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Ethnic differences in the contribution of insulin action and secretion to Type 2 diabetes in immigrants from the Middle East compared to native Swedes.

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Abstract

Aims: We investigated insulin action (insulin sensitivity index, ISI) and insulin secretion (oral disposition indices, DIo) and studied metabolic, demographic and lifestyle-related risk factors for type 2 diabetes and insulin action, in the largest non-European immigrant group to Sweden, immigrants from Iraq and native Swedes.

Methods: Population-based, cross-sectional study conducted 2010–2012 including residents 30 to 75 years of age born in Iraq or Sweden, in whom oral glucose tolerance tests were performed and sociodemography and lifestyle behaviors were characterized.

Results: In Iraqis compared to Swedes, ISI was more impaired (76.9 vs. 102.3, $p<0.001$) whereas corrected insulin response CIR was higher (226.6 vs 188.6, $p=0.016$). However, insulin secretion was inadequate given the substantial insulin resistance, as indicated by lower DIo indices in Iraqis than in Swedes(DIo 12 712.9 vs. 14 659.2, $p<0.001$). The crude ethnic difference in ISI was not offset by traditional risk factors like waist circumference, body mass index or family history of diabetes.

In Iraqis, ISI conveyed somewhat higher odds of type 2 diabetes than in Swedes (odds ratio OR 0.98, 95% CI 0.97–0.99) vs. OR 0.95, 0.92–0.99), as indicated by an interaction between country of birth and ISI ($P_{interaction}=0.044$).

Conclusion: This study reports ethnic differences in the contribution of insulin action to type 2 diabetes. Our data suggests that the impaired insulin action observed in immigrants from the Middle East to Sweden is not fully explained by established risk factors.

Keywords: Type 2 diabetes, insulin action, insulin secretion, waist circumference, Middle East

Introduction

Since the 1940s, Sweden has adopted an open-door policy on immigration, offering almost unparalleled healthcare, education and employment opportunities to immigrants who acquire legal residence within the country. Fifteen percent of the Swedish population is comprised of immigrants, of which the second largest group is from Iraq [1]. One of the most multicultural regions of Sweden is the area in and around the southern Swedish city of Malmö, where almost 9,000 of the ~300,000 inhabitants are from Iraq. Recently the population based MEDIM study (Impact of Migration and Ethnicity on Diabetes In Malmö) have shown that immigrants from Iraq have a twice as high prevalence of type 2 diabetes (11.6 vs. 5.8 %, $p<0.001$)[2]. This is in consistency with previous studies showing that migration and urbanization are established risk factors for type 2 diabetes, and that immigrants from the Middle East to Sweden have a high prevalence of type 2 diabetes [3]. This high prevalence is thought to be a consequence of obesity (body mass index (BMI) >30 kg/m^2), which is highly prevalent in non-European immigrants [4]. A recent study has reported ethnic differences in insulin secretion and action related to ethnic background with a higher insulin sensitivity in Japanese than Northern Europeans Caucasians whereas Northern Europeans presented with better beta cell response to glucose [5]. However, the beta cell response relative to the degree of insulin resistance was similar in Japanese and Caucasians and this study concluded that main determinants for ethnic differences in metabolic profile are body mass index and adipose tissue [5].

Still, little is known about the metabolic, lifestyle, socioeconomic and heritable risk factors that

underlie the observation that type 2 diabetes is highly prevalent amongst Middle Eastern immigrants to Northern Europe. To increase knowledge of early mechanisms that contribute to type 2 diabetes and define the modifiable and non-modifiable risk factors for type 2 diabetes in immigrant populations of Middle Eastern descent living in Western countries, studies on insulin secretion and action are warranted and necessary for design and successful implementation of optimal preventive interventions against diabetes in these populations. Hence, in the current report from the MEDIM study, we aimed to (1) investigate insulin action and secretion (2) study risk factors associated with type 2 diabetes and (3) investigate the contribution of metabolic-, demographic- and lifestyle-related risk factors for impaired insulin action (insulin sensitivity index, ISI) in immigrants from Iraq, with comparisons to native Swedes.

Subjects

Citizens of Malmö born in Iraq aged 30 to 75 years were randomly selected from the census register and invited by mail and phone to participate in a population-based survey. We aimed to recruit Swedish participants matched for sex and age distributions living in the same geographical area in Malmö. People with severe physical or mental illness or disabilities were excluded from the study. To minimize cohort effects and assessment biases, examinations were conducted within a relatively short timeframe (February 1, 2010 through December 31, 2012). A flow chart describing the recruitment of MEDIM participants is described previously [6].

Materials and Methods

5

Physical examination

Trained Swedish- and Arabic-speaking research nurses conducted standard physical examinations. Assessment of standard physical examinations and clinical variables such as blood pressure, height, weight, waist circumferences, and BMI was performed as described previously [7].

Abdominal obesity was defined as a waist circumference of ≥94 cm in men and ≥80 cm in women, as recommended for Middle Eastern and Caucasian populations by the International Diabetes Federation/American Heart Association/National Heart Lung and Blood Institute [8].

Blood samples and oral glucose tolerance test

Participants were instructed not to eat or drink anything but water and not to use tobacco after 10 pm the day before testing; they were also asked to bring a record of their current medications to the examination. The following morning, a 75-g oral glucose tolerance test (OGTT) was performed. Blood samples were collected prior to glucose loading and at 30, 60, 90 and 120 min thereafter; glucose was measured in fresh plasma from venous whole blood immediately after sampling using a photometer (HemoCue AB, Ängelholm, Sweden) as described previously [7]. Serum insulin, cholesterol, triglyceride (p-TG), high-density lipoprotein (p-HDL) and low-density-lipoprotein (p-LDL) levels were determined as previously described [7]. Serum insulin levels were determined using a radioimmunoassay (Access© Ultrasensitive Insulin, Beckman Coulter, USA)[9] and c-peptide was measured with a one-step immunometric sandwich-method using an electrochemiluminiscence immunoassay (ECLI) based on a ruthenium (Ru) derivative (Roche Diagnostics, Mannheim, Germany). High sensitive c-reactive protein (hs-CRP) was

measured by a commercial kit, according to the manufacturer's instructions (Roche Diagnostics, Mannheim, Germany). HbA1c was estimated by high-pressure liquid chromatography (HPLC) with a VARIANT™ TURBO Hemoglobin A1c Kit 2.0 (Bio-Rad).

Normal glucose tolerance (NGT) was considered in participants with fasting glucose level of <6.1 mmol/l and 2-hplasma glucose level of <7.8 mmol/l. Impaired fasting glucose (IFG) was defined as a fasting plasma glucose level of ≥6.1 mmol/l and <7.0 mmol/l and a 2-h plasma glucose level of <7.8 mmol/l [10]. Impaired glucose tolerance (IGT) was defined as a fasting plasma glucose level of <6.1 mmol/L and a 2-h plasma glucose level of ≥7.8 mmol/l and <11.1 mmol/l [10] and impaired glucose regulation (IGR) was defined as IFG in combination with IGT. IFG, IGT and IGR are in this paper referred to as 'prediabetes'.

New cases of type 2 diabetes were confirmed by a fasting plasma glucose level of ≥7.0 mmol/L and/or by a 2-h plasma glucose level of ≥11.1 mmol/L. If only one glucose value was pathologic, the OGTT was repeated on another day within 2 weeks with the same fasting procedures. Two values exceeding these thresholds were needed for diagnosis [10]. Participants with previously known diabetes confirmed by medication with oral hypoglycaemic agents and/or insulin, or by a fasting glucose level of ≥7.0 mmol/L, did not undergo an OGTT.

Insulin sensitivity index (ISI), *corrected insulin response (CIR)* and *oral disposition index (DIo)* were assessed using the Matsuda indices that were calculated from the OGTT results as follows:

$$\text{ISI} = 10{,}000 / \sqrt{[(\text{f-glc (mmol/L)} \times \text{f-insulin (mIE/L)}) \times (\text{mean OGTT glc conc. (mmol/L)} \times \text{mean OGTT insulin conc. (mIE/L)})]} \ [11].$$

CIR, is a measure of glucose-stimulated insulin secretion at 30 min of OGTT and provides an estimation of beta-cell function and was calculated as follows:, We have tried to clarify this in

the revised version.

CIR = (100 × insulin at 30 min (mIE/L) / (glc30 (mmol/L)× (glc30 - 3.89 mmol/L)) [12] and requiring that glucose at 30 minutes (glc30) >4.44 mmol/l and glc30>f-glc [13].

DIo provides an estimate of beta-cell function adjusted for insulin resistance and takes the degree of insulin sensitivity into account as CIR is driven both by glucose and insulin sensitivity. DIo is calculated as CIR multiplied by ISI [14].

Questionnaires

Information on lifestyle habits, previous diagnosis of diabetes, current medication, family history of diabetes (in biological parents and/or siblings) and sociodemography was collected in interviews by Arabic- and Swedish-speaking nurses using structured questionnaires in Swedish and Arabic. All questionnaires were translated and back-translated by two independent professional translators with Arabic as their native language [7].

First-degree family history of diabetes was considered as the presence of diabetes in biological parents, siblings and/or children: FH- no first-degree relatives, FH+ one or more first-degree relatives with diabetes.

Smoking habits: Non-smokers included never-smokers and participants who had stopped smoking more than 6 months previously. All others were considered active smokers [15].

Alcohol consumption: Participants drinking alcohol were considered alcohol consumers, regardless of how often or how much they stated they drank.

Hours physically active/week: Physical activity (PA) was estimated using questions developed by the Swedish National Board of Health and Welfare to estimate time spent physically active

8

[16]. Time spent doing non-strenuous PA (e.g., walking, cycling or gardening) and strenuous PA (e.g., jogging, swimming, basketball or football) was estimated by the participants in minutes. Time spent doing strenuous PA was multiplied by two and then added to time spent doing non-strenuous PA [16]. Total minutes per week were transformed to hours per week.

Economic difficulties: Difficulties in paying for food, rent or bills on one or several occasions during the last 12 months [1].

Education level was categorized as (1) high school or less (≤HS) or (2) above HS.

Statistical analysis

Analyses were performed using STATA IC/12.1. Skewed variables were $\log_{10}$-transformed before analysis to approximate normal distributions. Least squares means were derived after age and sex adjustment using linear regression, whereas differences in proportions were adjusted for age and sex using logistic regression. Associations with type 2 diabetes were assessed using multivariate logistic regression analysis with original units (Table 2a) and units standardized within ethnicity (z-scores, Table 2b); these data are expressed as odds ratios (OR) with 95% confidence intervals (CIs) (Table 2). Associations with ISI were estimated using multivariate linear regression analysis; these data are expressed as β coefficients with 95% CIs (Table 3). In the multivariate model (Table 3), regression coefficients (beta β) for the continuous independent variables were standardized to a unit variance (per 1 standard deviation (SD)), in strata of ethnicity and sex.

All tests were two-sided and a *p*-value of <0.05 was considered statistically significant.

In order to minimize the multiple testing burden, interactions were considered only when the included marginal effects were significant.

In the regression model Table 2, adjusting for BMI in a univariate model increased the risk of type 2 diabetes. However, when waist circumference was added in the model, BMI contributed with reduced odds of type 2 diabetes and hence BMI was excluded because its collinearly with waist circumference (VIF=4.1). Multicollinearity was assessed using the variance inflation factor (VIF). Multicollinearity was not considered an issue, as VIF values in the final multivariate regression models were <3.5.

Ethical considerations

All participants provided written informed consent and the Ethics Committee at Lund University approved the study (application nos. 2009/36 and 2010/561). This investigation conforms to the principles outlined in the Declaration of Helsinki [17].

Results

Characteristics of the study population in relation to glucose tolerance

In Iraqi (*n*=1398) compared to Swedish (*n*=757) participants, type 2 diabetes was twice as prevalent (11.6 vs. 5.8%, *p*<0.001) and diabetes onset occurred more than six years earlier (Table 1). The prevalence of family history was positively correlated with the degree of glucose intolerance and was twice as frequent in Iraqis compared with Swedes across the full spectrum of glucose intolerance (Table 1).

Insulin action (as estimated by ISI) as well as beta cell function estimated from insulin response relative to the degree of insulin resistance (DIo) were generally lower in Iraqis as compared to Swedes (ISI 76.9 vs. 102.3, *p*<0.001 (mmol/L*mIE/L)$^{-1}$; DIo 12712.9 vs. 14659.2 (mmol/L^{-1*} mmol/L^{-1*} mmol/L^{-1}), *p*<0.001). Irrespective of the adequacy of ISI, in participants without type 2 diabetes, insulin secretion (as estimated by CIR) was generally higher in immigrants from Iraq (Figure 1). Although ISI, CIR and DIo generally decreased with state of glucose intolerance, ISI as well as beta cell function (DIo) were lower in the normoglycaemic and prediabetic stages in Iraqis versus Swedes (Table 1, Figure 2).

Further, normoglycaemic Iraqis presented a less advantageous lipid profile and higher body fat measurements (waist circumference and BMI) compared to Swedes (Table 1). In all glucose tolerance stages, immigrants from Iraq were less physically active and had a higher socioeconomic burden than ethnic Swedes (Table 1).

In a subset of participants with normal waist circumference (Iraqis n=304, Swedes n=239; waist circumference <94 cm in men and <80 cm in women [8]), ISI (age and sex adjusted data) was more severely impaired (106.6 vs. 149.6 mmol/L^{-1*}mIE/L^{-1}, *p*<0.001), DIo lower (14 933 vs.

18215 mmol/L^{-1*} mmol/L^{-1*}mmol/L^{-1}, *p=0.022*) and p-TG higher (1.4 vs. 0.9 mmol/L, *p<0.001*)

in immigrants from Iraq versus native Swedes. Similar results were seen in non-obese

participants (BMI<25 kg/m^2).

ISI, CIR and associations with type 2 diabetes

Studying the odds of type 2 diabetes, adjusting for age, sex, family history of diabetes, BMI and

waist circumference, in Iraqis, ISI conveyed higher standardized odds of type 2 diabetes than in

Swedes (Table 2a); the difference between the magnitude of these relationships was confirmed

by a statistically significant interaction between country of birth and ISI ($P_{interaction}$=0.044). There

was no interaction between country of birth and CIR. Data standardized within the strata of

ethnicity did not change the outcome of our data (Table 2b).

Ethnic background and association with insulin action, ISI, Table 3

In a stepwise regression model we studied factors associated with higher ISI in the total

population. The crude difference in ISI according to ethnicity remained significant even when

adjusting for metabolic-, anthropometric-, and lifestyle factors. The addition of lipoproteins in

the last step of the model reduced the coefficient substantially, but did not offset the difference in

ISI related to country of birth. We also observed interactions between country of birth and p-TG

($P_{interaction}$<0.001) and between FH+ and p-TG ($P_{interaction}$=0.018) that were associated with ISI.

Representativeness of the study sample

Although the participants in this study were somewhat older compared to the eligible background population (Iraqis by 1.7 years, 95% CI 0.9-2.5, $p<0.001$; Swedes 4.5 by years, 95% CI 3.5-5.6, $p<0.001$), the prevalence of self-reported diabetes in participants versus non-participants did not differ significantly (data not shown).

Discussion

To our knowledge, this is the first study to examine metabolic risk factors for type 2 diabetes and insulin action in an immigrant population from the Middle East (Iraq) to a northern European country and compare these risk factors with those observed in the native population. The key findings of this study are that there are ethnic differences in the relationship of insulin action with type 2 diabetes; our study suggests that ethnic background modifies the effect of insulin action on the risk of type 2 diabetes and further that the impaired insulin action in this Arabic population is only partly explained by excess waist circumference or other known risk factors for insulin action.

Ethnic differences in insulin action and secretion as risk factors for type 2 diabetes A recent systematic review and meta-analysis reported ethnic differences in the relationship between insulin sensitivity and insulin secretion by comparing Caucasians with Africans and East Asians [18]. Another study including 270 participants, reported higher insulin sensitivity and lower insulin secretion in Japanese compared with Caucasians of Northern European background [5]. In that study, disposition indices were similar for Japanese and Caucasians at all glucose tolerance states, indicating similar beta-cell response to glucose relative to the degree of insulin resistance and that these differences were ascribed differences in body composition [5]. Our larger data set on the contrary indicate that in a Middle Eastern immigrant population without type 2 diabetes, the beta cells are unable to compensate for the substantial peripheral insulin resistance by ramping up insulin secretion. This contrasts with our findings in native Swedes and appears to be independent of differences in body composition between ethnic groups. Defining

14

the mechanisms underlying these observations would be an important focus of future research. However, the metabolic characteristics of the leaner Iraqi participants in this study resembles those seen in patients with non-alcohol fatty liver disease (NAFLD) [19-21], which is a risk factor for type 2 diabetes [22] and shares its genetic risk factors with other intermediate metabolic risk factors such as impaired insulin sensitivity and hypertriglyceridemia [20].

Another explanation for the higher degree of insulin resistance in Iraqis compared with native Swedes in this study may be increased intramyocellular fat that is often seen in association with skeletal muscle insulin resistance [23]. Our finding of an interaction between higher p-TG level and family history influencing insulin action is in concordance with recent studies reporting disturbed lipid metabolism and skeletal muscle mitochondrial dysfunction in family history-positive versus family history-negative individuals [24, 25].

Strengths and limitations

The major strengths of this study are that it was conducted in Sweden, where health care, education, and employment are equally accessible to immigrant and non-immigrant populations; thus, confounding and biases attributable to these factors are likely to be less than in other study settings where immigrant and native populations are compared. Our study is population-based and represents a large fraction of the Iraqi population in the region. It is also distinct from other studies of this topic in that it includes detailed metabolic phenotyping and assessments of lifestyle exposures. The study is limited by the participation of more Iraqi men than women, which may reflect attitudes towards scientific research and other gender-specific sociocultural factors. We did not analyze liver enzymes to test for NAFLD, however studies have reported that

most individuals with NAFLD have normal levels of liver transaminases [26]. Another limitation is the cross-sectional, observational design, making it difficult to draw conclusions regarding causality in relation to type 2 diabetes as well as to insulin secretion and action.

Conclusions

This study shows ethnic differences in the contribution of insulin action and secretion to type 2 diabetes. Our data suggest that the impaired insulin action observed in the largest non-European immigrant group to Sweden, citizens born in Iraqis not fully explained by traditional risk factors such as body fat or family history of diabetes and that future research should focus on identifying the mechanisms behind this finding.

We conclude that Middle Eastern immigrant populations born in Iraq are likely to benefit greatly from interventions focused on improving insulin sensitivity, such as that deployed by the Diabetes Prevention Program [27] and the Finnish Diabetes Prevention Study [28].

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Table and figure legends

Table 1. Characteristics of citizens of Malmö born in Iraq and Sweden in relation to glucose tolerance state.

Table 2. Associations between type 2 diabetes and diabetes associated risk factors in immigrants from Iraq and native Swedes expressed as odds ratios (OR) with 95% confidence intervals (CI). There was an interaction between country of birth and Insulin Sensitivity Index, $P_{interaction}$=0.044).

Table 3. Factors associated with higher insulin sensitivity index (ISI) in immigrants from Iraq and native Swedes, associations expressed as β coefficients with 95% confidence intervals.

Figure 1. Insulin secretion (CIR), in relation to insulin sensitivity index (ISI) in participants without diabetes born in Iraq or Sweden.

Figure 2. Median level of insulin action and secretion estimated with Matsuda indices for insulin sensitivity index, ISI, corrected insulin response, CIR, and oral disposition index, DIo, in participants born in Iraq or Sweden with normal glucose tolerance, prediabetes (IFG, IGT or IGR) and type 2 diabetes, data presented with 95% CI.

Table 1. Characteristics of citizens of Malmö born in Iraq and Sweden in relation to glucose tolerance state.

Variable	Normal Glucose Tolerance			IFG, IGT or IGR			Type 2 Diabetes		
	Iraq N= 884	Sweden N=511	p	Iraq N= 348	Sweden N=198	p	Iraq N= 162	Sweden N=44	p
Age (years)	44.2 (8.9)	47.4 (10.6)	<.001	48.1(9.3)	53.1 (11.2)	<.001	53.5 (9.3)	58.5 (9.7)	.002
Age at diabetes onset (years)	-	-		-	-		47.6 (9.7)	53.4 (11.9)	.001
Male sex, n (%)	520 (58.8)	266 (52.1)	.014	192 (55.2)	105 (53.0)	.629	105 (64.8)	28 (63.6)	.885
First degree history of diabetes, n (%)	415 (46.9)	209 (27.6)	<.001	199 (57.2)	63 (31.8)	<.001	109 (67.3)	18 (40.9)	.001
Waist circumference men (cm)	97.6 (10.2)	95.4 (10.9)	.002	100.6 (9.8)	101.5 (11.1)	.894	105.5 (11.6)	106.5 (13.8)	.677
Waist circumference women (cm)	91.2 (10.1)	86.8 (13.1)	<.001	94.0 (10.8)	92.9 (14.1)	.146	102.2 (11.4)	104.4 (15.2)	.366
Body mass index (BMI) (kg/m^2)	28.7 (4.3)	26.4 (4.2)	<.001	29.9 (4.4)	28.7 (5.0)	.001	31.4 (5.1)	30.9 (6.1)	.987
Abdominal obesity (men ≥94 cm; women ≥80 cm)	651 (73.6)	314 (61.4)	<.001	287 (82.5)	156 (78.8)	.067	143 (88.3)	39 (88.6)	.693
Fasting glucose (mmol/L)	5.3 (.4)	5.3 (.4)	.237	6.1 (.5)	6.2 (.6)	.236	8.7 (2.8)	8.6 (3.1)	.326
30 min glucose (mmol/L)	7.8 (1.5)	7.6 (1.5)	.001	9.1 (1.7)	8.8 (1.8)	.021	11.9 (2.2)	13.1 (4.2)	.306
2-h glucose (mmol/L)	5.2 (1.3)	5.2 (1.3)	.282	7.6 (2.2)	7.2 (2.2)	.001	12.7 (3.9)	15.3 (5.7)	.093
Mean glucose 0, 30, 60, 120 min (mmol/L)	6.5 (0.9)	6.2 (0.9)	.001	8.3 (1.9)	7.9 (1.3)	.001	11.7 (2.2)	13.5 (4.2)	.054
Fasting insulin (mIE/L)	10.7 (6.7)	8.3 (5.9)	<.001	13.4 (9.3)	11.2 (8.2)	.005	14.8 (10.8)	14.8 (14.4)	.596
30 min insulin (mIE/L)	72.5 (54.1)	51.4 (34.6)	<.001	59.9 (40.7)	53.0 (49.7)	.114	42.3 (36.9)	42.5 (35.0)	.811
Mean insulin, 0, 30, 60, 120 min (mIE/L)	55.2 (36.2)	39.0 (25.6)	<.001	63.2 (40.5)	51.0 (44.9)	.001	53.6 (35.6)	44.9 (33.0)	.479
C-peptide (nmol/l)	.80 (.30)	.66 (.30)	<.001	.89 (.37)	.86 (.36)	.096	.93 (.39)	.96 (.51)	.503
Total cholesterol (mmol/L)[c]	5.0 (0.9)	5.3 (1.1)	<.001	4.8 (0.9)	5.1 (0.9)	.003	4.6 (1.3)	4.7 (1.1)	.337
p-LDL (mmol/L)[c]	3.3 (0.8)	3.4 (0.9)	.043	3.1 (0.8)	3.2 (0.8)	.551	2.9 (1.0)	2.9 (0.9)	.533
p-HDL (mmol/L)[c]	1.3 (0.3)	1.5 (0.4)	<.001	1.2 (0.3)	1.4 (0.4)	<.001	1.1 (0.3)	1.4 (0.5)	.005
p-TG (mmol/L)[c]	1.6 (0.9)	1.2 (0.8)	<.001	1.5 (1.0)	1.3 (0.8)	.022	1.9 (1.1)	1.6 (0.7)	.119
Hs-CRP (mg/L)	2.7 (3.3)	2.1 (3.3)	.002	3.3 (5.4)	2.9 (3.0)	.139	4.3 (5.9)	3.9 (2.9)	.926
Systolic blood pressure (mmHg)[d]	126 (15.6)	132 (18.4)	<.001	132 (17.3)	141 (20.7)	<.001	138 (17.9)	150 (21.1)	.003
Diastolic blood pressure (mmHg)[d]	77 (9.9)	80 (10.9)	<.001	80 (10.6)	84 (12.2)	.010	80 (11.3)	85 (10.3)	.007
Hours physically active/week	1.9 (2.1)	4.1 (2.4)	<.001	1.8 (2.0)	3.9 (2.6)	<.001	1.9 (2.1)	3.3 (1.9)	.001
Smokers, n (%)	216 (24.4)	132 (25.8)	.358	78 (22.4)	51 (25.8)	.154	40 (24.7)	10 (22.7)	.733
Alcohol consumers, n (%)	166 (18.8)	417 (81.6)	<.001	54 (15.5)	163 (82.3)	<.001	33 (20.4)	34 (77.3)	<.001
Education level ≤HS, n (%)	248 (28.1)	76 (14.9)	.001	86 (24.7)	53 (26.8)	.593	50 (30.9)	14 (31.8)	.888
Econ.diff..≥ once the last 12 months, n (%)	467 (52.8)	79 (15.5)	.015	164 (47.1)	30 (15.2)	.072	83 (51.2)	5 (11.4)	<.001

Data presented in means (standard deviation, SD), numbers (percentages) or medians (interquartile range, IQR). Differences in means between groups were adjusted for age and sex using linear regression models (for continuous variables) while differences in proportions between groups (but for male sex and family history of diabetes) were studied using logistic regression adjusting for age and gender.

All tests were two-sided and a *p*-value of <0.05 was considered statistically significant.

[a] Data presented as IQR.

[b] CIR and DI only included cases where the glucose level at 30 min was >4.44 mmol/l and greater than the fasting glucose level [19].

[c] Differences also adjusted for treatment with medication lowering cholesterol levels (i.e. statins or similar medication).

[d] Differences also adjusted for blood pressure lowering medication

Abbreviations: Econ. diff. Economic difficulties; CIR corrected insulin response; DIo disposition index; HDL high density lipoprotein; Hs-CRP high sensitive C-reactive protein; HS high school; IFG impaired fasting glucose; IGT impaired glucose tolerance; IQR interquartile range; ISI insulin sensitivity index; LDL low density lipoprotein; SD standard deviation; TG triglycerides.

Table 2a. Associations between type 2 diabetes and diabetes associated risk factors in immigrants from Iraq and native Swedes expressed in original units as odds ratios (OR) with 95% confidence intervals (CI). There was an interaction between country of birth and Insulin Sensitivity Index, $P_{interaction}$=0.044.

Risk factors	Type 2 diabetes Born in Iraq N=1144 R^2= 0.42			Type 2 diabetes Born in Sweden N=666 R^2= 0.45		
	OR	95% CI		OR	95% CI	
Age (years)	1.03	0.98	1.07	1.03	0.97	1.10
Male sex	0.64	0.26	1.57	0.90	0.25	3.27
Waist circumference (cm)	**1.05**	**1.01**	**1.10**	1.05	0.99	1.12
Insulin Sensitivity Index, (mmol/L*mIE/L)$^{-1}$	**0.98**	**0.97**	**0.99**	**0.95**	**0.92**	**0.99**
Corrected insulin response [a], (mIE/L*mmol/L^{-1*}mmol/L^{-1})	**0.97**	**0.96**	**0.98**	**0.98**	**0.97**	**0.99**
Family history of diabetes (yes/no)	1.05	0.46	2.41	1.58	0.43	5.85

Table 2b. Associations between type 2 diabetes and diabetes associated risk factors in immigrants from Iraq and native Swedes expressed in standardized units (mean=0; SD=z-scores) as odds ratios (OR) with 95% confidence intervals (CI).

Risk factors	Type 2 diabetes Born in Iraq N=1148 R^2= 0.43			Type 2 diabetes Born in Sweden N=644 R^2= 0.43		
	OR	95% CI		OR	95% CI	
Age, per 1 SD	1.03	0.99	1.08	1.04	0.98	1.10
Waist circumference, per 1 SD	**1.05**	**1.01**	**1.09**	1.06	0.99	1.12
Insulin Sensitivity Index, per 1 SD	**0.98**	**0.97**	**0.99**	**0.96**	**0.93**	**0.99**
Corrected insulin response [a], per 1 SD	**0.97**	**0.96**	**0.98**	**0.98**	**0.97**	**0.99**

Associations in Table 2a and 2b were assessed using multivariate regression analysis adjusting for age, waist circumference, insulin sensitivity index, corrected insulin response. Table 2a was

also adjusted for the dichotomous variables male sex and family history of diabetes. Body mass index was not included in the model due to collinearity with waist circumference, variance inflation factor (VIF) =4.1.

[a]CIR only included cases where the glucose level at 30 min was >4.44 mmol/l and greater than the fasting glucose level (1).

[*] Bold-faced numbers are statistically significant.

Table 3. Factors associated with higher insulin sensitivity index (ISI) in immigrants from Iraq and native Swedes, associations expressed as β

coefficients with 95% confidence intervals.

Variable	Model 1 N=1915 R^2 0.05	Model 2 N=1854 R^2 0.09	Model 3 N=1842 R^2 0.34	Model 4 N=1644 R^2 0.36	Model 5 N=1572 R^2 0.42
Born in Sweden	Reference	Reference	Reference	Reference	Reference
Born in Iraq	**-.120** -.146 to -.095	**-.111** -.137 to -.085	**-.120** -.142 to -.097	**-.122** -.146 to -.099	**-.117** -.139 to -.094
Age (years), per 1 SD		**-.022** -.034 to -.009	.001 -.011 to .011	-.006 -.017 to .006	-.008 -.020 to .003
Female sex		Reference	Reference	Reference	Reference
Male sex		**-.096** -.121 to -.071	**-.092** -.113 to -.071	**-.100** -.122 to -.077	**-.098** -.120 to -.076
Family history of diabetes					
- No		Reference	Reference	Reference	Reference
- Yes		**-.043** -.068 to -.017	-.021 -.043 to .002	-.023 -.046 to .001	-.018 -.040 to .004
Waist circumference, per 1 SD			**-.098** -.118 to -.078	**-.097** -.118 to -.076	**-.086** -.106 to -.065
Body mass index (kg/m^2), per 1 SD			**-.051** -.071 to -.032	**-.049** -.069 to -.028	**-.039** -.059 to -.018
Hours physically active/week, per 1 SD				**.013** .008 to .018	**.026** .015 to .037
Current tobacco smoking				.028 .002 to .054	**.038** .012 to .063
High sensitive CRP (mg/L), per 1 SD					-.010 -.021 to .001
Plasma triglycerides (mmol/L), per 1 SD					**-.044** -.056 to -.032
Plasma high density lipoprotein (mmol/L), per 1 SD					**.025** .012 to .037

β-coefficients were standardized (SD) per 1 SD unit variance for the continuous independent variables. Standardizations were done in the strata of ethnicity and sex.

Collinearity waist circumference and BMI < 3.5.

[*] Bold-faced numbers are statistically significant.

Figure 1. Insulin secretion (CIR), in relation to insulin sensitivity index (ISI) in participants without diabetes born in Iraq or Sweden.
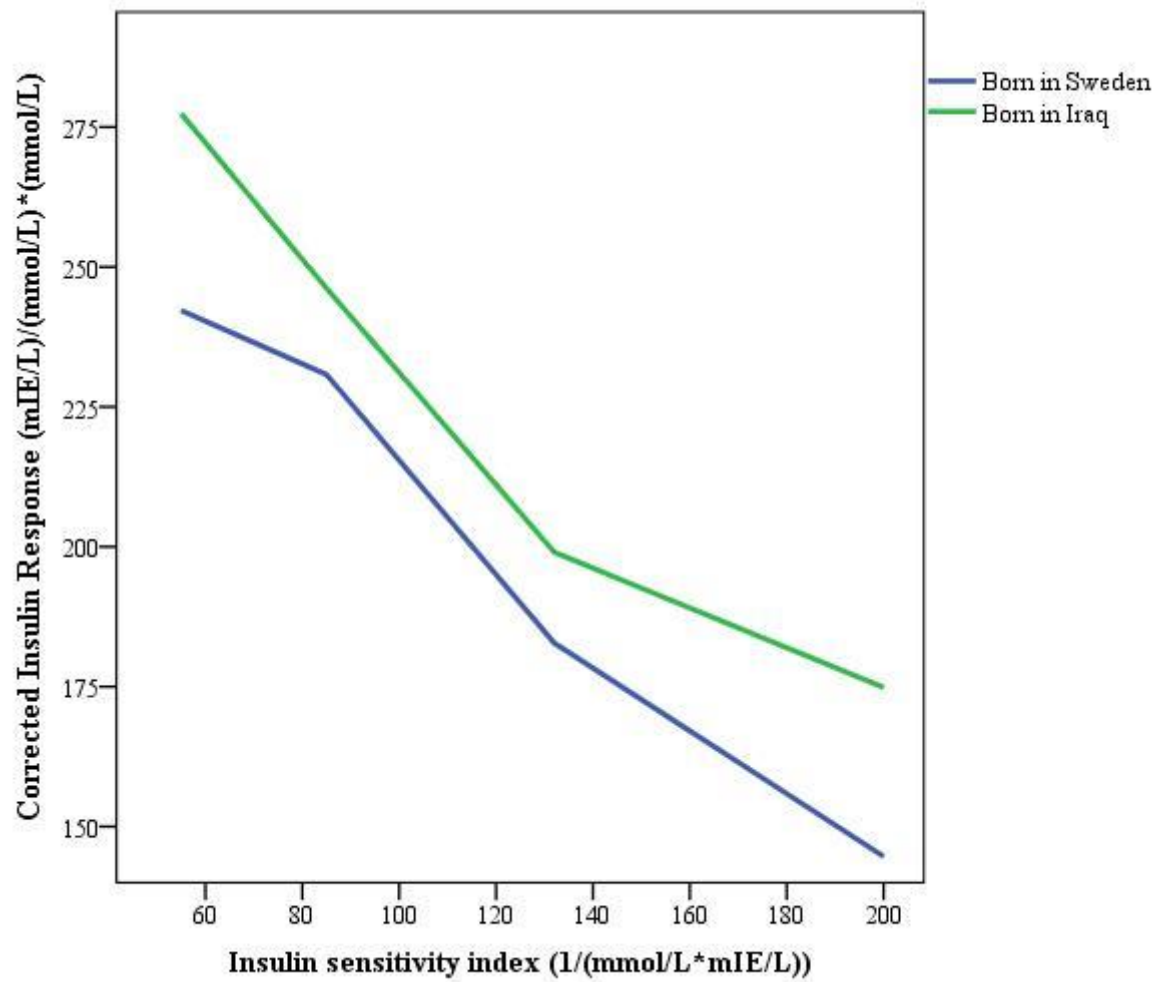
Figure 2. Median level of insulin action and secretion estimated with Matsuda indices for insulin sensitivity index, ISI, corrected insulin response, CIR, and oral disposition index, DIo, in participants born in Iraq or Sweden with normal glucose tolerance, prediabetes (IFG, IGT or IGR) and Type 2 diabetes, data presented with 95% CI.