Received: 1 April 2020 | Revised: 8 October 2020 | Accepted: 14 October 2020

DOI: 10.1002/dmrr.3419

RESEARCH ARTICLE

WILEY

Adult-onset diabetes in Middle Eastern immigrants to Sweden: Novel subgroups and diabetic complications—The All New Diabetes in Scania cohort diabetic complications and ethnicity

Louise Bennet[1,3] | Christopher Nilsson[1,2] | Dina Mansour-Aly[4] | Anders Christensson[1,2] | Leif Groop[1,5] | Emma Ahlqvist[1,4]

[1]Department of Clinical Sciences, Lund University, Malmö, Sweden

[2]Department of Nephrology, Skåne University Hospital, Malmö, Sweden

[3]Department of Family Medicine, Lund University, Malmö, Sweden

[4]Department of Clinical Sciences, Genomics, Diabetes and Endocrinology, Lund University Diabetes Centre, Lund University, Malmö, Sweden

[5]Finnish Institute of Molecular Medicine Finland (FIMM), Helsinki University, Helsinki, Finland

Correspondence
Louise Bennet, Department of Clinical Sciences, Clinical Research Center, Jan Waldenströms gata 35 205 02 Malmö, Sweden.
Email: louise.bennet@med.lu.se

Funding information
Crafoordska Stiftelsen; Vetenskapsrådet, Grant/Award Numbers: 2009-1039 (Exodiab), 2015-558, 2017-02688, 349-2006-237 (Linneus grants); Diabetesförbundet; Hjärt-Lungfonden; Novo Nordisk Foundation Center for Basic Metabolic Research; Insamlingsstiftelsen Diabetes Wellness Network Sverige, Grant/Award Number: 25-420; Stiftelsen för Strategisk Forskning, Grant/Award Number: IRC15-0067; Direktör Albert Påhlssons Stiftelse

Abstract

Background: Middle Eastern immigrants to Europe represent a high risk population for type 2 diabetes. We compared prevalence of novel subgroups and assessed risk of diabetic macro- and microvascular complications between diabetes patients of Middle Eastern and European origin.

Methods: This study included newly diagnosed diabetes patients born in Sweden ($N = 10641$) or Iraq ($N = 286$), previously included in the All New Diabetes in Scania cohort. The study was conducted between January 2008 and August 2016. Patients were followed to April 2017. Incidence rates in diabetic macro- and microvascular complications were assessed using cox-regression adjusting for the confounding effect of age at onset, sex, anthropometrics, glomerular filtration rate (eGFR) and HbA1c.

Findings: In Iraqi immigrants versus native Swedes, severe insulin-deficient diabetes was almost twice as common (27.9 vs. 16.2% $p < 0.001$) but severe insulin-resistant diabetes was less prevalent. Patients born in Iraq had higher risk of coronary events (hazard ratio [HR] 1.84, 95% CI 1.06–3.12) but considerably lower risk of chronic kidney disease (CKD) than Swedes (HR 0.19; 0.05–0.76). The lower risk in Iraqi immigrants was partially attributed to better eGFR. Genetic risk scores (GRS) showed more genetic variants associated with poor insulin secretion but lower risk of insulin resistance in the Iraqi than native Swedish group.

Interpretation: People with diabetes, born in the Middle East present with a more insulin-deficient phenotype and genotype than native Swedes. They have a higher risk of coronary events but lower risk of CKD. Ethnic differences should be considered in the preventive work towards diabetes and its complications.

Nilsson Christopher and Mansour-Aly Dina contributed equally to this study.

KEYWORDS
ethnicity, GRS, macrovascular diabetic complications, microvascular diabetic complications, novel subgroups of diabetes, SIDD, SIRD

1 | INTRODUCTION

During recent decades, political instability in the Middle East has forced millions of people to flee their homelands. Many subsequently take refuge in Europe, in general, and in Sweden and Germany in particular. In Sweden today, the largest immigrant groups originate from Iraq and Syria, most of whom reside in the three largest Swedish cities: Stockholm, Gothenburg and Malmö.

For many years it has been acknowledged that Middle Eastern immigrants are at high risk of developing type 2 diabetes[1] but the contributing mechanisms have been poorly understood. Migration, socioeconomy and urbanisation are well known risk factors for type 2 diabetes.[2] Further, studies have shown indications of different contributing mechanisms for type 2 diabetes in different ethnic populations,[3–5] and that, for instance, type 2 diabetes patients originating from non-Westernised countries display worse metabolic control as compared to diabetes patients born in Sweden.[6] The increased migration contributes to the growing diabetes epidemic in Europe, which we still do not fully understand how to prevent or treat.[4]

To address the risk of type 2 diabetes in the large proportion of Middle Eastern immigrants in Sweden, the MEDIM study (the impact of Migration and Ethnicity on Diabetes In Malmö) a population based cohort study, was conducted in Malmö from 2010 to 2012, and included Iraqi born immigrants and native Swedes that lived in the same socioeconomic area.[7] The increased risk of type 2 diabetes in the Middle Eastern population was primarily attributable to obesity, family history of diabetes in biological first degree relatives, sedentary lifestyles and unhealthy diets; however, the study also showed that Middle Eastern ethnicity in itself contributed to an increased risk of type 2 diabetes.[7] The study also showed that a large proportion of the Iraqi immigrant population, still free from diabetes, presented with relative insulin deficiency and hyperglycaemia.[8] Although the insulin secretion was higher than in native Swedes, it was still not sufficient enough to compensate for the profound insulin resistance, which resulted in relative deficiency of insulin secretion (as reflected by lower disposition index), and higher HbA1c values in the immigrant population.[8]

In spite of the inferior glycaemic control, the Middle Eastern immigrant population, as compared to the native Swedish population, paradoxically displayed lower blood pressure levels as well as better kidney function, as measured by estimated glomerular filtration rate (eGFR) based on both creatinine and cystatin C.[9] In this immigrant population, the long-term impact of lower blood pressure levels and better kidney function on cardiovascular disease risk (CVD), in general, and diabetic macro- and microvascular complications, in particular, remains to be unravelled.

Recently, novel subgroups of adult-onset type 2 diabetes were defined in the All New Diabetes in Scania study (ANDIS). In the ANDIS study newly diagnosed adult diabetes patients were clustered based on presence or absence of GAD65 autoantibodies, age at diabetes onset, BMI, HbA1c, insulin secretion(HOMA2-B) and Homeostatic model assessment for insulin resistance (HOMA2-IR).[10] Five subgroups were identified: 'severe autoimmune diabetes' (SAID), 'severe insulin-deficient diabetes' (SIDD), 'severe insulin-resistant diabetes' (SIRD), mild obesity-related diabetes (MOD) and mild age-related diabetes (MARD). Patients with SIRD had increased risk of diabetic kidney disease whereas patients with SIDD had increased risk of diabetes retinopathy.[10]

Still, differences in risk of developing diabetic complications across ethnicities and contributing mechanisms remain largely unknown. Predicting diabetic complications could enable individualised preventive actions and therapy, thus contributing to reduced morbidity and mortality and health related costs, as well as reduced health inequities.[11] In order to provide sufficient prevention strategies and treatment across ethnic groups, the risk of diabetic complications remains to be assessed and characterised.

The aim of this study was to study the prevalence of novel subgroups of adult-onset diabetes within the ANDIS framework, and assess risk of diabetic macro- and microvascular complications across Middle Eastern and European ethnicities.

2 | MATERIALS AND METHODS

2.1 | Study population and setting

The ANDIS study is an ongoing longitudinal study, started on 1 January 2008, that includes patients diagnosed with diabetes in the Scania region in Sweden (approximately 1 200 000 inhabitants http://andis.ludc.med.lu.se/). Patients were included in this study until 18 August 2016 and followed for chronic kidney disease (CKD) to 31 Dec 2016 and CVD to 5 April 2017. The included participants were newly diagnosed diabetes patients born in either Iraq or Sweden, diagnosed in primary health care in Region Skåne and included in ANDIS. The recruiting process is described in detail previously.[10] Diabetes was defined according to definitions set by the World Health Organization.[12] Patients with diabetes duration over two years or with missing data were excluded. All participants received oral and written information about the study and signed an informed consent form.

2.2 | Measurements

After an overnight fast of at least 10 h, fasting blood samples were drawn assessing fasting glucose, C-peptide and glutamic acid decarboxylase antibodies (GADA).

HbA_{1c} was measured at diagnosis. Follow-up data on serum creatinine was used for calculating eGFR based on the Modification of Diet in Renal Disease Study (MDRD) formula.[13] During the 8-year follow-up, these measurements were regularly assessed and updated from the clinical chemistry database. Plasma creatinine analyses were isotope dilution mass spectrometry (IDMS)-traceable during this period. DNA was extracted from blood drawn at registration. ANDIS was genotyped with InfiniumCoreExome-24v1-1 BeadChip arrays (Illumina), at Lund University Diabetes Centre, Malmö, Sweden.

2.3 | Cluster analysis

All patients included in this study were part of the previously published cluster analysis that identified five novel subgroups of diabetes.[10] The analysis was based on HbA1c, Body Mass Index (BMI), age at onset of diabetes, homoeostasis model assessment (HOMA) assessing two estimates of beta cell function (HOMA2-β) and insulin resistance (HOMA2-IR) based on c-peptide concentrations[14] and the presence or absence of GADA antibodies. GADA antibodies have been measured using ELISA. Presence or absence of GADA was included as a binary variable (Table 1). No de novo cluster analysis was performed for this study.

2.4 | Definitions

Novel subgroups of diabetes were defined as previously described[10]: Briefly, *SAID* had early diabetes onset, low BMI, high HbA1c, insulin deficiency (low HOMA2-β) and presence of GADA; *SIDD* had the same characteristics as SAID but were GADA negative; *SIRD* high HOMA2-IR, and high BMI; *MOD* early diabetes onset, high BMI and low HOMA-IR; *MARD*, high age at onset, with modest metabolic derangements regarding BMI, HbA1c, insulin resistance and insulin deficiency.

The analysis of genetics and diabetic complications was restricted to individuals with T2D, defined by the absence of GAD autoantibodies, in order to minimise confounding by individuals with T1D. A separate analysis of individuals with T1D was not feasible due to the small number in the Iraqi group.

CKD was defined as an eGFR of <60 mL/min per 1.73 m^2 (stage 3A) or <45 mL/min per 1.73 m^2 (stage 3B) for >90 days.

Diabetic retinopathy was diagnosed based on fundus photographs, and assessments conducted by a skilled ophthalmologist. Patients with at least moderate retinopathy were considered as cases.

Coronary events (angina pectoris, ischaemic heart disease and atherosclerotic heart disease) *and Stroke* were captured via the hospital register and defined by International Classification of Diseases (ICD-10). Coronary events were defined by the following diagnosis codes I20, I21, I24; I251 and I253-I259. Stroke was defined by the diagnosis codes I60-I61 and I63-I64.

Ethnicity was defined by patients and both parents' country of birth (in this study Iraq or Sweden) and self-reported at registration in the ANDIS study.

2.5 | Genetic risk scores

The analysis of genetic risk scores (GRS) included Iraqi individuals ($N = 232$) as cases and Swedish individuals ($N = 8619$) as controls. As mentioned, GADA antibodies positive individuals were excluded ($N = 728$). GRS were constructed using $r2 = 0.1$, and 250 kb window, as implemented in PLINK v1.9/2. The weighted T2D-GRS was calculated using the effect size of known T2D associated variants[15] ($n = 353$, minor allele frequency >1% in ANDIS) or their proxies ($r2 > 0.8$) after clumping ($r2 = 0.5$, 250 kb window) in PLINK. GRS for insulin secretion rate (ISR-wGRS) and Insulin Sensitivity Index (ISI-wGRS) included the known T2D SNPs[15] were calculated using the effect sizes reported in published GWASs of ISI and ISR as weights.[16,17] The BMI-GRS was calculated based on the published genetic effect of SNPs associated with high BMI with genome-wide significance.[18] Included SNPs and weights (effect sizes) are listed in Tables S1–S4.

2.6 | Statistical analysis

Statistical analysis was performed using SPSS version 23 (SPSS Inc). Comparisons of quantitative data was done using linear regression adjusted for age at diagnosis, sex and BMI (except for analysis of age at diagnosis). Comparisons between categorical data were performed using binary logistic regression models adjusted for age at diagnosis, sex and BMI (but for sex).

The hazard ratios (HR) of macro- and microvascular diabetic complications were calculated using Cox regression, including covariates as described in the Tables and Results section. Analysis of GRS was done by logistic regression of z-score GRS in *R*.

2.7 | Role of the funding source

The study sponsors had no roles in the design, collection of the data, analysis, interpretation of the data in writing the report or in the decision to submit the paper for publication. The corresponding author had full access to the data and had final responsibility for the decision to submit for publication.

3 | RESULTS

3.1 | Cluster analysis

The initial study population consisted of 13 720 patients. After excluding those with diabetes >2 years duration, 12 191 patients

TABLE 1 Basic characteristics of the study population

	Born in Iraq $N = 183$	Born in Sweden $N = 7044$	*p*-value unadjusted	*p*-value adjusted
Age at diagnosis, years	51.4 (10.4)	61.2 (12.5)	<0.001	<0.001
Male sex, %, *n*	71 (130)	59.9 (4218)	0.003	0.025
BMI, kg/m^2	30.6 (5.1)	30.6 (5.7)	0.872	0.060
HbA1c, mmol/mol[a]	66.9 (25.6)	62.7 (24.8)	0.012	0.656
C-peptide, nmol/L[a]	1.1 (0.4)	1.3 (0.6)	0.002	0.984
HOMA2-β[a]	84.7 (45.1)	90.7 (45.7)	0.132	0.203
HOMA2-IR[a]	2.8 (1.4)	3.3 (1.9)	0.001	0.067
eGFR ml/min/1.73m^2 at diagnosis	107.1 (27.6)	90.1 (24.9)	<0.001	<0.001
GADA positive, % (*n*)	2.2 (4)	7.0 (496)	0.016	0.001
GADA concentration in GADA positive (ELISA), (kE/L)	148.3 (117.7)	159.6 (105.1)	0.830	0.977
Hypertension. % (*n*)	45.4 (83)	72.9 (5125)	<0.001	<0.001
Chronic kidney disease, % (*n*)				
Stage 3A (eGFR <60 ml/min/1.73 m^2)	0.5 (1)	6.4 (448)	0.012	0.184
Stage 3b (eGFR <45 ml/min/1.73 m^2)	-	1.6 (111)	0.995	0.995

Notes: Continuous data presented as means (SDs). Categorical data presented with percentage (numbers). Comparisons between means were assessed using linear or logistic regression with or without adjustment for age at diagnosis, sex and BMI.

Abbreviations: BMI, Body Mass Index; eGFR, glomerular filtration rate; ELISA, Enzyme linked immuno assay; GADA, glutamic acid decarboxylase antibodies; HOMA, homoeostasis model assessment; SD, standard deviation.

[a]Non-normally distributed data were natural logarithmised.

remained in the study. Of these, a total of 10 927 were included in the study by being born in Sweden $N = 10641$ or Iraq $N = 286$. In the cluster analysis, a total of 3700 patients (born in Sweden $N = 3597$; born in Iraq $N = 103$) were not included due to missing data, resulting in a total of 7 227 participants (born in Sweden $N = 7\,044$, Iraqi $N = 183$).

Basic characteristics are presented in Table 1. Diabetes onset occurred a decade earlier in patients born in Iraq as compared to patients born in Sweden. A larger proportion of Iraqi immigrants were males. Diabetes patients born in Iraq were insulin deficient to a higher extent, based on C-peptide and HOMA2-β. Kidney function was better in Iraqis at baseline and the prevalence of CKD stage 3A (eGFR <60 mL/min/1.73 m^2) was considerably lower at onset. No Iraqi born patient had CKD stage 3b (eGFR<45 mL/min/1.73 m^2). Further, a considerably smaller proportion of diabetes patients born in Iraq were diagnosed with hypertension.

The distribution of diabetes clusters across Middle Eastern and European ethnicities is presented in Figure 1. In Iraqi immigrants, MOD was the most prevalent subgroup followed by SIDD. MOD and SIDD were 1.5–2 times as prevalent as in native Swedes (MOD 39.3 vs. 19.1% $p < 0.001$; SIDD 27.9 vs. 16.2% $p < 0.001$). On the contrary, in native Swedes, MARD, SIRD and SAID respectively, were 2–3 times as prevalent as in Iraqi immigrants. In Iraqi born patients SIRD and SAID accounted for only a few per cent of the cases (MARD 41.3 vs. 25.1% $p < 0.001$; SIRD 16.3 vs. 5.5% $p < 0.001$; SAID 7.0 vs. 2.2% $p = 0.016$).

Regarding insulin-deficient diabetes, SIDD was more prevalent in Iraqi immigrants whereas SAID was more prevalent in native Swedes.

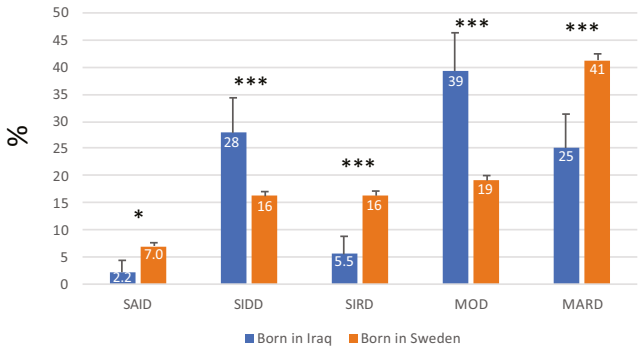

FIGURE 1 Distribution of novel diabetic subgroups in diabetes patients born in Iraq or Sweden. Error bars show 95% CI, *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$; MARD, mild age-related diabetes; MOD, mild obesity-related diabetes; SAID, severe autoimmune diabetes; SIDD, severe insulin-deficient diabetes; SIRD, severe insulin-resistant diabetes

In the Swedish born population, the proportion of SIDD and SIRD was equal, whereas in the Iraqi born population, SIDD was more than five times as prevalent as SIRD.

3.2 | Coronary events

Out of the eligible study population of 10 927 patients born in Sweden or Iraq, those with missing data and/or coronary event prior to diabetes onset were excluded, resulting in a follow-up of 7021

patients (born in Sweden $N = 6817$; born in Iraq $N = 204$). In total, 390 coronary events (3.2%) were registered during the 8-year follow-up (born in Sweden $N = 376$; born in Iraq $N = 14$), Figure 2. Patients born in Iraq had 84% higher risk of coronary event than native Swedes (Table 2). Females were at considerably lower risk than males, and patients with higher BMI at baseline were also slightly protected from coronary events during follow-up. HbA1c at onset did not predict coronary events.

3.3 | Chronic kidney disease

In total 7668 (born in Sweden $N = 7461$; born in Iraq $N = 207$) out of the eligible study population of 10 927 patients were included in the analysis. During the 8 year follow-up a total of 957 patients (born in Sweden $N = 955$; born in Iraq $N = 2$) were recorded with stage 3A CKD (eGFR of <60 mL/min per 1.73 m^2), Figure 3. Iraqi immigrants had a considerably lower risk of developing CKD as compared to native Swedes (HR 0.19; 0.05 - 0.76) adjusted for sex, age at diabetes onset, baseline BMI and HbA1c, Table 2. After adjusting the model for eGFR, the trend remained but was no longer significant (HR 0.30; 0.074 to 1.20, $p = 0.088$). Females were at considerably higher risk than males of developing CKD (HR 1.32; 1.16 - 1.50).

3.4 | Stroke

After excluding those with missing data or a known history of stroke prior to diabetes onset, a total of 7551 (born in Sweden $N = 7341$; born in Iraq $N = 210$) out of the initial 10 927 diabetes patients were included in the follow-up. A total of 254 events of stroke (born in Sweden $N = 250$; born in Iraq $N = 4$) were observed. We could not observe any significant differences in the incidence of stroke across ethnicities during follow-up. Younger age at diabetes onset predicted increased risk for stroke (HR 1.06; 1.05 - 1.08) whereas HbA1c and BMI did not. Female diabetes patients had decreased stroke risk as compared to males (HR 0.75; 0.58 to 0.97).

3.5 | Diabetes retinopathy

Fundus photography was conducted in 55 Iraqis and 1907 Swedes. The prevalence of patients displaying at least moderate retinopathy was almost twice as high in first generation immigrants (12.7 vs. 7.3%, $p = 0.141$), but the difference was not statistically significant, possibly due to the small sample size.

3.6 | GRS analysis

Finally, we performed a GRS analysis comparing the load of genetic risk variants associated with T2D, BMI, ISR and ISI in Iraqi and Swedish individuals (Table 3). The Iraqi group had higher GRS for

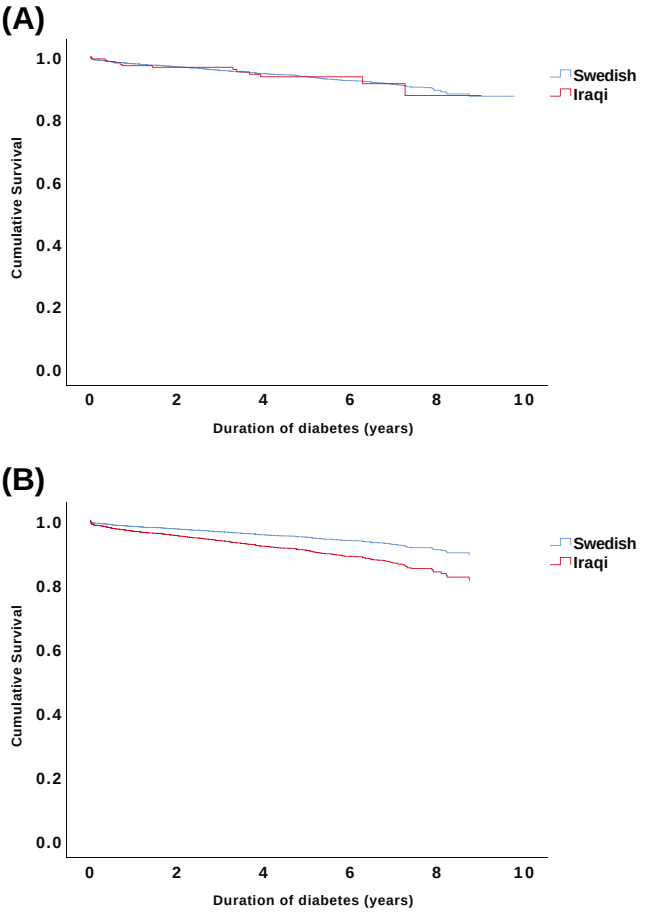

FIGURE 2 Development of coronary events during 8 years follow-up in diabetes patients born in Iraq or Sweden. Iraqi born individuals had higher adjusted hazard ratios for coronary events than native Swedes. (A) Unadjusted cumulative survival (HR 1.03; 0.60–1.75, $p = 0.92$). (B) Cumulative survival after adjustment for sex, age at diabetes onset, BMI and HbA1c (HR 1.84; 1.06–3.12, $p = 0.029$); BMI, body mass index; HR, hazard ratio

T2D, that is, higher genetic risk for T2D ($P = 0.008$) but lower GRS for BMI, that is, lower genetic risk of obesity ($P = 0.013$). The Iraqi group also had lower ISR-GRS (<0.001), that is, higher load of genetic variants associated with impaired insulin secretion, and higher ISI-GRS which means lower genetic risk of insulin resistance.

4 | DISCUSSION

4.1 | Key findings

This is one of the first studies investigating novel subgroups of diabetes and its impact on diabetic complications across newly diagnosed diabetes patients of Middle Eastern and European ancestry. The key and novel findings of this study is that MOD as well as insulin-deficient diabetes SIDD are the most common subtypes of diabetes in Iraqi immigrants with almost 40% presenting with MOD and every fourth diabetes patient with SIDD. Further, we show that

TABLE 2 Cox regression of HR, (95% CI) for coronary events and chronic kidney disease in Iraqi immigrants and native Swedes diagnosed with type 2 diabetes

Coronary events												
Variable	HR	95% CI		HR	95% CI		HR	95% CI				
Country of birth (Sweden ref.)	1.03	0.60–1.75	0.918	1.56	0.91–2.69	**0.104**	**1.84**	1.06–3.12	**0.029**			
Age at onset				**1.04**	1.03–1.05	**<0.001**	**1.04**	1.03–1.05	**<0.001**			
Sex (male sex ref.)				**0.42**	0.34–0.52	**<0.001**	**0.41**	0.32–0.51	**<0.001**			
BMI				**0.99**	0.97–1.01	0.342	0.99	0.97–1.01	**0.189**			
HbA1c mmol/mol							1.00	0.99–1.01	0.551			
Chronic kidney disease, CKD												
Variable	**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**		**HR**	**95% CI**	
Country of birth (Sweden ref.)	**0.09**	0.03–0.28	**<0.001**	**0.26**	0.08–0.80	**0.026**	**0.19**	0.05–0.76	0.19	0.30	0.074–1.20	0.088
Age at onset				**1.10**	1.09–1.11	**<0.001**	**1.11**	1.10–1.12	**<0.001**	**1.05**	1.04–1.06	**<0.001**
Sex (male sex ref)				**1.29**	1.15–1.44	**<0.001**	**1.32**	1.16–1.50	**<0.001**	1.07	0.94–1.22	0.295
BMI				**1.03**	1.02–1.04	**<0.001**	**1.03**	1.02–1.04	**<0.001**	**1.02**	1.01–1.03	0.004
HbA1c mmol/mol							**1.01**	1.00–1.01	**<0.001**	**1.01**	1.00–1.01	**<0.001**
First eGFR										**0.93**	0.92–0.93	**<0.001**

Notes: Bold values are statistically significant.

Abbreviations: BMI, Body Mass Index; CKD, chronic kidney disease; eGFR, glomerular filtration rate; HR, hazard ratio.

the risk of coronary events is higher in Iraqi born versus native Swedish patients, whereas the risk of CKD is considerably lower. After adjustment for initial eGFR the lower risk of CKD in Iraqi immigrants was no longer statistically significant. However, the lower risk remained low, indicating this could be mostly a power issue, and that the lower risk of CKD was not fully explained by the initial better eGFR. Differences in risk of coronary events across diabetes patients of Middle Eastern and European ethnicities were not fully explained by age at onset, HbA1c, BMI or sex. Contributing mechanisms across ethnicities needs to be further evaluated.

4.2 | Severe insulin-deficient diabetes

The distribution of SIDD and SIRD was equal in the Swedish born population, whereas in the Iraqi born population, SIDD was five times more prevalent than SIRD. A higher proportion of SIDD than SIRD patients has also been reported in China (approximately 14% vs. 8%).[19] However, the proportion of SIDD in the Iraqi born population is considerably higher than in the Asian population with every fourth diabetes patient born in Iraq displaying SIDD.

We have previously demonstrated that Iraqi immigrants are exposed to relative insulin deficiency long before they develop diabetes.[8] Diabetes onset occurs six to seven years earlier compared to the background European population, and at lower BMI.[20] The early diabetes onset represents a characteristic of the subgroup SIDD[10] and as reported previously an important contributor to diabetic complications.[10] Thus the Middle Eastern population display similarities with the South Asian population being insulin resistant in the non-diabetic stages and subsequently developing beta cell exhaustion and insulin deficient type 2 diabetes at younger ages than the European population.[4]

Genetic insulin secretion risk scores show significant associations with SIDD, MARD and MOD,[10,21] all representing the most common diabetes subgroups in the Iraqi immigrant population. Iraqi immigrants have a high family burden of type 2 diabetes[22] suggesting a high genetic risk.[23] This is in line with our findings from the GRS analysis where the Iraqi group had higher risk scores for T2D. Previously we have shown that with increasing family burden, insulin secretion decreases, however, the level of insulin resistance remains consistent.[22] Since diabetes risk variants influencing insulin secretion contributes to SIDD rather than SIRD, our previous findings indicate that genetic risk variants may be more prevalent and contribute to a higher extent to diabetes development in the Iraqi than in the native Swedish population.[10,21] This is also in agreement with the GRS analysis we present here, where the strongest association was observed for GRS of ISR with more genetic variants associated with poor insulin secretion in the Iraqi group. The Iraqi group also had slightly lower genetic risk of insulin resistance (high scores for ISI). However, these associations should be interpreted with caution given the small number of individuals included. Genetic risk variants may also impact diabetic complications including protecting mechanism for CKD but remains to be further investigated.

The prevalence of SAID was considerably lower in Iraqi born people with diabetes as compared to native Swedes. The proportion of antibody positive diabetes patients corresponds well with previous data from the United Arab Emirates which showed that people with diabetes originating from the Middle Eastern are less prone to

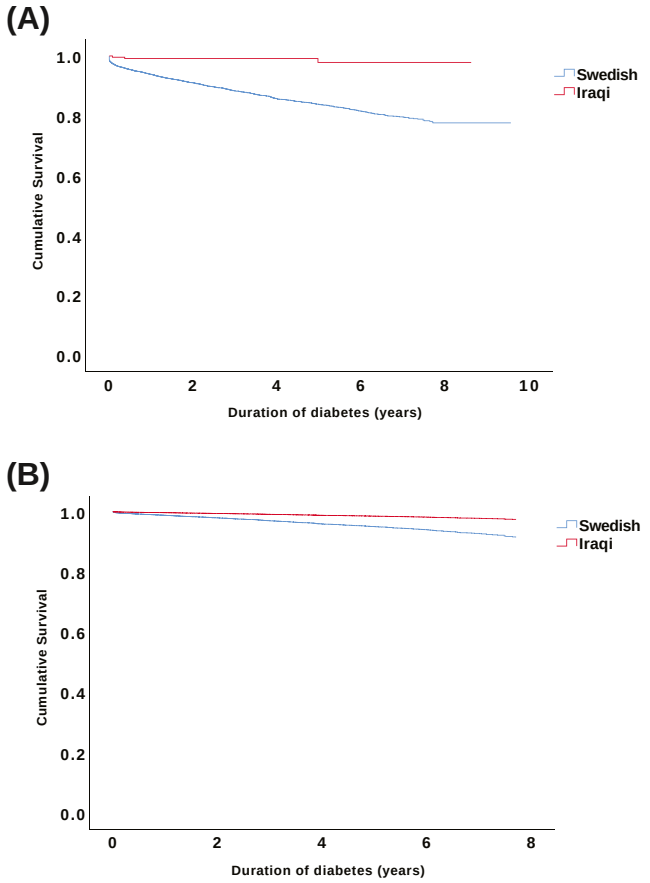

FIGURE 3 Development of CKD 3A during 8 years follow-up in diabetes patients born in Iraq or Sweden. Iraqi born individuals had lower hazard ratios for CKD than native Swedes. (A) Unadjusted cumulative survival (HR 0.09; 0.03–0.28, $p = 3.1 \times 10^{-5}$). (B) Cumulative survival after adjustment for sex, age at diabetes onset, BMI, HbA1c and eGFR (HR (HR 0.30; 0.074–1.20, $p = 0.088$). BMI, body mass index; CKD, chronic kidney disease; eGFR, glomerular filtration rate; HR, hazard ratio

TABLE 3 GRS analysis GADA negative individuals of Iraqi origin compared to native Swedes

Trait	OR (95% CI)	*p*
T2D	1.19 (1.046–1.353)	<0.001
ISR	0.729 (0.643–0.827)	<0.001
ISI	1.179 (1.035–1.343)	0.013
BMI	0.828 (0.726–0.944)	<0.001

Note: Logistic regression of standardised GRS. Included SNPs and weights (effect sizes) are listed in Tables S1–S4 (high ISI = low insulin resistance).

Abbreviations: BMI, Body Mass Index; GADA, Glutamic acid decarboxylase antibodies; GRS, genetic risk score; ISI, Insulin Sensitivity Index; ISR, insulin secretion rate.

develop adult autoimmune diabetes.[24] Human leucocyte antigen class II genes contribute to the genetic susceptibility of type 1 diabetes[25] and display the greatest genetic effect on type 1 diabetes through protective and susceptibility alleles at the DRB1, DQA1 and DQB1 loci.[26] However, the disease association varies across populations of different ethnicities[27] and clusters of different Arabic populations.[28,29] Thus one can only speculate if and to what extent genetic or gene environment interactions are involved.

4.3 | Mild obesity-related diabetes and mild age related diabetes

The largest proportion of diabetes patients born in Iraq presented with mild obesity-related diabetes. Previous data indicate that MOD patients are relatively stable in their metabolic control over the years and in general have good metabolic control and low risk of diabetic complications.[10] The National Diabetes Registry has previously shown that being overweight protects from diabetes related mortality but the mechanisms are still unknown.[30] A large proportion (approximately 40%) of Iraqi immigrants in Sweden are obese[7] and hence at risk of MOD.[7] Identifying this subgroup of diabetes patients is beneficial since individualised treatment in MOD patients can focus on living habits, weight loss and diet with the addition of metformin rather than on aggressive and expensive pharmacological treatment.[10]

Diabetes onset occurs at lower BMI cut-offs in Middle Eastern immigrants than in native Swedes,[20] hence our data of higher prevalence of MOD in Middle Eastern immigrants than in native Swedes with type 2 diabetes may be underestimated and the true prevalence rates of MOD are even higher in Middle Eastern immigrants.

The lower prevalence of MARD in Middle Eastern immigrants with Type 2 diabetes may be influenced by earlier diabetes onset as well as shorter life expectancy; diabetes onset occurs 6–7 years earlier in Middle Eastern immigrants than in native Swedes[8] and life expectancy in Middle Eastern immigrants with diabetes is approximately 6.5 years shorter than in native Swedes (64.0 vs. 70.5 years; the Swedish National Board of Health and Welfare). Altogether, this could explain the low prevalence of MARD in people with diabetes born in the Middle East.

4.4 | Microvascular complications

Our data corresponds well with previous findings showing that CKD to a higher extent develops in diabetes patients with SIRD whereas retinopathy to a higher extent develops in SIDD patients.[10] Given that diabetes retinopathy and CKD both represent different entities of microvascular disease, our findings that diabetes patients born in the Middle East are exposed to retinopathy but rather protected from kidney disease, reflects heterogeneity in microvascular disease across ethnicities.

This study lacks sufficient data on blood pressure and smoking, which are strong contributors to cardiovascular complications. Previous studies of diabetes patients show strong relationships between higher blood pressure, renal function and progression to CKD.[31–33] Despite the poorer cardiometabolic control (higher prevalence of

obesity, hyperlipidaemia, prediabetes and diabetes), Iraqi immigrants paradoxically, present with lower blood pressure and better renal function as compared to the Swedish born population.[9] The lower blood pressure and better renal function in the non-diabetic stages preceding the development of diabetes might have a protective effect and reduce the risk of subsequent renal dysfunction in diabetes patients of Iraqi origin, but needs to be further investigated.

Although not in the level of significance, our data shows higher prevalence of diabetes retinopathy in Middle Eastern than in native Swedish diabetes patients. These findings are in accordance with other studies of diabetic complications in patients originating from the Middle East.[34–36] Considering the characteristics in SIDD patients, exhibiting earlier diabetes onset and higher HbA1c at diagnosis than the other subgroups,[10] hyperglycaemia appears to be an important trigger for retinopathy, with higher HbA1c being an independent risk factor in developing retinopathy.[37] The ANDIS study has previously shown that insulin deficient diabetes increases the risk of retinopathy[10] and we hypothesise this could contribute to the higher prevalence of retinopathy in the insulin deficient Iraqi group. In a clinical setting, this emphasises the importance of active diagnosis and glucose management in this group.

4.5 | Macrovascular complications

During this 8-year follow-up of the ANDIS study, we show that irrespective of age at onset, baseline HbA1c or BMI, coronary events are more common amongst Iraqi than native Swedish diabetes patients. This is consistent with data from the impact of Migration and Ethnicity on Diabetes In Malmö (MEDIM) study where we have previously shown that in Middle Eastern immigrants without diabetes, the odds of CVD are lower in than in native Swedes. However, in diabetes patients, the odds of CVD are three times higher in Middle Eastern immigrants. This indicates that diabetes is a stronger risk factor for CVD in the Middle Eastern immigrant population compared to native Swedes.[38] Diabetes patients of south Asian origin also develop CVD complications to a higher extent than the native populations, concluding that in order to prevent CVD in this ethnic group, the prevention of diabetes is particularly important given the size of the population at risk.[39] In the Whitehall study, it was concluded that higher inflammatory levels in the non-diabetic stages increases the risk for type 2 diabetes and CVD.[40] This is consistent with our previous findings that the Middle Eastern immigrant population displays higher inflammatory levels than the native Swedish population, which may possibly contribute to the higher cardiometabolic risk we observe amongst diabetes patients in this population.[41]

The risk of CVD was significantly higher among Iraqi immigrants than in native Swedes. The cohort of Iraqi immigrants is relatively small and we can only speculate on contributing mechanisms to the excess CVD risk in Iraqi born diabetes patients. It may be due to traditional CVD risk factors (such as smoking) but needs to be further investigated.

4.6 | Strengths and limitations

The strength is the thorough sampling of patient data together with the longitudinal study design and long study duration (8-year follow-up). Another strength is the comparison with the large population based study MEDIM, sampled during the same period in the same city, enabling comparisons of clinical characteristics in these populations before and after the development of diabetes. In the MEDIM study, age at onset and sex distribution amongst the approximately 200 diabetes patients born in Iraq or Sweden were similar as in this study (mean value 'age at onset' Iraq 47.6 years, Sweden 53.4 years; distribution 'male sex' Iraq 64.8%; Sweden 63.6%). All creatinine analyses were IDMS traceable.

The study lacks baseline data on lifestyle, socioeconomy, blood pressure and lipids, which are limitations. Lifestyle, genetics and gene-environment interactions are other plausible contributors to differences in risk of developing macro- and microvascular complications not investigated within this study. The small study sample of Iraqi immigrants contributes to uncertain data regarding retinopathy and stroke. The interpretation of GRS is limited by the low number of Iraqi born participants.

The formula estimating GFR is derived from the MDRD formula that was used in the original publication 2018.[10] This formula was developed in a population of American patients with CKD and may be less accurate in our cohort of patients with rather high GFR-levels. Furthermore, MDRD is not validated in an Iraqi population. In the near future, we plan to examine the correctness of eGFR-formulae in this population as well. The percentage with missing data for the cluster analysis were equal between Iraqis and Swedes (36% and 34% respectively). Furthermore, since the data was collected using the same routines, we do not conclude there are any systematic difference across ethnicities between populations with and without missing data.

4.7 | Clinical implications

Middle Eastern immigrants represent the largest non-European immigrant population in Sweden today and, due to the continuous political instability, a growing population in Europe. This population exhibits clustering of diabetes related risk factors and high risk of diabetes. Our data indicate that in people with diabetes, Middle Eastern immigrants present with a more insulin deficient phenotype and genotype than native Swedes. They have a higher risk of coronary events but lower risk of CKD.

In patients of Middle Eastern ancestry with diabetes, it is important to continue lifestyle actions but in particular identify those with insulin deficiency which is common in this population, and monitor them for diabetic complications. Identifying patients with MOD is also beneficial since their risk of diabetic complications is low and focus in this group could be on lifestyle and metformin rather than more intense pharmacological treatment.

Culturally adapted lifestyle interventions increases the chance of successfully changing lifestyle and reducing diabetes risk.[42] By targeting lifestyle change and obesity, primary preventive actions addressing Middle Eastern immigrants in the non-diabetic stages may contribute to reducing the risk of MOD as well as the risk of SIDD for the latter through reducing insulin resistance and decreasing the risk of beta cell exhaustion.

ACKNOWLEDGEMENTS

We acknowledge our native English medical writer Patrick Reilly for editing the manuscript. We also acknowledge Jasmina Kravic for assisting with data management and processing throughout the study. The guarantor of the study is Professor Leif Groop. This study was supported by the Swedish Research Council, Strategic Research Area Exodiab, Dnr 2009-1039; the Swedish Foundation for Strategic Research Dnr IRC15-0067; the Swedish Research Council, Linnaeus grant, Dnr 349-2006-237 awarded Louise Bennet Grants from Diabetes Wellness Sweden (25-420 PG), awarded Emma Ahlqvist, the Swedish Research Council (Dnr. 2017-02688 to Emma Ahlqvist, 2015-2558 to Leif Groop and an infrastructure grant to Leif Groop), the Swedish Heart and Lung Foundation, the Swedish Diabetes Foundation, the Crafoord Foundation, the Albert Påhlsson Foundation and the Novo Nordisk Foundation (NNF18OC0034408). The genotyping of ANDIS was funded by Pfizer.

CONFLICT OF INTEREST

All authors declare they have no financial nor personal conflicts of interests.

ETHICS STATEMENT

The study was approved by the Regional Ethics Committee at Lund University 2007 584/2006 and 2013: 2012/676. All participants were provided with oral and written information about the study and every participant signed written informed consent prior to their participation.

AUTHORS CONTRIBUTIONS

Louise Bennet contributed to the research aims, acquisition of data, data analysis, data interpretation, in writing the manuscript and in draughting the article. Christopher Nilsson and Anders Christensson contributed to interpretation of the data and writing the manuscript. Dina Mansour-Aly contributed to data analysis. Leif Groop designed the study and its concept, contributed to acquisition of data, data analysis and interpretation of the data. Emma Ahlqvist contributed to acquisition of data and analysis and interpretation of the data. All authors contributed to the draughting of the article, revising it critically and finally approving the version to be submitted.

DATA AVAILABILITY STATEMENT

The individual level data that support the findings of this study are available upon request but restrictions apply. These data are not publicly available due to ethical and legal restrictions related to the Swedish Biobanks in Medical Care Act (2002:297) and the Personal Data Act (1998:204), EU's General Data Protection Regulation (GDPR) 2016/679, and the Data Protection Act 2018:218.

ORCID

Louise Bennet https://orcid.org/0000-0001-7101-1290
Christopher Nilsson https://orcid.org/0000-0001-8399-8854

REFERENCES

1. Wandell PE, Wajngot A, de Faire U, Hellenius ML. Increased prevalence of diabetes among immigrants from non-European countries in 60-year-old men and women in Sweden. *Diabetes Metab*. 2007;33(1):30-36.
2. White JS, Hamad R, Li X, et al. Long-term effects of neighbourhood deprivation on diabetes risk: quasi-experimental evidence from a refugee dispersal policy in Sweden. *Lancet Diabetes Endocrinol*. 2016;4:517-524.
3. Kodama K, Tojjar D, Yamada S, Toda K, Patel CJ, Butte AJ. Ethnic differences in the relationship between insulin sensitivity and insulin response: a systematic review and meta-analysis. *Diabetes Care*. 2013;36(6):1789-1796.
4. Sattar N, Gill JM. Type 2 diabetes in migrant south Asians: mechanisms, mitigation, and management. *Lancet Diabetes Endocrinol*. 2015;3(12):1004-1016.
5. Nanditha A, Ma RC, Ramachandran A, et al. Diabetes in Asia and the Pacific: implications for the global epidemic. *Diabetes Care*. 2016;39(3):472-485.
6. Rawshani A, Svensson AM, Rosengren A, Zethelius B, Eliasson B, Gudbjörnsdottir S. Impact of ethnicity on progress of glycaemic control in 131,935 newly diagnosed patients with type 2 diabetes: a nationwide observational study from the Swedish National Diabetes Register. *BMJ Open*. 2015;5(6):e007599.
7. Bennet L, Groop L, Lindblad U, Agardh CD, Franks PW. Ethnicity is an independent risk indicator when estimating diabetes risk with FINDRISC scores: a cross sectional study comparing immigrants from the Middle East and native Swedes. *Prim Care Diabetes*. 2014;8:231-238.
8. Bennet L, Groop L, Franks PW. Ethnic differences in the contribution of insulin action and secretion to type 2 diabetes in immigrants from the Middle East compared to native Swedes. *Diabetes Res Clin Pract*. 2014;105(1):79-87.
9. Nilsson C, Christensson A, Nilsson PM, Bennet L. Renal function and its association with blood pressure in Middle Eastern immigrants and native Swedes. *J Hypertens*. 2017;35(12):2493-2500.
10. Ahlqvist E, Storm P, Karajamaki A, et al. Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. *Lancet Diabetes Endocrinol*. 2018;6:361-369.
11. van Dieren S, Beulens JW, van der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil*. 2010;17(Suppl 1):S3-S8.
12. World Health Organization. *Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications: Report of a WHO Consultation. Part 1. Diagnosis and Classification of Diabetes Mellitus*. Geneva, Switzerland: World Health Organization; 1999.
13. Levey AS, Coresh J, Greene T, et al. Using standardized serum creatinine values in the modification of diet in renal disease study equation for estimating glomerular filtration rate. *Ann Intern Med*. 2006;145(4):247-254.
14. Levy JC, Matthews DR, Hermans MP. Correct homeostasis model assessment (HOMA) evaluation uses the computer program. *Diabetes Care*. 1998;21(12):2191-2192.
15. Mahajan A, Taliun D, Thurner M, et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density

imputation and islet-specific epigenome maps. *Nat Genet*. 2018;50(11):1505-1513.
16. Wood AR, Jonsson A, Jackson AU, et al. A genome-wide association study of IVGTT-based measures of first-phase insulin secretion refines the underlying physiology of type 2 diabetes variants. *Diabetes*. 2017;66(8):2296-2309.
17. Walford GA, Gustafsson S, Rybin D, et al. Genome-wide association study of the modified stumvoll insulin sensitivity index identifies BCL2 and FAM19A2 as novel insulin sensitivity loci. *Diabetes*. 2016;65(10):3200-3211.
18. Locke AE, Kahali B, Berndt SI, et al. Genetic studies of body mass index yield new insights for obesity biology. *Nature*. 2015;518(7538):197-206.
19. Zou X, Zhou X, Zhu Z, Ji L. Novel subgroups of patients with adult-onset diabetes in Chinese and US populations. *Lancet Diabetes Endocrinol*. 2019;7(1):9-11.
20. Bennet L, Stenkula K, Cushman SW, Brismar K. BMI and waist circumference cut-offs for corresponding levels of insulin sensitivity in a Middle Eastern immigrant versus a native Swedish population - the MEDIM population based study. *BMC Publ Health*. 2016;16(1):1242.
21. Mansour Aly D, Prakash Dwivedi O, Prasad RB, et al. Aetiological differences between novel subtypes of diabetes derived from genetic associations. *MedRxiv*. 2020. https://www.medrxiv.org/content/10.1101/2020.09.29.20203935v1.
22. Bennet L, Franks PW, Zoller B, Groop L. Family history of diabetes and its relationship with insulin secretion and insulin sensitivity in Iraqi immigrants and native Swedes: a population-based cohort study. *Acta Diabetol*. 2018;55(3):233-242.
23. Lyssenko V, Jonsson A, Almgren P, et al. Clinical risk factors, DNA variants, and the development of type 2 diabetes. *N Engl J Med*. 2008;359(21):2220-2232.
24. Maddaloni E, Lessan N, Al Tikriti A, Buzzetti R, Pozzilli P, Barakat MT. Latent autoimmune diabetes in adults in the United Arab Emirates: clinical features and factors related to insulin-requirement. *PLoS One*. 2015;10(8):e0131837.
25. Davies JL, Kawaguchi Y, Bennett ST, et al. A genome-wide search for human type 1 diabetes susceptibility genes. *Nature*. 1994;371(6493):130-136.
26. Kawabata Y, Ikegami H, Kawaguchi Y, et al. Asian-specific HLA haplotypes reveal heterogeneity of the contribution of HLA-DR and -DQ haplotypes to susceptibility to type 1 diabetes. *Diabetes*. 2002;51(2):545-551.
27. She JX. Susceptibility to type I diabetes: HLA-DQ and DR revisited. *Immunol Today*. 1996;17(7):323-329.
28. Al-Jenaidi FA, Wakim-Ghorayeb SF, Al-Abbasi A, et al. Contribution of selective HLA-DRB1/DQB1 alleles and haplotypes to the genetic susceptibility of type 1 diabetes among Lebanese and Bahraini Arabs. *J Clin Endocrinol Metab*. 2005;90(9):5104-5109.
29. Hajjej A, Almawi WY, Arnaiz-Villena A, Hattab L, Hmida S. The genetic heterogeneity of Arab populations as inferred from HLA genes. *PLoS One*. 2018;13(3):e0192269.
30. Edqvist J, Rawshani A, Adiels M, et al. BMI and mortality in patients with new-onset type 2 diabetes: a comparison with age- and sex-matched control subjects from the general population. *Diabetes Care*. 2018;41(3):485-493.
31. National Kidney F. KDOQI clinical practice guideline for diabetes and CKD: 2012 update. *Am J Kidney Dis*. 2012;60(5):850-886.
32. Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. *JAMA*. 2003;289(19):2560-2572.
33. Dennis JM, Shields BM, Henley WE, Jones AG, Hattersley AT. Disease progression and treatment response in data-driven subgroups of type 2 diabetes compared with models based on simple clinical features: an analysis using clinical trial data. *Lancet Diabetes Endocrinol*. 2019;7(6):442-451.
34. Oya J, Jorgensen ME, Lund-Andersen H, Carstensen B, Andersen GS. Incidence of diabetic eye disease among migrants: a cohort study of 100,000 adults with diabetes in Denmark. *Diabetes Res Clin Pract*. 2018;144:224-230.
35. Glans F, Elgzyri T, Shaat N, Lindholm E, Apelqvist J, Groop L. Immigrants from the Middle-East have a different form of Type 2 diabetes compared with Swedish patients. *Diabet Med*. 2008;25(3):303-307.
36. Sivaprasad S, Gupta B, Crosby-Nwaobi R, Evans J. Prevalence of diabetic retinopathy in various ethnic groups: a worldwide perspective. *Surv Ophthalmol*. 2012;57(4):347-370.
37. American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care*. 2006;29(Suppl 1):S43-S48.
38. Bennet L, Agardh CD, Lindblad U. Cardiovascular disease in relation to diabetes status in immigrants from the Middle East compared to native Swedes: a cross-sectional study. *BMC Publ Health*. 2013;13(1):1133.
39. Yeo KK, Tai BC, Heng D, et al. Ethnicity modifies the association between diabetes mellitus and ischaemic heart disease in Chinese, Malays and Asian Indians living in Singapore. *Diabetologia*. 2006;49(12):2866-2873.
40. Tabak AG, Kivimaki M, Brunner EJ, et al. Changes in C-reactive protein levels before type 2 diabetes and cardiovascular death: the Whitehall II study. *Eur J Endocrinol*. 2010;163(1):89-95.
41. Memon AA, Sundquist J, Wang X, Palmér K, Sundquist K, Bennet L. The association between cytokines and insulin sensitivity in Iraqi immigrants and native Swedes. *BMJ Open*. 2013;3(11):e003473.
42. Siddiqui F, Kurbasic A, Lindblad U, Nilsson PM, Bennet L. Effects of a culturally adapted lifestyle intervention on cardio-metabolic outcomes: a randomized controlled trial in Iraqi immigrants to Sweden at high risk for Type 2 diabetes. *Metabolism*. 2017;66:1-13.

SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of this article.

How to cite this article: Bennet L, Nilsson C, Mansour-Aly D, Christensson A, Groop L, Ahlqvist E. Adult-onset diabetes in Middle Eastern immigrants to Sweden: Novel subgroups and diabetic complications—The All New Diabetes in Scania cohort diabetic complications and ethnicity. *Diabetes Metab Res Rev*. 2020;e3419. https://doi.org/10.1002/dmrr.3419