15.9%	0.472	0.004
	18	Age, sex, Matsuda index, IGT, BMI, and family history of diabetes	1.26 (0.80–1.97)	79.4%	<0.001	0.002

- Matsuda index is better than HOMA-IR for both explaining the ethnic difference and predicting diabetes.

JCEM 2012 97(3)

Urban South African blacks

- HOMA-IR, log HOMA-IR, and QUICKI from OGTT
- Glucose disposal rate (M) from the clamp study



Log HOMA IR and QUICKI were comparable to the hyperinsulinaemic euglycaemic glucose clamp and these surrogate indexes provided a valid method to estimate insulin sensitivity/resistance.

Diab Vasc Dis Res. 2010 7(2)

IR and CV risk in Finnish offspring of T2DM

- 272 nondiabetic Finnish offspring of type 2 diabetic individuals (age, 24-50 yrs, 55% female)

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

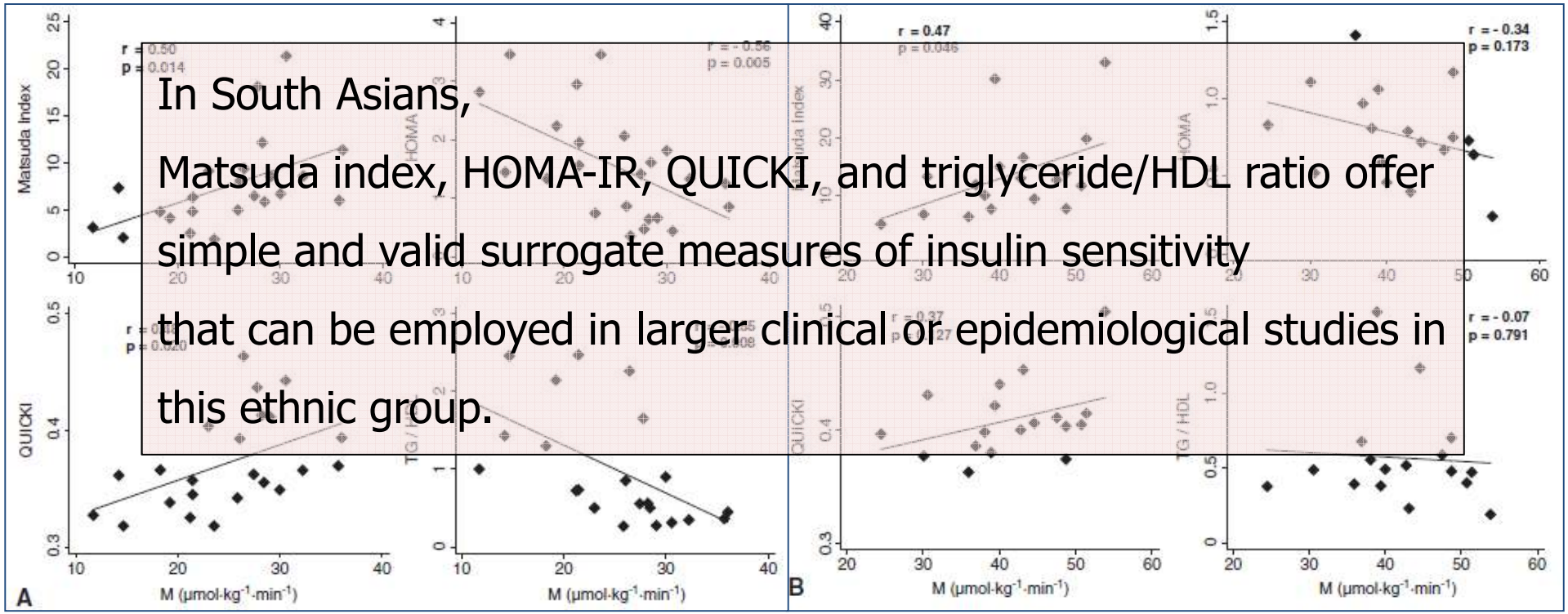
	Metabolic syndrome	M_{LBM}/I lower quartile
M_{LBM}/I	0.802	
Indexes based on fasting values		
Fasting glucose	0.740[d]	0.644[f]
Raynaud	0.820	0.876
HOMA IR	0.835	0.869
ISI_{basal}	0.836	0.868
QUICKI	0.836	0.869
Belfiore's $ISI(gly)_{basal}$	0.835	0.869
McAuley	0.895[c,d]	0.859
measurements		
2-h glucose	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

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.

JCEM 2010 95(11)

Comparison of insulin sensitivity measures in South Asians

- 23 South Asians vs. 18 Caucasians (age, BMI matched)



In South Asians,

Matsuda index, HOMA-IR, QUICKI, and triglyceride/HDL ratio offer simple and valid surrogate measures of insulin sensitivity that can be employed in larger clinical or epidemiological studies in this ethnic group.

Metabolism 2013 62(10)

Insulin resistance in women with PCOS

- 62 non-diabetic women with PCOS
- Compare M value from clamp study vs. various IR indices

Table 4. Correlation Coefficients among M-value and Various Insulin Sensitivity Indexes from OGTT in Women with PCOS

	Normal weight	Overweight/Obese	Total
$HOMA_{(IR)}$ (mmol/L) · (μU/mL)	-0.11	-0.40*	-0.34†
QUICKI (mmol/L) · (μU/mL)	0.11	0.40*	0.34†
G/I ratio (mg/dL) · $(\mu U/mL)^{-1}$	0.08	0.05	0.22
$ISI_{(COMP)}$ (mg/dL) · (μU/mL)	0.36	0.36	0.47‡
MCR_{est}-OGTT[1] (mL/kg · min)	0.49†	0.76‡	0.74‡
ISI_{est}-OGTT[1] (μmol/kg · min) · $(pmol/L)^{-1}$	0.50†	0.63‡	0.71‡
MCR_{est}-OGTT[2] (mL/kg · min)	0.45†	0.58†	0.57‡
ISI_{est}-OGTT[2] (μmol/kg · min) · $(pmol/L)^{-1}$	0.40*	0.42*	0.53‡

* $P < 0.05$.

† $P < 0.01$.

‡ $P < 0.001$, by Spearman's correlation coefficients.

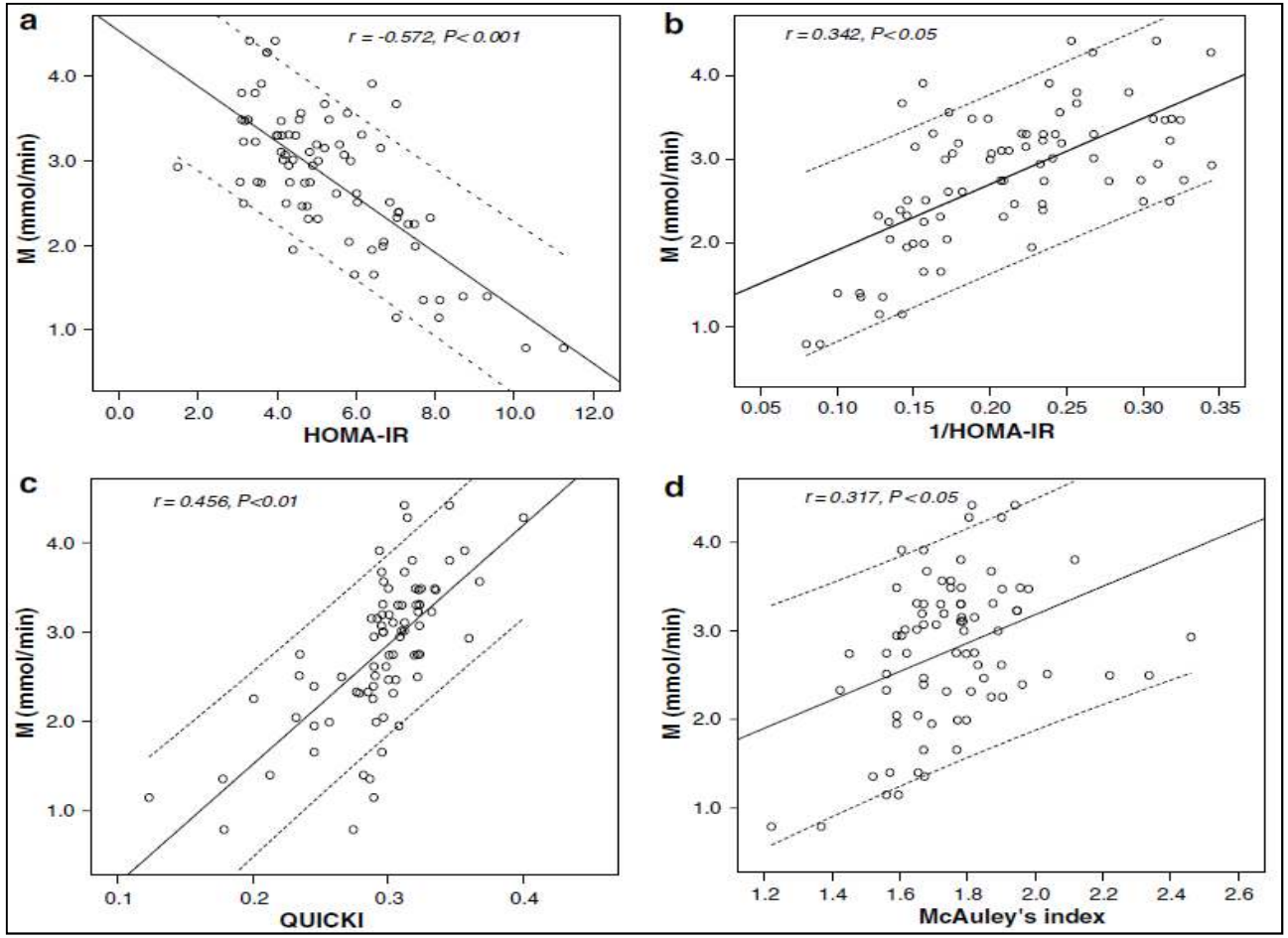
- MCRest-OGTT and ISIest-OGTT were the most reliable and easily accessible insulin sensitivity indexes for measuring of insulin sensitivity in women with PCOS regardless of obesity.

DMJ 30(4), 2006

Diabetic Patients

Patients with hypertension and type2 DM

- 78 Greek patients with hypertension and type 2 diabetes

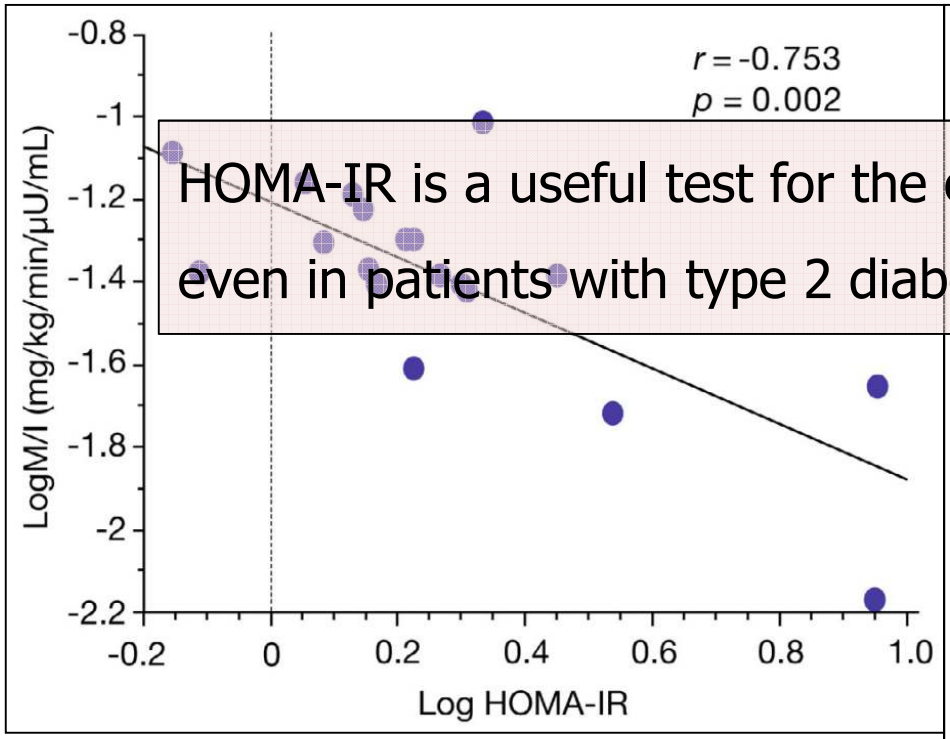


HOMA-IR, 1/HOMA-IR and QUICKI are valid estimates of clamp-derived IS.

J Hum Hypertens. 2007 Sep;21(9)

Patient with type 2 diabetes on insulin therapy

- 156 Japanese type 2 diabetics (60±11 yrs, A1C 9.4± 1.7%)



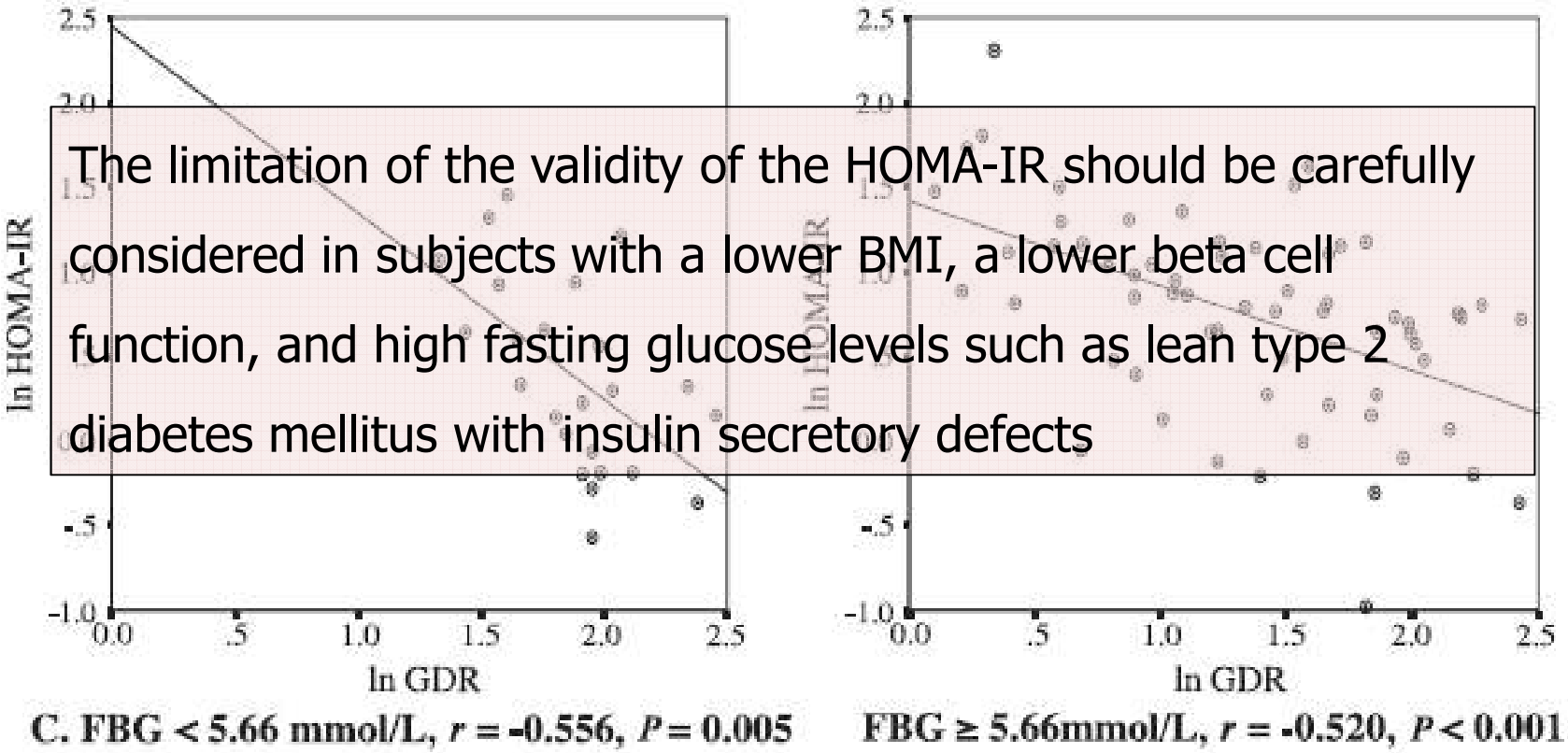
HOMA-IR is a useful test for the evaluation of insulin sensitivity even in patients with type 2 diabetes treated with insulin.

	r	*p*
Age (years)	-0.292	0.0002
Body mass index (kg/m^2)	0.499	<0.0001
[illegible]	[illegible]	0.0001
Estimated visceral fat area (cm^2)	0.401	<0.0001
[illegible]	0.121	0.1338
Diastolic blood pressure (mmHg)	0.223	0.0054
Log triglyceride (mg/dL)	0.497	<0.0001
LDL-C (mg/dL)	0.006	0.9451
HDL-C (mg/dL)	-0.342	<0.0001
HbA1c (%)	0.027	0.41
Urinary C-peptide (μg/day)	0.216	0.0099
ΔCPR (ng/mL)	0.496	<0.0001
Log insulinogenic index	0.325	0.0002
Log adiponectin (μg/mL)	-0.309	0.0006
Log KITT (%/min)	-0.264	0.0009

ΔCPR: increment of C-peptide from the glucagon stimulation test, KITT: K value from insulin tolerance test, HOMA-IR: homeostasis model assessment of insulin resistance.

Limitation of the validity of HOMA

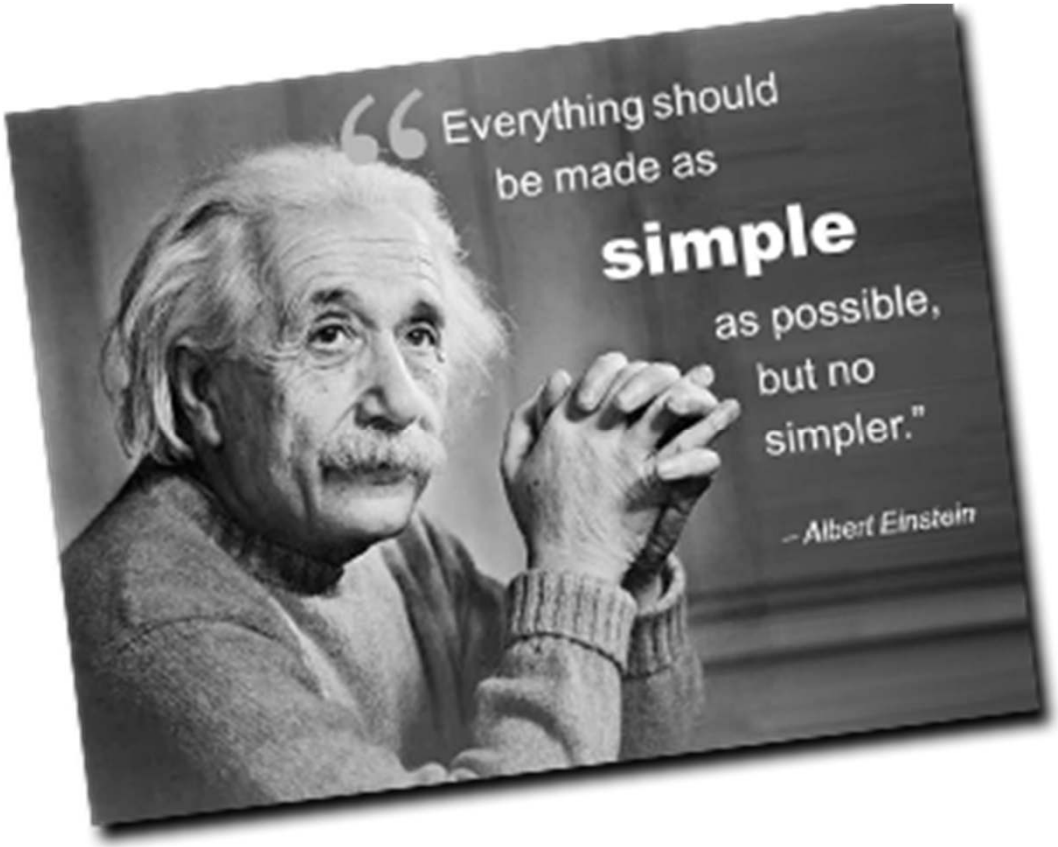
- Korean subjects with type 2 diabetes (n = 47), impaired glucose tolerance (n = 21), and normal glucose tolerance (n = 22)



The limitation of the validity of the HOMA-IR should be carefully considered in subjects with a lower BMI, a lower beta cell function, and high fasting glucose levels such as lean type 2 diabetes mellitus with insulin secretory defects

Metabolism. 2005 54(2)

- **The simple indexes of insulin resistance, even derived from fasting samples, are useful in most cases except specific population.**


"Everything should
be made as
simple
as possible,
but no
simpler."
– Albert Einstein