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Country of birth modifies the association of fatty liver index with insulin action in Middle Eastern immigrants to Sweden

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ABSTRACT

Aims: Non-alcohol fatty liver disease (NAFLD) is a strong risk factor for insulin resistance and type 2 diabetes. The prevalence of NAFLD varies across populations of different ethnic backgrounds but the prevalence in Middle Eastern populations, which are at high risk of type 2 diabetes, is largely unknown. Using fatty liver index (FLI) as a proxy for NAFLD the aim was to calculate the odds of NAFLD (FLI ≥ 70) given country of origin and further to investigate the associations between ISI and FLI.

Methods: In 2010–2012 we conducted a population-based study of individuals aged 30–75 years born in Iraq or Sweden, in whom anthropometrics, fasting blood samples and oral glucose tolerance tests were performed and sociodemography and lifestyle behaviors characterized.

Results: A higher proportion of Iraqis ($N = 1085$) than Swedes ($N = 605$) had a high probability of NAFLD (FLI ≥ 70 , 32.5 vs. 22.6%, $p < 0.001$, age- and sex-adjusted data) and ISI was more severely impaired (70.7 vs. 95.9%, $p < 0.001$). Independently of traditional risk factors for NAFLD, being born in Iraqi increased the risk of FLI ≥ 70 (OR 1.59: 95% CI 1.15, 2.20). Furthermore, country of birth presented a stronger association between ISI and FLI ≥ 70 in Iraqis than in Swedes ($P_{\text{interaction}} = 0.019$).

Conclusions: Our data indicate that immigrants from Iraq are at higher risk of NAFLD. The finding that country of birth modifies the relationship of FLI with ISI, suggests that liver fat may be a stronger determinant of impaired insulin action and increased risk of type 2 diabetes in Iraqis than in Swedes.

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Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; CIR, corrected insulin response; DIO, disposition index; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; IQR, interquartile range; ISI, insulin sensitivity index; LDL, low-density lipoprotein; p, plasma; SD, standard deviation; TGs, triglycerides.

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1. Introduction

Immigrants from the Middle East represent the largest non-European immigrant group to Sweden and are, compared to the native Swedish population, at high risk of impaired insulin action and type 2 diabetes [1]. The higher prevalence is partly explained by an excess prevalence of abdominal obesity and family history of diabetes; nonetheless, our data has shown that being born in Iraq is an independent risk factor for diabetes [2]. Furthermore, the MEDIM (impact of Migration and Ethnicity on Diabetes in Malmö) study has shown that insulin sensitivity index (ISI) is lower in Iraqis than in Swedes, and that ISI may have a stronger impact on type 2 diabetes risk in Iraqis than in Swedes [1]. The lower ISI values in immigrants from Iraq are not fully explained by traditional risk factors such as family history of diabetes, abdominal obesity or physical inactivity, as illustrated by the fact that in individuals with a normal waist circumference and/or body mass index (BMI), ISI is more impaired than in Iraqis than in Swedes with equivalent levels of adiposity [1]. This suggests that mechanisms other than abdominal obesity or other traditional risk factors for insulin resistance may influence insulin action in Iraqis.

The mechanisms underlying the profound insulin resistance in the Iraqi born population are poorly understood, which motivated the current study. Whilst insulin action is influenced by abdominal and visceral obesity, other organs such as peripheral muscle and the liver are also involved [3]. For instance, non-alcohol fatty liver disease (NAFLD) represents a strong risk factor for impaired insulin action, pre-diabetes and type 2 diabetes [4]. Patients diagnosed with NAFLD also have a higher release of inflammatory markers than patients without NAFLD [5] and they also have a higher risk of cardiovascular disease (CVD) [6]. These results are in consistency with previous findings from the MEDIM study, showing that the association between lower ISI and inflammatory markers – such as cytokines – irrespective of other risk factors [7] is stronger and that the prevalence of CVD in diabetics is higher in Iraqis than in Swedes [8]. Altogether these findings indicate that NAFLD may be more prevalent and have a greater impact on insulin action and diabetes risk in Iraqis than native Swedes.

Globally, NAFLD is the most prevalent type of liver disease [9–11] and its prevalence differs according to ethnic background [12], with 12 to 15% in Asians [13] and 30% in Americans [14] affected. Although the characteristics of the Iraqi immigrant population resemble those of patients with NAFLD, the prevalence of NAFLD and association with insulin action in Middle Eastern populations has to the best of our knowledge not been investigated before. Thus, using the fatty liver index (FLI) as a proxy for NAFLD [15], in the MEDIM study we determined whether FLI levels differed between immigrants from Iraq and native Swedes and sought to characterize the factors underlying these differences. Further, we sought to study associations between insulin sensitivity index (ISI) and FLI.

2. Subjects

Citizens of Malmö born in Iraq and 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. According to the census register, the population of Iraqi immigrants 30 to 75 years of age in Malmö consisted in 2010 of 4397 persons with a mean age of 44.8 years and of whom 57.8% were men. Swedish born citizens living in the same geographical area in Malmö were randomly selected from the census register to reach a similar age and gender distribution as the Iraqi population (mean age 45.2 years, $p = 0.08$; 57.4% males $p = 0.74$). Iraqi and Swedish individuals were then contacted and invited by mail and phone to participate in the study. We aimed to recruit a final sample of 2:1 Iraqi and Swedish participants with the goal to reach a similar age and sex distribution amongst the final participants as amongst the original background population. People with type 1 diabetes, severe physical or mental illness or disabilities were excluded from the study. A prerequisite for inclusion in the study was also that all values included in the FLI (gamma-glutamyl transferase (p-GGT), BMI, waist circumference and/or plasma triglycerides (p-TG)) were assessed.

To minimize cohort effects and assessment biases, examinations were conducted within a relatively short time-frame (February 1, 2010 through December 31, 2012). A flow chart describing the recruitment and participation rate of MEDIM is presented in a supplementary figure. All participants conducting an oral glucose tolerance test (OGTT) that did not have excessive alcohol habits (<9 standard glasses/week for women and <14 standard glasses/week for men) were included in the study.

3. Materials and methods

3.1. Physical examination

Standard physical examinations were performed by trained Swedish- and Arabic-speaking research nurses and clinical variables such as blood pressure, height, weight, waist circumferences, BMI and abdominal obesity were assessed and defined as previously described [16,17].

3.2. Blood samples and oral glucose tolerance tests

Participants were instructed to be fasting and not to eat or drink anything but water and not to use tobacco after 10 pm the day before testing. In the following morning, fasting blood samples were taken and a 75-g OGTT was performed and blood samples for plasma glucose and serum insulin at 30, 60, 90 and 120 min were collected thereafter. Blood glucose, serum insulin, HbA1c, total cholesterol, p-TG, high-density lipoprotein cholesterol (p-HDL) and low-density-lipoprotein cholesterol (p-LDL) levels were determined as previously described [16,18]. Plasma alanine aminotransferase (p-ALT, IU/L), aspartate aminotransferase (p-AST, IU/L) and gamma-glutamyl transferase (GGT, IU/L) were measured using a Cobas analyzer (Roche Diagnostics, Mannheim, Germany).

Normal glucose tolerance (NGT), impaired fasting glucose (IFG), impaired glucose tolerance (IGT), impaired glucose regulation (IGR, IFG in combination with IGT) and type 2 diabetes were defined according to World Health Organization criteria [19]; NGT, fasting glucose level of <6.1 mmol/L and a

2-h plasma glucose level of <7.8 mmol/L; IFG, 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, IGT, 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 and type 2 diabetes fasting plasma glucose level of ≥ 7.0 mmol/L and/or 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 [19]. IFG, IGT and IGR are in this paper collectively referred to as 'prediabetes'. Estimation of insulin sensitivity (ISI) and beta cell function (corrected insulin response, CIR and oral disposition index, DIo) were assessed using the Matsuda indices calculated from the OGTT as described previously [20–23].

FLI was calculated as previously described by Balkau et al. [15]:

$$FLI = \frac{e^L}{(1 + e^L) \times 100}$$

where $L = 0.953 (\log_e p\text{-TG}) + 0.139 \times \text{BMI} + 0.718 (\log_e \text{GGT}) + 0.053 \times \text{waist circumference} - 15.745$.

Liver fat score was calculated as previously described by Kotronen et al. [24]:

$$\text{Liver fat score} = -2.89 + 1.18 \times \text{metabolic syndrome [17]} (\text{yes} = 1/\text{no} = 0) + 0.45 \times \text{type 2 diabetes} (\text{yes} = 2/\text{no} = 0) + 0.15 \times \text{fasting S-insulin (mU/L)} + 0.04 \times \text{fasting S-AST (U/L)} - 0.94 \times \text{AST/ALT}$$

3.3. Questionnaires

Information on previous diagnoses of diabetes, current medication, family history of diabetes (in biological parents and/or siblings), lifestyle habits and sociodemography was collected in interviews by Arabic- and Swedish-speaking nurses using structured questionnaires in Swedish and Arabic. Questionnaires were translated and back-translated by two independent professional translators with Arabic as their native language [16].

Smoking habits, alcohol consumption and hours physically active/week were assessed as described previously [1].

3.4. Statistical analysis

Analyses were performed using STATA IC/12.1. Least squares means were derived after age and sex adjustment using general linear models; differences in proportions were adjusted for age and sex using logistic regression. Associations with $FLI \geq 70\%$ were assessed using stepwise logistic regression analysis and associations with ISI (log transformed) were assessed by linear regression analysis. Units were standardized in strata of ethnicity and sex per 1 standard deviation (SD) unit variance for the continuous independent variables. Data are expressed as odds ratios (ORs) (FLI as the dependent variable) and β coefficients (ISI as the dependent variable) with 95% confidence intervals (CIs) (Tables 2a and 2b). 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.

Multicollinearity was not considered an issue, as variance inflation factor (VIF) values in the final multivariate regression models were <3.1.

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). The MEDIM study conforms to the principles outlined in the Declaration of Helsinki [25].

4. Results

In total, 1085 participants born in Iraq and 605 participants born in Sweden were included in the study. Despite the Iraqi as compared to the Swedish population was younger than the Swedish population (45.2 vs. 49.1 years, $p < 0.001$) their FLI values were higher (54.6 vs. 43.2, $p < 0.001$) and their insulin sensitivity was more impaired (ISI 70.7 vs. 95.9%, $p < 0.001$). A higher proportion of Iraqis than Swedes had a high probability of fatty liver ($FLI \geq 70$, 32.5 vs. 22.6%, $p < 0.001$, age- and sex-adjusted data, Fig. 1).

Amongst participants with a high probability of NAFLD ($FLI \geq 70$), the Iraqis were paradoxically younger, had lower total cholesterol levels and lower p-LDL levels as compared to the Swedes. Furthermore, their prevalence of the metabolic syndrome was lower and in women waist circumference was smaller than in Swedes (Table 1). In participants with low ($FLI < 20$) and medium FLI values ($FLI 20\text{--}69$), Iraqis had worse glucose and lipid metabolism, as indicated by lower ISI values, higher BMI, lower p-HDL levels, higher p-TG levels and higher fasting glucose levels (Table 1).

In a stepwise logistic regression model we studied risk factors associated with $FLI \geq 70$ (Table 2a). Adjusting for the confounding effect of other known risk factors for NAFLD such as age, sex, abdominal obesity, type 2 diabetes and/or alcohol consumption, being born in Iraq remained an independent risk factor for $FLI \geq 70$. Other risk factors independently contributing to higher odds of $FLI \geq 70$ were female sex, type 2 diabetes and last but not least abdominal obesity that contributed with over 27 times the odds of $FLI \geq 70$. Together, all risk factors explained 34% of the variance (R^2) in liver fat scores (Table 2a). The variance did not differ between ethnicities (data not shown).

Correlation between FLI and ISI (log-transformed) in participants without abdominal obesity who were born in Iraq or Sweden are presented in Fig. 2. This figure shows that with decreasing ISI, FLI increased even more in Iraqis than in Swedes, indicating a stronger influence of NAFLD on insulin resistance in the Iraqi population. We then analysed associations between ISI and traditional risk factors for insulin resistance after adjusting for FLI (Table 2b). Being born in Iraq remained an independent risk factor for impaired ISI in the full multivariate model. Furthermore, we observed that country of birth modified the effect of $FLI \geq 70$ ($P_{\text{interaction}} = 0.019$), indicating a stronger association between ISI and $FLI \geq 70\%$ in Iraqis than in Swedes. Together, all risk factors explained 35% of the variance (R^2) in ISI.

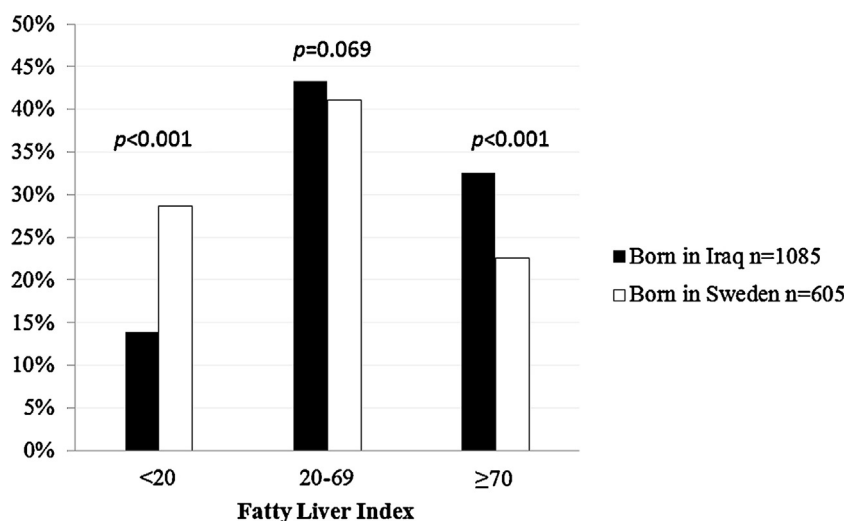


Fig. 1 – Distribution of low (<20), medium (20–69) and high (≥70) fatty liver index (FLI) values in participants born in Iraq or Sweden. High FLI values were more prevalent in Iraqis than in Swedes (32.5 vs. 22.6%, $p < 0.001$), whereas low FLI values were less prevalent (13.9 vs. 28.7%, $p < 0.001$).

4.1. Representativeness of the study sample

In immigrants from Iraq the age and sex distribution did not differ in study participants compared to the eligible background population. Participants born in Sweden were older (49.1 vs. 44.8 years, $p < 0.001$), but the sex distribution did not differ compared to the eligible native Swedish population (data not shown).

5. Discussion

A key novel finding from this study is that irrespective of other traditional risk factors for fatty liver disease, Iraqis had a higher risk of NAFLD (FLI ≥ 70) than native Swedes. Furthermore, high FLI and Iraqi origin were independently associated with impaired insulin action irrespective of traditional risk factors such as physical inactivity, abdominal obesity and type 2 diabetes.

The finding that country of birth modifies the relationship of FLI with ISI, suggests a stronger effect of fatty liver on insulin action in Iraqis than in Swedes, and opens a possible effect of fatty liver as a strong contributor to impaired insulin action and increased risk of type 2 diabetes in this population that to our knowledge has not been reported before.

5.1. NAFLD and insulin resistance

Diminished insulin secretion and action are important pathological determinants of type 2 diabetes [26]. Insulin action is not only regulated by abdominal or visceral obesity but that other organs and tissues, such as peripheral muscle and the liver are also involved [3]. NAFLD is associated with impaired insulin action and was previously identified as an independent risk factor for pre-diabetes and type 2 diabetes

[3,4]. Previous data from the MEDIM study showed stronger associations between type 2 diabetes and insulin action in Iraqis than in Swedes, indicating that in Iraqis impaired insulin action appears to have a greater impact on type 2 diabetes [1].

The metabolic characteristics of the Iraqi participants in the MEDIM study resemble a NAFLD phenotype [19–21], with pronounced insulin resistance, high plasma TG levels and a high prevalence of diabetes despite less abdominal obesity [1]. Further, patients diagnosed with NAFLD are reported to have a higher release of inflammatory markers than patients without NAFLD [5]. Consistent with those findings, we previously showed that the associations between lower ISI and inflammatory markers such as cytokines are stronger in Iraqis than in Swedes, irrespective of other risk factors [7]. We have also shown that the association between cardiovascular disease (CVD) in Iraqis depends on diabetes status, with three-fold higher odds of CVD in Iraqis with diabetes as compared Swedes with diabetes; amongst individuals without diabetes the odds of CVD amongst Iraqis half that observed in Swedes [8]. This is consistent with a previous study of diabetes patients which reported that patients diagnosed with NAFLD having a higher prevalence of CVD than those without NAFLD [6]. Since these data altogether indicate that a high proportion of the Iraqi population may have NAFLD in this study we investigated whether differences in NAFLD could explain the profound insulin resistance in the Iraqi born group. As a proxy for NAFLD we included FLI ≥ 70 in our analysis. By doing that the variance increased more than three-fold (from 0.13 to 0.34), reflecting the strong influence of NAFLD on insulin resistance. Still being born in Iraq remained an independent risk factor for ethnic differences in insulin resistance indicating there are additional genetic-, behavioral or metabolic risk factors influencing insulin resistance in this immigrant population that remain to be detected.

Table 1 – Characteristics of the study population born in Iraq or Sweden that underwent an oral glucose tolerance test in relation to low (<20), medium (20–69) or high (≥70) fatty liver index values [15].

Variable	Fatty liver index <20			Fatty liver index 20–69			Fatty liver index ≥70		
	Born in Iraq N = 168 (13.9%)	Born in Sweden N = 188 (28.7%)	p	Born in Iraq N = 524 (43.3%)	Born in Sweden N = 269 (41.1%)	p	Born in Iraq N = 393 (32.5%)	Born in Sweden N = 148 (22.6%)	p
Age (years)	41.9 (9.0)	46.8 (10.7)	<0.001	45.7 (9.4)	49.4 (11.1)	<0.001	46.2 (8.5)	50.6 (11.3)	<0.001
Male gender, n (%)	50 (29.8)	63 (33.5)	0.448	299 (57.1)	162 (60.2)	0.393	296 (75.3)	104 (70.3)	0.234
BMI (kg/m ²)	24.6 (2.2)	23.2 (2.2)	<0.001	27.8 (2.6)	27.0 (2.7)	<0.001	32.4 (4.1)	32.3 (4.3)	0.419
Waist men (cm)	85.3 (4.9)	84.1 (7.4)	0.329	93.9 (6.2)	94.9 (6.4)	0.301	105.9 (9.1)	107.7 (8.9)	0.231
Waist women (cm)	81.4 (6.6)	78.6 (7.1)	0.005	92.1 (5.9)	93.0 (6.6)	0.219	103.9 (7.6)	109.9 (9.9)	<0.001
ISI ^a (mmol/L × mU/L ⁻¹)	121.8 (97.8–161.0)	157.9 (112.2–211.8)	<0.001	83.2 (59.8–18.3)	94.1 (72.1–133.9)	<0.001	53.2 (37.0–74.8)	56.2 (43.0–76.7)	0.177
CIR ^a (mU/L × mmol/L ⁻¹ × mmol/L ⁻¹)	150.8 (95.0–252.8)	130.8 (76.5–204.9)	0.135	164.4 (92.7–267.8)	146.0 (86.9–214.5)	0.973	199.8 (116.8–347.3)	180.9 (111.1–289.4)	0.399
Dio ^a	19021.9 10605.3–33537.2)	20263.8 (12719.3–30.958.4)	0.221	12879.6 (7302.2–23703.2)	13689.1 (7934.4–24145.3)	0.010	10454.7 (5522–18235)	9801.3 (5186.2–17701.5)	0.834
Total cholesterol (mmol/L)	4.4 (0.8)	4.9 (1.0)	<0.001	4.8 (0.9)	5.3 (1.0)	<0.001	5.2 (1.0)	5.5 (1.1)	0.001
p-LDL (mmol/L)	2.8 (0.7)	3.0 (0.8)	0.110	3.2 (0.8)	3.4 (0.9)	0.023	3.4 (0.9)	3.7 (1.0)	0.007
p-HDL (mmol/L)	1.4 (0.3)	1.7 (0.4)	<0.001	1.2 (0.3)	1.4 (0.4)	<0.001	1.1 (0.3)	1.1 (0.3)	0.728
p-TGs (mmol/L)	0.8 (0.3)	0.7 (0.2)	0.008	1.3 (0.6)	1.2 (0.5)	<0.001	2.2 (1.2)	2.0 (1.1)	0.551
p-ALT (IU/L)	9.3 (3.3)	8.9 (3.2)	0.573	11.3 (4.9)	12.5 (8.5)	0.011	14.5 (9.1)	13.7 (7.9)	0.879
p-AST (IU/L)	22.9 (6.0)	23.7 (6.3)	0.491	25.9 (6.6)	27.4 (12.1)	0.027	29.8 (10.3)	29.0 (9.4)	0.386
p-GGT (IU/L)	13.9 (7.3)	16.4 (9.4)	0.125	27.7 (16.9)	32.3 (32.0)	0.019	54.0 (52.6)	59.8 (63.3)	0.210
Fasting glucose (mmol/L)	5.5 (0.6)	5.4 (0.5)	0.024	5.7 (0.6)	5.6 (0.6)	0.051	5.6 (0.8)	5.8 (1.0)	0.382
2-h glucose (mmol/L)	5.5 (1.6)	5.4 (1.6)	0.274	5.8 (1.9)	5.6 (1.9)	0.052	6.3 (2.5)	6.6 (2.6)	0.742
Liver fat score [24]	−3.5 (1.1)	−3.8 (1.1)	0.051	−2.2 (1.5)	−2.4 (1.3)	0.134	−0.6 (1.9)	−0.6 (2.1)	0.598
New cases of type 2 diabetes, n (%)	0	0	0.314	10 (1.9)	2 (0.7)	0.220	16 (4.1)	6 (4.1)	0.947
Metabolic syndrome [17], n (%)	19 (11.3)	12 (6.4)	0.066	213 (40.6)	101 (37.5)	0.022	294 (74.8)	125 (84.5)	0.036

Participants with excessive alcohol consumption (≥9 standard glasses/week in women and ≥14 standard glasses/week in men) were excluded from the study. Data are presented as the mean (standard deviation, SD), number (percentage) or median (interquartile range, IQR). Differences in means between groups were adjusted for age and sex using general linear models (for continuous variables) while differences in proportions between groups were studied using logistic regression adjusted 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 CIR and Dio only included cases where the glucose level at 30 min was >4.44 mmol/L and was greater than the fasting glucose level [22].

Table 2a – Risk factors associated with fatty liver index ≥ 70 in the total study population.

Variable	Model 1	Model 2	Model 3
	($R^2 = 0.09$)	($R^2 = 0.10$)	($R^2 = 0.34$)
	OR	OR	OR
	95% CI	95% CI	95% CI
Born in Sweden	Reference	Reference	Reference
Born in Iraq	1.73	1.71	1.59
	1.38 to 2.18	1.36 to 2.16	1.15 to 2.20
Age (years), per 1 SD	1.16	1.14	1.02
	1.04 to 1.30	1.02 to 1.28	0.90 to 1.15
Female sex	Reference	Reference	Reference
Male sex	2.84	2.85	4.78
	2.26 to 3.56	2.27 to 3.58	3.71 to 6.15
No diabetes		Reference	Reference
Type 2 diabetes		3.72	3.30
		1.77 to 7.82	1.48 to 7.34
No alcohol consumption			Reference
Alcohol consumption			1.05
			0.77 to 1.44
No abdominal obesity			Reference
Abdominal obesity			27.04
			16.43 to 44.49

Associations were studied using stepwise logistic regression and expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The variance is expressed as R^2 . Odds ratios were standardized (SD) in the strata of ethnicity and sex per 1 SD unit variance for the continuous independent variables.

5.2. NAFLD and ethnic differences

Studies of the Pima Indians, a population that shares similarities with Iraqis in that they are highly insulin resistant and have one of the highest prevalence rates of type 2 diabetes in the world, have shown that increased lipid content in the

liver independently links hypoadiponectinaemia, hypertrophic obesity and increased visceral adiposity with peripheral and hepatic insulin resistance [27]. These findings are consistent with our finding that type 2 diabetes and abdominal obesity increased the odds of NAFLD ($FLI \geq 70$). Our findings that being born in Iraq was an independent risk factor for NAFLD together with the finding that country of birth modified the effect of $FLI \geq 70$ on insulin action, suggests that NAFLD has a potentially crucial role in the development of type 2 diabetes in Iraqis, representing the largest non-European immigrant group in Sweden. Our data further suggests that the Iraqi population with NAFLD is younger than the Swedish born population. This may reflect an earlier onset of disturbed fat metabolism contributing to insulin resistance and an earlier diabetes onset in Iraqi immigrants that we have previously reported [28].

Increased knowledge of the mechanisms triggering insulin action in different populations is important for better understanding in this high risk population for type 2 diabetes.

To our knowledge, there is a dearth of data on NAFLD from Iraq. However, our data of an estimated prevalence of NAFLD of over 30% in this population correspond with previous studies conducted in the Middle East region. For instance a comparison between populations of Arabs and South Asians in Kuwait revealed a prevalence of NAFLD in 33.3 and 29.0%, respectively [29] whereas the prevalence of NAFLD in Israelis was reported to 30% [30] in both studies NAFLD was verified by abdominal ultrasonography. Further ethnic as well as gender differences in the prevalence of NAFLD is reported in studies of Blacks, Hispanics and Whites conducted in the USA, with a higher prevalence in Hispanics than in Blacks and a higher prevalence in men than in women [14,29,30]. The latter is

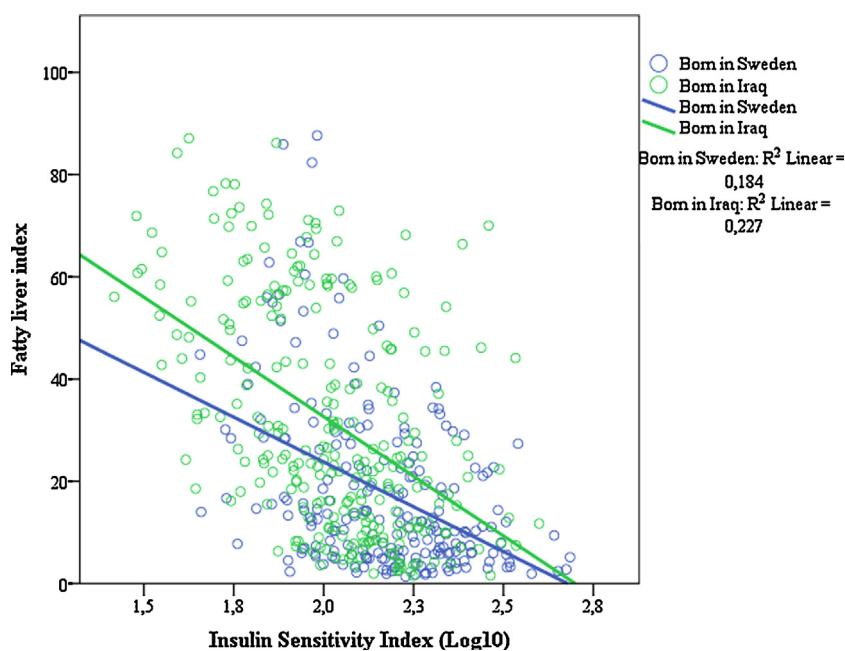


Fig. 2 – Correlation between fatty liver index (FLI) and insulin sensitivity index (ISI, log-transformed) in participants without abdominal obesity who were born in Iraq or Sweden. The association between ISI and $FLI \geq 70$ was modified by country of birth ($P_{\text{interaction}} = 0.019$), indicating that fatty liver disease may have a stronger impact on insulin action in Iraqis than in Swedes.

Table 2b – Risk factors associated with insulin sensitivity index (log-transformed) in the total study population.

Variable	Model 1	Model 2	Model 3	Model 4	Model 5
	R ² = 0.09 β 95% CI	R ² = 0.10 β 95% CI	R ² = 0.13 β 95% CI	R ² = 0.34 β 95% CI	R ² = 0.35 β 95% CI
Born in Sweden	Reference	Reference	Reference	Reference	Reference
Born in Iraq	–.12 –.15 to –.10	–.13 –.14 to –.09	–.12 –.15 to –.10	–.09 –.11 to –.07	–.11 –.13 to –.08
Age (years), per 1 SD	–.02 –.04 to –.01	–.02 –.03 to –.01	–.03 –.04 to –.01	–.01 –.02 to .01	–.01 –.02 to .01
Female sex	Reference	Reference	Reference	Reference	Reference
Male sex	–.10 –.12 to –.07	–.10 –.13 to –.08	–.10 –.13 to –.08	–.08 –.11 to –.06	–.08 –.11 to –.06
No family history of diabetes		Reference	Reference	Reference	Reference
Family history of diabetes		–.04 –.07 to –.02	–.04 –.07 to –.02	–.02 –.04 to .01	–.02 –.04 to .01
Physical activity (h/week), per 1 SD			.04 .03 to .06	.03 .02 to .04	.03 .02 to .04
No abdominal obesity				Reference	Reference
Abdominal obesity				–.14 –.17 to –.12	–.14 –.17 to –.11
No type 2 diabetes				Reference	Reference
Type 2 diabetes				–.14 –.22 to –.06	–.14 –.22 to –.06
Fatty liver index <70				Reference	Reference
Fatty liver index ≥70				–.19 –.22 to –.16	–.24 –.28 to –.19
Born in Iraq × Fatty liver index ≥70					.06 .01 to .12

Associations were studied using stepwise linear regression and are expressed as β coefficients with 95% confidence intervals (CIs). The variance is expressed as R². β-coefficients were standardized (SD) in the strata of ethnicity and sex per 1 SD unit variance for the continuous independent variables. Variance inflation factor (VIF) <3.8. Numbers highlighted in bold are statistically significant.

consistent with our data showing higher odds of FLI ≥70 in men than in women, irrespective of abdominal obesity or other risk factors for NAFLD. A higher prevalence of NAFLD in different populations could also be caused by genetics. For instance, NAFLD shares genetic risk factors with other intermediate metabolic risk factors such as diminished insulin sensitivity and hypertriglyceridemia [20] and genetic factors is shown to contribute to disturbed fat metabolism and increased fat storage in the liver, causing steatohepatitis and subsequently fibrosis [3].

5.3. Strengths and limitations

Our study is population-based and represents a large fraction of the Iraqi population in the studied 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 inability to infer causality due to the cross-sectional design. The participating Swedes were somewhat older than the corresponding native Swedish background population, which may have introduced selection bias. However, we consider our data reliable since age is adjusted for in the multivariate regression models. FLI or other estimations of NAFLD have been developed in a Caucasian population and has not been studied or validated before in Middle Eastern populations. Another limitation is that the study lacks quantitative information on liver fat content assessed by abdominal ultrasound or magnetic resonance imaging (MRI).

6. Conclusions

This study reports that irrespective of traditional risk factors, immigrants from Iraq have a higher probability of NAFLD and worse insulin action than native Swedes. Although liver fat content was not investigated by ultrasound or MRI in the present study, our data indicate that Iraqis and in particular Iraqi males have a very high probability of NAFLD, and that this probability increases further in those with abdominal obesity. Our data suggests that liver fat content may play a stronger role in insulin action in the Iraqi compared to the Swedish population. Population-based focused on objectively verifying liver fat content and studying the influence of NAFLD on type 2 diabetes risk in Middle Eastern populations may be warranted.

Conflict of interest statement

Louise Bennet, Leif Groop and Paul W. Franks declare that they have no conflict of interest.

Statement of human and animal rights

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008 (5).

Statement of informed consent

Informed consent was obtained from all patients for being included in the study.

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L.B. designed the study, wrote the manuscript, and obtained, analyzed and interpreted the data. L.G. contributed to the design of the study, interpretation of the data and discussions of the study's findings. P.W.F. contributed to interpretation of the data, discussions of the study's findings and writing the manuscript. All authors revised/edited the article critically and approved the final version of the manuscript.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <http://dx.doi.org/10.1016/j.diabres.2015.07.011>.

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