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Comparison between indexes of insulin resistance for risk prediction of cardiovascular diseases or development of diabetes

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ABSTRACT

Aim: The predictive effect of various insulin resistance indexes for risk of cardiovascular diseases (CVD) or type 2 diabetes (T2DM) is still unclear.

Methods: One thousand and forty-nine 71-years-old male subjects from the Swedish ULSAM study, mean follow-up 9 years. All subjects performed the euglycemic insulin clamp for *M/I* [glucose disposal/mean insulin], and 75-g oral glucose tolerance test for Ceder-IR: 1/glucose uptake rate/[mean glucose × log mean insulin]; Matsuda-IR: 1/10,000/square root [glucose0 × insulin0 × glucose120 × insulin120]; Belfiore-IR: 1/([glucose0 + glucose120]/normal mean glucose×[insulin0 + insulin120]/normal mean insulin)+1); and HOMA-IR: [glucose0 × insulin0]/22.5.

Results: Bland–Altman plots showed best agreement between *M/I* versus Belfiore-IR and Ceder-IR with mean difference near zero, −0.21 to −0.46, while −0.68 to −0.77 for the other indexes.

ISI-Ceder was the strongest predictor for incident nonfatal/fatal ischemic heart disease (CHD) or CVD at Cox regression in all subjects, and for incident T2DM at logistic regression in 1024 subjects with no baseline T2DM, with significantly higher hazard ratios or odds ratios than with all other indexes, also with best model fit, after adjusting for clinical characteristics and the traditional cardiovascular risk factors, including metabolic syndrome for CVD risk.

Conclusion: Ceder-IR performed strongest as independent predictor for incidences of CHD/CVD and T2DM.

1. Introduction

Several studies have indicated that increased insulin resistance is a predictor for the development of type 2 diabetes [1,2], and also significantly contributes to accelerated atherosclerosis as a risk factor for cardiovascular disease (CVD) [3–5]. The euglycemic insulin clamp technique is regarded as the reference method for an accurate assessment of in vivo insulin resistance [6,7]. However, this method is laborious,

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expensive and considered unsuitable for larger-scale or epidemiological studies. Other measures at the fasting state have been presented to be more useful and clinically suitable resistance indexes, like the plasma insulin concentration or the Homeostasis Model Assessment (HOMA-IR) test [8–10]. However, clinically available indexes of insulin resistance are also available using glucose and insulin values during the standard 75-g oral glucose tolerance test (OGTT). The Matsuda index at OGTT [11,12] was reported to have a somewhat better correlation with the insulin clamp than the Cederholm index at OGTT [13,14]. Accordingly, the Matsuda index has often been used as a surrogate resistance measure in recent years. However, a large long-term observational study [15] found that the Cederholm index clearly was the strongest predictor for the development of type 2 diabetes mellitus among a large group of various indexes at fasting including HOMA-IR [8], or at OGTT including the Belfiore index [16]. Furthermore, another large observational Framingham study [17] found that the Cederholm index was the strongly significant risk factor for incident CVD, while HOMA-IR was not. However, these studies were not able to include the Matsuda index.

The aim of this study was to evaluate the association between the Cederholm index and the euglycemic insulin clamp, and to estimate the effect of the Cederholm index as a predictor for the risk of CVD and for development of manifest type 2 diabetes. We also made a comparison regarding these associations with HOMA-IR, the Belfiore index and the Matsuda index, which often has been applied in recent clinical studies. This is also the first presentation in the literature of the Matsuda and Belfiore indexes as predictors of incidences of both the CVD diabetes in a large observational study.

2. Methods

2.1. Subjects

All men born between 1920 and 1924 in Uppsala, Sweden, were invited to a health survey in 1970, in which 2322 men (82%) participated; the ULSAM study [18]. After 20 years, at 71 years of age, 1221 (73%) of the 1681 still living subjects were invited for reinvestigation in 1991–1995, which also was the baseline of this study [19]. The study was approved by the Ethics Committee of the Faculty of Medicine at Uppsala University and it complies with the principles of the Declaration of Helsinki. Written informed consent was obtained from all subjects. Patients with data available for all analysed variables in this study were 1049 subjects. This sample was used for analysis of agreement between indexes of insulin resistance, and for analysis of the effect of these indexes on the risk for cardiovascular diseases.

A subgroup of 1024 participants was those with normal or impaired glucose tolerance (IGT) at baseline, excluding those with manifest diabetes, and with data available for all analysed variables. This subgroup was used to analyse insulin resistance indexes on risk for development of type 2 diabetes. IGT and type 2 diabetes at baseline were defined according to the 1999 World Health Organization criteria [20].

2.2. Baseline investigations

Baseline investigations in 1991–1995 consisted of an euglycemic insulin clamp test, 75-g OGTT, LDL-, and HDL-cholesterol, triglycerides, cystatin C, microalbuminuria, body weight, and height, systolic blood pressure under standardised conditions, and smoking (present or not) [19,21,22]. Charlson index was also included for classification of a range (score) of co-morbid diseases and conditions that may affect outcomes in prospective studies [23].

Glucose tolerance was assessed by 75-g OGTT, separated in time by 1 week from the euglycemic insulin clamp procedure [22]. Blood samples for fasting concentrations were collected after overnight fasting, and blood samples were also collected at 2-hour during the OGTT. Concentrations of plasma glucose were analysed by the glucose dehydrogenase method (Gluc-DH; Merck, Darmstadt, Germany). Plasma immune-reactive insulin (IRI) was determined with the enzymatic immunologic assay Enzymmun (Boehringer Mannheim, Mannheim, Germany) [21].

BMI was calculated as weight/height/height (kg/m^2). The metabolic syndrome was defined according to the harmonised criteria by the International Diabetes Federation [24]. Albuminuria was measured as the urinary albumin excretion rate (μg/min).

2.3. Insulin resistance measures

The euglycemic insulin clamp is considered gold standard for measurement of insulin sensitivity [20–22]. Insulin was infused at a constant rate of 56 mU/min/m^2 calculated to achieve nearly complete suppression of hepatic glucose output [21,22]. The target level of plasma glucose (measured every 5th minute during the 2-hour clamp) was 5.1 mmol/L. Median was 5.1 mmol/L, 5th percentile 5.0 mmol/L, 95th percentile 5.4 mmol/L, and mean ± SD 5.2 ± 1.3 mmol/L. The insulin sensitivity index (Clamp *M/I*) was calculated as glucose disposal rate (glucose infused in mg/min/kg body weight) divided by the mean plasma insulin concentration per 100 mU/L during the last 60-min of the 2-hour euglycemic insulin clamp.

The Cederholm index was originally presented as an insulin sensitivity index at 75-g OGTT [13] and defined as: the glucose uptake rate (*M*), divided by mean blood glucose (MBG), and divided by log mean insulin (log MSI): *M*/MBG/log MSI. *M* was defined as [75,000 (mg)/120 (min)] + [[0-min glucose (mmol/L)–120-min glucose (mmol/L)] × 0.19 × body weight (kg) × 180/120 (min)], where 0.19 × body weight calculated the glucose space, and the factor 180 transformed plasma glucose mmol/L to mg/L. As the glucose load was constant, *M* (mg/min) was determined solely by the difference between fasting and 120-min glucose concentrations and the body weight. *M* was considered as the net glucose uptake rate in all target tissues, such as muscles, fat, and the liver. An uninhibited glucose production by the liver should raise 120-min glucose and in this manner decrease *M*. The metabolic clearance rate (MCR) was calculated as M/MBG, where MBG (Mean Blood Glucose) was defined as [0-min glucose (mmol/L) + 120-min glucose (mmol/L)]/2. MCR was estimated to avoid the influence of different blood glucose levels on *M*. Log MSI (Mean Serum Insulin) was defined as log

[0-min insulin (mU/L) + 120-min insulin (mU/L)]/2, and the quotient MCR/log MSI was chosen as the insulin sensitivity index: M/MBG/log MSI = MCR/log MSI (mg × L^2/min × mmol × mU). This index was originally using 0-min, 30-min, 60-min and 120-min values of glucose and insulin at OGTT to estimate MBG and MSI, but it has later been shown by Gutt et al. that use of only 0-min and 120-min values achieves the same correlation with the euglycemic insulin clamp [14]. The inverse of the sensitivity index is used in this study as the resistance index, Ceder-IR, and defined as: 100/sensitivity index.

HOMA-IR was described as an index of insulin resistance by Matthews et al. with the formula: [0-min glucose (mmol/L)×0-min insulin (mU/L)]/22.5 [8]. HOMA-IR formula values [8] have been shown to be highly correlated ($r = 0.98$) with computer-derived HOMA-IR model values [9] in the Framingham study [10], and only results using the former are presented here.

The Matsuda sensitivity index using 75-g OGTT was defined as 10,000/square-root [0-min glucose (mg/dL)×0-min insulin (mU/L)×120-min glucose (mg/dL)×120-min insulin (mU/L)] [11]. It was presented as a composite measure of whole-body insulin sensitivity encompassing both hepatic and peripheral tissues. The factor 10,000 simply was a constant allowing to obtain suitable number ranging, and square-root conversion was applied to correct for non-linear distribution. This index was originally using 0-min, 30-min, 60-min, 90-min and 120-min glucose and insulin values to estimate MBG and MSI, but the authors later showed that use of only 0-min and 120-min values could achieve the same correlation with the euglycemic insulin clamp [12]. The inverse of the sensitivity index is used here as the resistance index, Matsuda-IR, defined as: 10/the sensitivity index.

The Belfiore sensitivity index [16] was defined as: 2/{[0-min glucose (mmol/L) + 120 min glucose (mmol/L)]/normal MBG×[0-min insulin (mU/L) + 120-min insulin (mU/L)]/normal MSI) + 1}. The inverse resistance index, Belfiore-IR, was defined as: 1/the sensitivity index.

2.4. Follow-up and outcomes

All patients were followed-up median 10 years (censor date 31st December, 2001). All CVD and total mortality events were retrieved by data linkage with the Swedish Cause of Death and Hospital Discharge Registers, a reliable validated alternative to revised hospital discharge and death certificates [25,26]. Nonfatal/fatal coronary heart disease (CHD) was defined as ICD-10 codes I20-25. Nonfatal/fatal stroke was ICD-10 codes I61, I63, I64. Nonfatal/fatal CVD was the composite of CHD and stroke, whichever came first.

Type 2 diabetes during follow-up was defined as fasting plasma glucose ≥7.0 mmol/L in reinvestigations at age 77 years, or as new use of oral hypoglycaemic agents detected by questionnaire or in medical records during the follow-up period.

2.5. Statistical analysis

Table 1 shows baseline clinical features, given as means (SD) or frequencies (%), and also median and interquartile range for the indexes. Fig. 1A–D shows Bland–Altman plots used for the agreement between Clamp *M/I* and each index, more correct for comparison than correlation [27]. The mean difference (with all indexes expressed per 1 SD to allow for comparison) is the estimated bias between *M/I* and an index, and SD measures the random fluctuations around this mean. If mean difference differs from 0, it indicates presence of systematic bias. The 95% limits (mean ± 1.96 SD) demonstrate how far apart measurements by two methods are more likely to be for most individuals. Spearman coefficients, in case of skewed distribution, were also estimated for the correlation between *M/I* and each of the indexes.

Cox regression analysis estimated hazard ratios (HR) with 95% confidence intervals (CI) for fatal/nonfatal CVD, fatal CVD, and fatal/nonfatal CVD as outcomes, comparing the indexes as predictors (Table 2). Covariance adjustment was performed for the traditional cardiovascular risk factors and clinical characteristics: LDL-cholesterol, smoker, cystatin C, Charlson index, and a history of CVD (Model 1), and additionally BMI, systolic BP, HDL-cholesterol, triglycerides, microalbuminuria, and the metabolic syndrome (Model 2). A Wald χ^2 statistic with *p* value indicates strength of the association between an index predictor and the outcome. Higher Likelihood ratio (LR) χ^2

Table 1 – Clinical baseline characteristics in 1049 male subjects aged 70 years.

Characteristics	All patients
Type of glycaemia	
Normoglycaemia	59.0
Impaired glucose tolerance	30.8
Manifest type 2 diabetes	10.2
Fasting glucose, mmol/L	5.7 ± 1.4
2-h glucose, mmol/L	8.3 ± 4.1
Fasting insulin, mU/L	12.8 ± 8.3
2-h insulin, mU/L	70.1 ± 52
Ceder-IR, units	4.8 ± 3.0; 3.8 (2.9–5.6)
Matsuda-IR, units	3.6 ± 2.7; 2.8 (1.8–4.7)
Belfiore-IR, units	1.5 ± 0.82; 1.3 (0.93–1.8)
HOMA-IR, units	3.4 ± 2.7; 2.7 (1.9–4.0)
Clamp *M/I*, 100 × mg/kg/min/m/L	5.1 ± 2.5; 4.8 (3.2–6.6)
Systolic BP, mmHg	147.1 ± 19
Diastolic BP, mmHg	83.7 ± 9.5
BMI, kg/m^2	26.3 ± 3.4
LDL cholesterol, mmol/L	3.89 ± 0.88
HDL cholesterol, mmol/L	1.29 ± 0.35
Triglycerides, mmol/L	1.41 ± 0.69
Ratio triglycerides/HDL	1.24 ± 0.85
Microalbuminuria, μg/min	25.3± 95
Cystatin C, mg/L	1.24 ± 0.27
Smoker	20.7
Charlson index	
Level 0	61.0
Level 1	20.8
Level 2	10.8
Level 3	4.5
Levels 4–7	2.9
A history of CHD	8.5
A history of stroke	3.6
A history of CVD	11.3

Data given are means ± SD or frequencies (%), and also median (interquartile range) for the indexes.

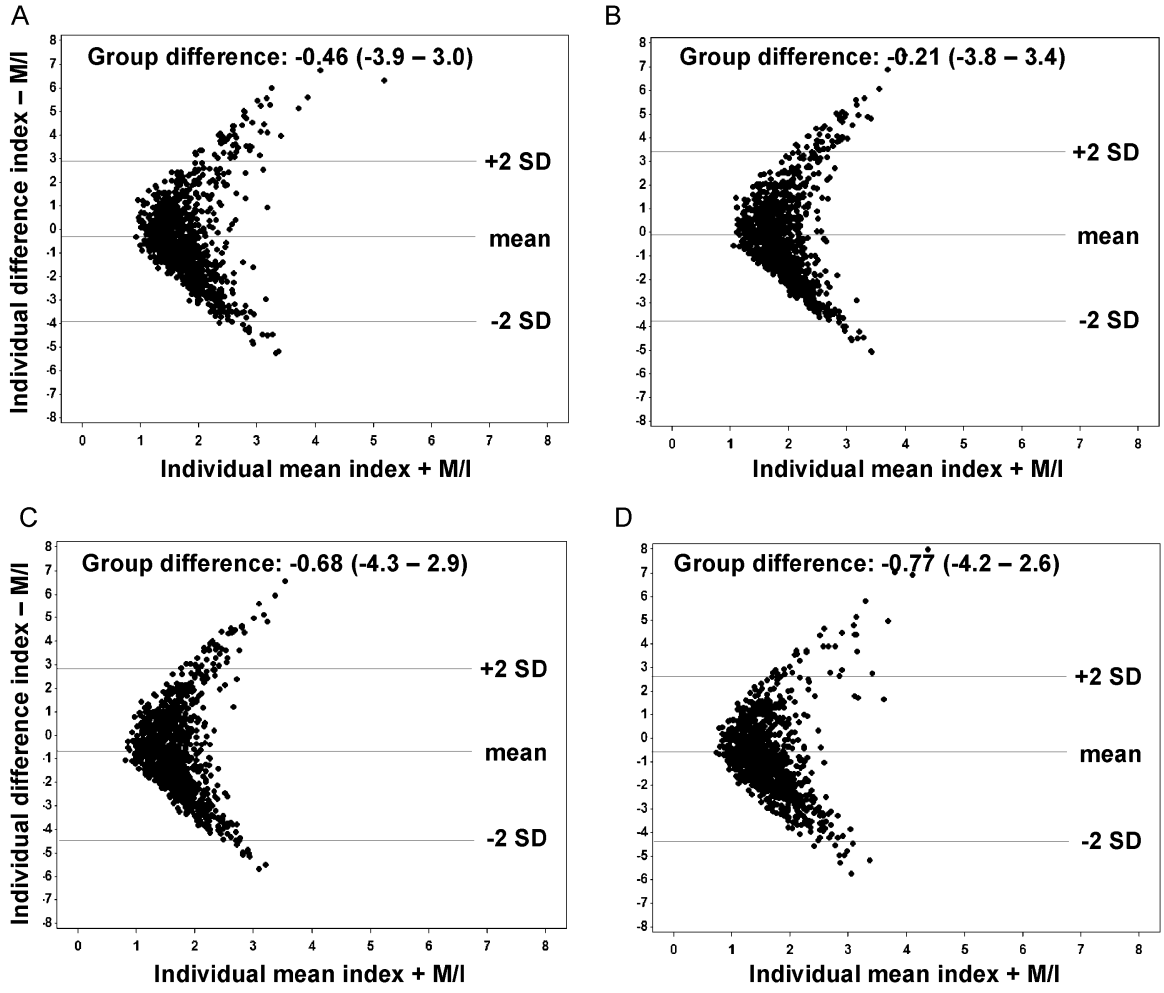

Fig. 1 – (A–D) Bland–Altman plots in 1049 male subjects aged 70 years comparing Clamp *M/I* with each of four indexes of insulin resistance: A/Ceder-IR; B/Belfiore-IR; C/Matsuda-IR; D/HOMA-IR. *M/I* and each index were expressed per 1 SD to allow for direct comparison. Each diagram shows individual dots for the difference between *M/I* and an index against the average of *M/I* and the index. Mean differences are given as horizontal lines, with lines for 95% limits (1.96 × SD).

statistic and lower Akaike Information Criteria (AIC) values indicate better global model fit. The proportional hazards assumption at the Cox regression analyses was confirmed with the test of all time-dependent covariates simultaneously introduced. Calibration of Ceder-IR compared predicted risk with observed incidence at Kaplan–Meier analysis, and discrimination was described with the *c*-statistic.

Logistic regression was used to analyse the indexes as predictors for development of type 2 diabetes as dependent variable (Table 3). Odds ratios (OR) with 95% CI are given per 1 SD increase of an index predictor, with Wald χ^2 statistics and p values, as well as Likelihood ratio χ^2 statistics and AIC values for global model fit. Adjustments were made for BMI, systolic BP, HDL cholesterol (Model 1), and additionally for smoking and Charlson index (Model 2). Calibration was described with the Hosmer–Lemeshow test, and discrimination with the *c*-statistic.

Wald χ^2 values of two hazard ratios or odds ratios were compared between Ceder-IR and each of the other indexes, using the Probchi function (SAS) to estimate significance levels of these comparisons.

A Cox model was also used to estimate 10 year event rates (1-survival rate) for CHD, where model output was 10-year CHD rate in each participant adjusted for covariates as given in Table 2. A cubic regression spline estimated 10-year event rates across the distribution of Ceder-IR (Fig. 2A). Similarly, a logistic model was used to estimate a cubic regression spline for incidence of diabetes across the distribution of Ceder-IR (Fig. 2B).

All statistical analyses were performed with SAS version 9.3 (SAS Institute, USA). A two-sided p value <0.05 was considered statistically significant.

3. Results

Table 1 shows baseline characteristics in all participants. Mean ± SD values of Clamp *M/I* was 5.1 ± 2.5 units, Ceder-IR

Table 2 – The ability of various indexes of insulin resistance to predict cardiovascular diseases, Cox regression in 1049 male subjects aged 70 years followed for mean 9 years.

Outcome (cases n)	Index	Model	All patients: Hazard ratio[a] (95% CI)	Wald χ^2	Wald p value	LRχ^2	AIC	Q4 versus Q1: Hazard ratio[b] (95% CI)	Wald χ^2	p value
Nonfatal or fatal CHD (n = 135)	Ceder-IR	Model 1	1.31 (1.15–1.50)	15.7	<0.001	36	1789	2.58 (1.53–4.34)	12.6	<0.001
	Belfiore-IR	Model 1	1.24 (1.08–1.43)	8.9**	0.003	32	1793	2.20 (1.31–3.69)	8.9***	0.003
	Matsuda-IR	Model 1	1.23 (1.07–1.43)	8.1**	0.005	31	1794	2.53 (1.47–4.34)	11.2	<0.001
	HOMA-IR	Model 1	1.18 (1.02–1.36)	5.0*	0.03	28	1797	1.70 (0.99–2.92)	3.6**	0.06
	Ceder-IR	Model 2	1.31 (1.13–1.52)	12.7	<0.001	60	1777	2.68 (1.45–4.96)	9.9	0.002
	Belfiore-IR	Model 2	1.18 (1.01–1.39)	4.1**	0.04	53	1784	2.11 (1.13–3.94)	5.5***	0.02
	Matsuda-IR	Model 2	1.18 (0.99–1.40)	3.7**	0.06	53	1784	2.29 (1.15–4.57)	5.5***	0.02
	HOMA-IR	Model 2	1.14 (0.96–1.35)	2.4*	0.1	52	1785	1.29 (0.66–2.53)	0.5**	0.6
Nonfatal or fatal CVD (n = 181)	Ceder-IR	Model 1	1.26 (1.12–1.42)	14.4	<0.001	27	2413	2.26 (1.43–3.58)	12.1	<0.001
	Belfiore-IR	Model 1	1.21 (1.07–1.37)	8.7***	0.003	23	2417	1.89 (1.21–2.96)	7.8***	0.005
	Matsuda-IR	Model 1	1.22 (1.07–1.38)	8.9***	0.003	23	2417	1.99 (1.27–3.12)	8.8	0.003
	HOMA-IR	Model 1	1.18 (1.04–1.33)	6.8**	0.009	21	2419	1.46 (0.94–2.28)	2.9**	0.09
	Ceder-IR	Model 2	1.26 (1.10–1.44)	11.5	<0.001	52	2401	2.40 (1.40–4.12)	10.1	0.002
	Belfiore-IR	Model 2	1.17 (1.01–1.35)	4.6**	0.03	46	2406	1.78 (1.04–3.03)	4.4***	0.04
	Matsuda-IR	Model 2	1.19 (1–02–1.38)	5.1**	0.02	46	2406	1.79 (1.01–3.14)	4.0***	0.04
	HOMA-IR	Model 2	1.16 (1.01–1.34)	4.5**	0.03	45	2407	1.14 (0.66–1.97)	0.2*	0.6
Fatal CVD (n = 50)	Ceder-IR	Model 1	1.47 (1.22–1.77)	17.0	<0.001	53	617	6.01 (2.05–18.2)	10.5	<0.001
	Belfiore-IR	Model 1	1.42 (1.16–1.73)	11.4***	0.003	50	621	3.77 (1.50–9.49)	7.9	0.005
	Matsuda-IR	Model 1	1.40 (1.13–1.72)	9.9**	0.002	49	622	4.16 (1.63–10.6)	8.9	0.003
	HOMA-IR	Model 1	1.26 (1.03–1.55)	5.1*	0.02	44	626	3.34 (1.28–8.72)	6.0***	0.01
	Ceder-IR	Model 2	1.57 (1.28–1.94)	18.5	<0.001	69	616	5.50 (1.59–19.0)	7.2	0.007
	Belfiore-IR	Model 2	1.42 (1.12–1.78)	8.8**	0.003	62	623	3.46 (1.18–10.2)	5.1	0.02
	Matsuda-IR	Model 2	1.44 (1.12–1.84)	8.2**	0.004	61	623	3.06 (0.98–9.55)	3.7	0.05
	HOMA-IR	Model 2	1.28 (0.99–1.65)	3.7*	0.056	57	627	2.74 (0.86–8.76)	2.9***	0.09

Likelihood ratio (LR) χ^2 statistics: a higher value indicates a better global model fit. AIC (Akaike Information Criteria): a lower value indicates a better trade-off between the likelihood of a model against its complexity. Adjustment with Model 1: smoker, LDL-cholesterol, cystatin C, Charlson index, and a history of CVD. Model 2: additionally BMI, systolic blood pressure, HDL-cholesterol, triglycerides, microalbuminuria, and the metabolic syndrome. Exclusion of the metabolic syndrome from Model 2 did not change significances.

Wald χ^2 statistic: a higher value indicates stronger association between a predictor and the outcome. Significance levels comparing Wald χ^2 values of hazard ratios between Ceder-IR and each of the other indexes in each of the Models using the Probchi test:

* $p < 0.001$

** $p < 0.01$

*** $p < 0.05$.

[a] All index variables introduced as increase per 1 SD for direct comparison between hazard ratios. CI: confidence interval.

[b] Highest quartile (Q4) compared to lowest quartile (Q1) as reference (cut-off values given in Table 1).

4.8 ± 3.0 units, Matsuda-IR 3.6 ± 2.7 units, Belfiore-IR 1.5 ± 0.82 units, and HOMA-IR 3.4 ± 2.7 units.

3.1. *Associations between Clamp M/I and insulin indexes*

Fig. 1A–D shows Bland–Altman plots for agreement between *M/I* and each index. A good agreement was seen for Ceder-IR (1A) and Belfiore-R (1B), mean difference only −0.46 and −0.21, although the 95% range indicates that the two compared methods do not consistently provide similar measures. Matsuda-IR (1C) and HOMA-IR (1D) showed less agreement with mean difference −0.68 and −0.77, while HOMA-IR also had the largest spread with higher SD value. Spearman correlation coefficients between Clamp *M/I* and each index were −0.71 for Ceder-IR, −0.75 for Belfiore-IR, −0.76 for Matsuda-IR, and −0.60 for HOMA-IR.

3.1.1. *Prediction of risk for CHD and CVD*

The associations between indexes and risks for fatal/nonfatal CHD, fatal/nonfatal CVD, or fatal CVD at Cox regression are shown in Table 2. All indexes were introduced per 1 SD increase to allow for direct comparison of HR. Adjustments were made for traditional cardiovascular risk factors and clinical characteristics by two models: smoking, LDL-cholesterol, cystatin C, Charlson index, and history of CVD (Model 1), and additionally BMI, systolic BP, HDL-cholesterol, triglycerides, microalbuminuria, and the metabolic syndrome (Model 2). Exclusion of the metabolic syndrome from Model 2 did not change significances. The strength of an index as predictor was evaluated in all patients with HR, Wald χ^2 with p value, as well as Likelihood ratio χ^2 and AIC for model fit, and finally by comparing highest (Q4) versus lowest (Q1) quartiles of an index. Number of events during mean 9 years of follow-up with 7625 person-years were 135 for fatal/nonfatal CHD, 181 for fatal/nonfatal CVD and 50 for fatal CVD.

Ceder-IR was a strongly significant independent predictor of fatal/nonfatal CHD, fatal/nonfatal CVD and fatal CVD, with a higher magnitude of effect than the other indexes according to higher Wald χ^2 in all participants (Models 1 and 2: $p < 0.001$) and comparing Q4 versus Q1 (p = 0.002–<0.001), as well as

Table 3 – The ability of various indexes of insulin sensitivity to predict development of manifest type 2 diabetes, logistic regression in 1024 male subjects aged 70 years, no diabetes at baseline 1991–1995, 56 events during follow-up until 2001.

		All patients						Q4 versus Q1–3		
Index	Model	Odds ratio[a] (95% CI)	Wald χ^2	p value	LR value	AIC value	c-statistics	Odds ratio[b] (95% CI)	Wald χ^2	p value
Ceder-IR	Model 1	2.37 (1.83–3.07)	42.9	<0.001	78	366	0.83	6.40 (3.42–11.9)	33.6	<0.001
Belfiore-IR	Model 1	1.64 (1.33–2.03)	20.9*	<0.001	46	398	0.75	4.96 (2.65–9.26)	25.1	<0.001**
Matsuda-IR	Model 1	1.63 (1.31–2.03)	19.6*	<0.001	46	399	0.75	3.64 (1.94–6.81)	16.2	<0.001*
HOMA-IR	Model 1	1.26 (1.04–1.53)	5.7*	0.02	32	412	0.70	2.29 (1.25–4.22)	7.1	0.008*
Ceder-IR	Model 2	2.43 (1.87–3.15)	44.3	<0.001	80	368	0.83	6.63 (3.52–12.6)	34.2	<0.001
Belfiore-IR	Model 2	1.69 (1.36–2.11)	22.1*	<0.001	48	400	0.76	5.12 (2.72–9.65)	25.5	<0.001**
Matsuda-IR	Model 2	1.68 (1.34–2.11)	20.6*	<0.001	48	401	0.76	3.67 (1.95–6.89)	16.3	<0.001*
HOMA-IR	Model 2	1.27 (1.05–1.54)	5.9*	0.01	33	415	0.71	2.30 (1.25–4.23)	7.1	0.008*

Likelihood ratio (LR) χ^2 statistics: a higher value indicates a better global model fit. AIC (Akaike Information Criteria): a lower value indicates a better trade-off between the likelihood of a model against its complexity.
Wald χ^2 statistic: a higher value indicates stronger association between a predictor and the outcome. Significance levels comparing Wald X^2 values of hazard ratios between Ceder-IR and each of the other indexes using the Probchi test:
* $p < 0.001$
** $p < 0.01$
[a] All odds ratio estimated per 1 SD increase in each index to allow for direct comparison between odds ratios. CI: confidence interval.
[b] Odds ratio for patients within the highest quartile (Q4) compared to the lower quartiles (Q1-3) as reference. Cut-off values for Q4 (75th percentile) were for Ceder-IR: 4.9; Belfiore-IR: 1.7; Matsuda-IR: 4.3; HOMA-IR: 3.6. Model 1: adjusted for BMI, systolic BP, and HDL cholesterol. Model 2: adjusted as in Model 1 and also for smoking, and Charlson index. CI: confidence interval.

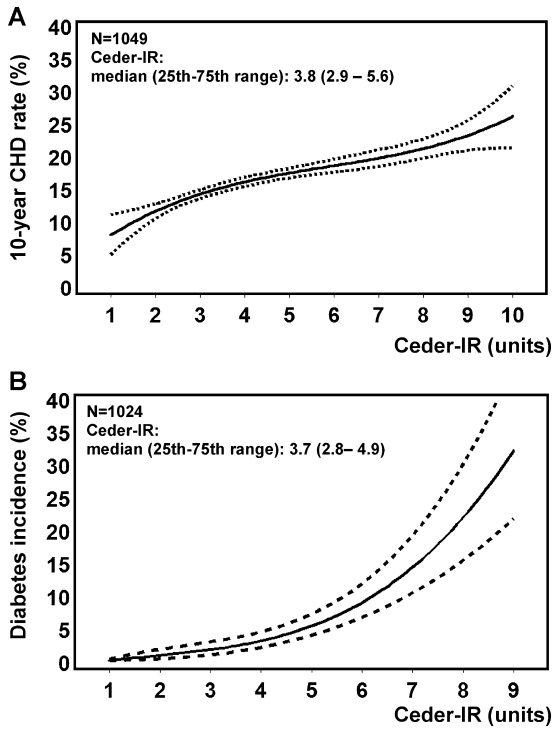

Fig. 2 – (A,B) Cubic regression splines in patients followed-up for incidences of CHD or type 2 diabetes: A/10 year CHD rates across the distribution of Ceder-IR at Cox regression in all 1049 subjects; B/incidence of type 2 diabetes across Ceder-IR at logistic regression in 1024 subjects with no diabetes at baseline. CHD rate and diabetes incidence are represented as solid lines, with 95% confidence interval as dotted lines.

higher Likelihood ratio χ^2 and lower AIC indicating better global model fit.

A significantly weaker but independent effect with Model 2 was seen for Belfiore-IR in all patients for fatal/nonfatal CHD and CVD ($p = 0.03$–0.04), and fatal CVD ($p = 0.003$). Comparing Q4 versus Q1, all outcomes were only weakly significant ($p = 0.02$–0.04). Concerning Matsuda-IR in all patients, the effect was significant with Model 2 only for fatal/nonfatal CVD ($p = 0.02$) and fatal CVD ($p = 0.004$). Comparing Q4 versus Q1, all outcomes were only weakly significant ($p = 0.02$–0.05).

Finally, HOMA-IR had a weakly significant effect with Model 2 in all patients only for fatal/nonfatal CVD ($p = 0.03$), and no significant effect comparing the quartiles.

Wald χ^2 values of two hazard ratios were compared between Ceder-IR and each of the other indexes in each of the Models, showing significant differences for all outcomes, both in all patients and generally with highest versus lowest quartiles, as given in Table 2.

3.2. *Prediction of risk for type 2 diabetes*

The indexes as predictors of risk for manifest type 2 diabetes were analysed with logistic regression, with each index introduced per 1 SD increase to allow for direct comparison between odds ratios (Table 3). Totally 56 new cases of type 2 diabetes were found during follow-up from baseline until 2001, in 1024 participants with no previous diabetes. Adjustments were made by two models: with BMI, systolic BP, and HDL-cholesterol (Model 1), and additionally with smoking and Charlson index (Model 2).

Ceder-IR was the strongest predictor in all participants, with significantly ($p < 0.001$) higher OR, 2.4, and a two-fold or higher Wald χ^2 compared to all other indexes, as well as with higher Likelihood ratio statistic and lower AIC indicating better global model fit,. Other indexes also had significant effect in all patients with weaker OR (1.3–1.7) and lower Wald

χ^2 ($p = 0.01$–<0.001). Comparing highest (Q4) versus the lower (Q1–3) quartiles, Ceder-IR had higher OR, 6.6 ($p < 0.001$), than all other indexes.

Wald χ^2 values of two odds ratios were compared between Ceder-IR and each of the other indexes in each of the Models, showing significantly higher OR with Ceder-IR, both in all patients and with highest versus lower quartiles, as given in Table 3.

3.3. *Splines for incidences of CHD and diabetes*

Fig. 2A shows a cubic regression spline for the association between 10 year rate of CHD versus Ceder-IR estimated in a Cox model among all 1049 participants (solid line, with 95% confidence limits as dotted lines), with no threshold effect. Applying the 75th percentile of Ceder-IR as a cut-off for high insulin resistance, 5.6 units corresponded to a high 10-year CHD rate of around 20%, while the median of 3.8 units corresponded to a lower rate of around 15%.

Another cubic spline shows the relationship between incidence of type 2 diabetes and Ceder-IR among the subgroup of participants without diabetes at baseline (Fig. 2B), showing a threshold effect with a sharply rising from the median of 4 units. The 75th percentile of Ceder-IR corresponded to a higher diabetes incidence of 6%, while the median corresponded to an incidence of 2–3%.

Ceder-IR included in Model 2 showed excellent calibration, with a ratio predicted risk/observed CHD incidence of 0.99 at Cox regression, and also with Hosmer–Lemeshow goodness-of-fit test $p = 0.8$ for diabetes incidence ($p > 0.05$ indicating good fit) at logistic regression. Concerning discrimination, adding Ceder-IR to the other covariates in Model 2 increased model fit and *c*-statistic from 0.68 to 0.70 for CHD incidence ($p = 0.001$), and increased model fit and *c*-statistic from 0.69 to 0.83 for diabetes incidence ($p < 0.001$). Sensitivity and specificity with the median as cut-off were 61% and 52% for CHD incidence, and were 93% and 53% for diabetes incidence.

4. Discussion

The present large cohort study including more than 1000 participants with data on both OGTT and gold standard euglycemic insulin clamp tests followed-up for 9 years showed cross-sectionally that Ceder-IR and Belfiore-IR at OGTT had slightly better agreement with the euglycemic insulin clamp test, compared to Matsuda-IR at OGTT and HOMA-IR based on fasting values only (Fig. 1A–D). The study also showed that, although both Belfiore-IR and Matsuda-IR were significantly independent predictors of risk for both CHD/CVD and type 2 diabetes during long-term follow-up, Ceder-IR was a considerably stronger predictor, with significantly higher adjusted HR and OR according to Wald χ^2 values found with Ceder-IR than with all other indexes, when analysing all patients as well as comparing highest with lower quartiles (Tables 2 and 3).

Ceder-IR was developed by Cederholm and Wibell (1990), originally using four values at OGTT (0-min, 30-min, 60-min and 120-min) for estimation of mean glucose and insulin during OGTT [13]. It was later shown by Gutt et al. that use of only 0-min and 120-min values to estimate mean glucose and insulin during OGTT achieved approximately the same correlation to the euglycemic insulin clamp index as use of four values [14]. This coincided with a large observational study of 3574 subjects followed for 5–8 years, including data from the San Antonio Heart Study, the Mexico City Diabetes Study and the Insulin Resistance Study, applied for analysis of a large number of insulin indexes as predictors for the development of manifest type 2 diabetes [15]. The study demonstrated that Ceder-IR consistently was the strongest predictor of incident manifest diabetes at Poisson regression, when using several statistical tests, after adjustment for age, sex, systolic BP, HDL cholesterol, and BMI. Other indexes compared in the study were based on fasting values: ISI-HOMA [8], fasting insulin [28], BMI, ISI [29], McAuley [30], FIRI [31], Raynaud [32], Quicki [33], Bennet [34], Belfiore basal [16]—or were based on OGTT values: Belfiore [16], Sluiter [29], Bennet [34], Stumwoll [35], and Avignon [36]. Comparing top 10% versus bottom 90% data at Poisson regression, the highest relative risk was found with Ceder-IR, 3.1, while only 1.8 with Belfiore-IR and HOMA-IR [15]. As the study demanded only 0-min and 120-min data at OGTT, Matsuda-IR could not be included as this index was only later developed from use of 4 values to only 0-min and 120-min values at the OGTT [12]. Concerning Belfiore-IR, the smaller study by DeFronzo et al. of 153 subjects including diabetes found a correlation of only 0.54 with the insulin clamp [11], while Spearman correlation was 0.75 in our study.

Another large observational study of 2898 subjects from the Framingham offspring study without CVD or type 2 diabetes at baseline followed for 7 years compared Ceder-IR, HOMA-IR, and the metabolic syndrome as predictors of risk for CVD [17]. Comparing the highest quartile versus the lowest of each index, Ceder-IR was a strongly significant predictor ($p = 0.004$), when adjusting for age, sex, smoking, LDL cholesterol, and also for the metabolic syndrome, which is comparable to findings in our study ($p < 0.001$).

HOMA-IR was not a significant predictor for CVD in the Framingham study [17], and other observational studies on HOMA-IR as risk factor for CVD have shown conflicting results. Some studies found a significant association after multiple adjustment [37–39], while other studies except for the Framingham Offspring Study found HOMA-IR non-significantly associated after multiple adjustment also including the metabolic syndrome [17,40,41]. The finding in our study that HOMA-IR was a considerably weak predictor of risks for both CVD and type 2 diabetes underlines, as stated in a recent review [42], that indexes based on only fasting glucose and insulin values seem to be of less usefulness compared to indexes based on OGTT. Furthermore, Quicki (33) and log HOMA-IR (identical HR and OR per 1 SD according to formula) had similar risk effect for CVD and diabetes as HOMA-IR (data not given).

Only one previous study has evaluated the association between Matsuda-IR and incident CVD, in 2356 Japanese subjects followed for 14 years [40], reporting no significantly increased risk for CVD (CHD or stroke combined) when comparing highest versus lowest quintiles of Matsuda-IR after adjustment for age, sex, total cholesterol, smoking, exercise, albuminuria, and the metabolic syndrome. Comparatively in our study, Matsuda-IR was a weakly significant predictor only for CVD ($p = 0.02$–0.04), but not for CHD.

A better performance with OGTT data by Ceder-IR than Belfiore-IR and Matsuda-IR as predictor of CVD and diabetes risks underlines that Ceder-IR was calculated based on a physiological oral approach, and expressing whole body insulin resistance. Importantly, the formula includes body weight to estimate the glucose space when calculating the glucose uptake rate. Furthermore, the metabolic clearance rate is estimated by adjusting to the mean plasma glucose level during OGTT, of importance especially with higher blood glucose levels. Finally, and most importantly, the metabolic clearance rate is related to the logarithm of mean insulin during the OGTT. This association has a sigmoidal curve form, showing a curve shift to the right in obese subjects and impaired glucose tolerance presumably due to increase in insulin receptor defects, and showing a combined right shift and lower maximal curve response with a lower ceiling in patients with manifest type 2 diabetes due to combined receptor and post-receptor defects, as previously demonstrated in repeated clamp tests in the same individual at lower and higher levels of 10–100–1000–10,000 mU/l [43]. An individual is assumed to reach a certain point along this sigmoidal curve according to achieved values of MCR and log MSI, and the quotient MCR/log MSI was therefore chosen as the index of insulin sensitivity. Reasonably, Ceder-IR should be able to capture the total body insulin resistance, based on both hepatic and peripheral dysfunctions.

The finding here that Ceder-IR was a strong predictor of CVD risk independently of traditional cardiovascular risk factors like BP, smoking, blood lipids, BMI, albuminuria, cystatin C, and especially, also independently of the metabolic syndrome, underlines that insulin resistance also may be associated with other risk factors like endothelial dysfunction [44], chronic subclinical inflammation [45], impaired fibrinolysis, and hypercoagulability [46]. A limitation may be that unmeasured covariates may have affected results, although relevant covariates were extensively applied. Analysis of hormonal changes during OGTT was not possible. Strengths of this study are the large number of participants performing the euglycemic insulin clamp test, and that outcomes retrieved by register linkages are reliable validated methods in Sweden [25,26]. Furthermore, it has been underlined in the literature that agreement among index methods is better estimated with Bland–Altman plots, as presented here, than with correlation [27].

5. Conclusion

The usefulness of surrogate indexes for insulin resistance in epidemiological studies depends on the strength of their correlation with criterion measures, but also importantly on the degree to which they predict type 2 diabetes and cardiovascular diseases in prospective analyses. This large observational study including euglycemic insulin clamp tests and 75-g OGTT has demonstrated that Ceder-IR and Belfiore-IR had slightly better agreement with Clamp *M/I* than Matsuda-IR and HOMA-IR, and that Ceder-IR performed considerably than better as long-term predictor for risks of CHD/CVD and type 2 diabetes than all other indexes analysed here. A threshold effect for diabetes incidence was seen at Ceder-IR of 4 units (median), but no threshold effect for CHD incidence. A cut-off value for higher resistance at the median seemed best to considerably minimize both these incidences, although the 75th percentile often is applied as cut-off. Although, HbA1c nowadays is used for diagnosis of diabetes, this study underlines the value of performing OGTT to achieve an easily available index of insulin resistance, useful in many clinical studies on treatment of cardiovascular risk factors and prediction of CVD risk, and nowadays also possibly useful for complementary evaluation of e.g., obese patients suitable for gastric bypass operations.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

JC and BZ designed the study, BZ acquired data, JC performed the statistical analyses, JC and BZ analysed and interpreted data, drafted and revised the manuscript, and finally approved for submission and publishing. Results and views of the present study represent the authors and not necessarily any official views of the Medical Products Agency where one author is employed (BZ).

Prior presentation

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