Associations of Insulin Resistance, B-Cell Functioning, and Cardiovascular Risk Factors with Prediabetes in a Working Age Population from Turkistan

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Astana, 2023

Abstract

The incidence of T2DM will increase each year since the prevalence of people with prediabetes is even higher. This study is aimed to describe the clinical, biochemical, and metabolic characteristics of people with prediabetes, analyse the effect of insulin resistance (IR) and impaired β-cell function identified by the homeostasis model assessment values on prediabetes, and identify the risk factors for prediabetes, IR and impaired function of β-cell. The data for the study was obtained from workers of the Khoja Akhmet Yassawi International Kazakh-Turkish University (Turkistan, Kazakhstan). The final sample contained 419 participants aged between 27-69, including 237 healthy and 182 prediabetic individuals. Multivariable logistic regression models were computed. This study demonstrated prediabetes population has older age, a high median BMI and systolic blood pressure, high obesity prevalence, and dyslipidemia characteristics. IR and impaired β-cell function are positively correlated with prediabetes. Waist circumference, age, systolic blood pressure, IR, and poor β-cell are risk factors for prediabetes. Prediabetes is positively associated with IR and poor β-cell function. No model was found to describe IR risk factors in the population. Still, it revealed that age and total cholesterol levels could be used to predict poor β-cell function in prediabetic individuals.

Introduction

In 2021, more than 450 million people around the world carried the tremendous health and economic burden of Type 2 Diabetes Mellitus (T2DM) and resulting complications (International Diabetes Federation (IDF), 2021; Udler M., 2021). The most common complications provoked by T2DM are cardiovascular diseases (CVD), diabetic kidney disease (DKD), neuropathy, lower-limb amputation, and retinopathy, which may lead to partial vision loss or even blindness (IDF, 2021). Moreover, it is predicted that the prevalence of the disease will increase each year since the current number of people with prediabetic conditions is even higher than diabetic patients (IDF, 2021). The necessity of early detection of prediabetes and timely preventive interventions are of global importance since, despite a higher risk of progressing to T2DM, the prediabetic population also have a possibility of returning to normoglycemia (Tabák et al., 2012).

Prediabetes is defined as an intermediate state of hyperglycemia characterized by the elevation of plasma glucose levels above normal levels but below the criteria of T2DM diagnosis. (Tabák et al., 2012). Prediabetic conditions are characterised by impaired fasting glucose (IFG) and/or glucose tolerance (IGT), which increase the risk of progression to T2DM and further disease-related health complications (IDF, 2021). The disturbances in glucose metabolism leading to prediabetes are caused by insulin resistance (IR) and insufficient insulin production by pancreatic β-cells for its compensation. If no interventions are applied, after some time, these conditions lead to hyperglycemia which is a pathological condition of T2DM. (Armato et al., 2018; Hjellvik et al., 2012; Wagner et al., 2021). It is suggested that the factors affecting the development of IR and impaired β-cell function and further progression to the disease are heterogeneous since variable combinations and the accumulation of many risk factors may affect this development (Bellou et al., 2018; Mendez et al., 2022). Such heterogeneity in the pathogenesis of T2DM makes the prevention of the disease challenging. However, several factors were found to be strongly associated with a higher risk of disease development.

Accumulative data from studies demonstrated that common risk factors for T2DM include elevated glucose levels, obesity, genetic predisposition and cardiovascular risk (CVR) factors such as dyslipidemia characterised by high triglycerides levels and low high-density lipoprotein (HDL) cholesterol levels, as well as hypertension, and genetic predisposition (American Diabetes Association, 2022; American Heart Association, 2021; Ding et al., 2015; Hjellvik et al., 2012; Wu et al., 2014). Nevertheless, despite the risk factors for T2DM have been determined for over a decade, the controversy about the specific characteristics of those in a prediabetic state still exists.

Current criteria suggested by the American Diabetes Association (ADA) and the World Health Organization (WHO) evaluate blood glucose levels only, which ignores heterogeneity in the pathogenesis of prediabetes and T2DM (Méndez et al., 2022). Moreover, despite the same borders (7.8-11.1 mmol/L) for the diagnosis of isolated IGT by measuring plasma glucose levels 2 hours after 75-g oral glucose tolerance test (OGTT), the thresholds of isolated IFG established by ADA and WHO are different (Beulens et al., 2019). The updated recommendations by the ADA (2022) suggest a cut-off of 5.6-6.9 mmol/L of fasting glucose levels to diagnose prediabetic patients. On the other hand, the WHO (2006) proposed a range of 6.1-6.9 mmol/L of fasting glucose levels for IFG to characterize prediabetic conditions. Although lowering the IFG threshold by ADA results in two

to three times more individuals with prediabetes and includes people at low risk of disease development, who may not need and benefit from any preventive manipulations, the rationale behind lowering the threshold by ADA is that an IFG level close to 6.1 mmol/L is linked to an increased likelihood of vascular complications, both at micro and macro levels (Glechner, 2018).

Nonetheless, earlier identification of prediabetic patients was advantageous even with a low risk of progressing to overt T2DM. It provides an opportunity for timely intervention to prevent, delay or at least alleviate the development of the disease and related complications (Glechner, 2018; Zhang, 2020). Several studies conducted in different parts of the world and among various ethnicities to evaluate the effectiveness of preventive measures for prediabetic patients demonstrated that the percentage of prediabetic people who returned to normoglycemia varies from 36 to 60% (Diabetes Prevention Program (DPP) Research Group, 2002; Bennasar-Veny, 2020; Luo et al., 2022). The DPP was the first national-wide study that showed a 58% reduction in new T2DM cases among the American population, including ethnic and racial minorities, after the administration of lifestyle intervention or pharmacological therapy using metformin (DPP Research Group, 2002). In another randomized controlled clinical trial conducted in China, Luo et al. (2022) found that 60.0% and 50.3 % of patients who underwent conventional and intensive lifestyle interventions, respectively, had their glycemic index back to normal. In a cohort study from Spain, researchers identified that from approximately 23,000 patients, 36% returned to normal glucose levels after lifestyle interventions (Bennasar-Veny, 2020). However, despite the strong correlation between healthy lifestyle interventions and reverting to normoglycemia, lifestyle factors do not explain the variations in reversion probability depending on the type of prediabetes: IGT or IFG (Giráldez-García, 2021). This suggests that the reason may lie in the genetic and ethnic differences (Sentell et al., 2012; Vicks et al., 2022), as well as the underlying reason of impaired glucose metabolism. That is whether prediabetes caused predominantly by IR, impaired β-cell function, or both.

Although there is a lack of studies, which addressed this hypothesis, some studies analyzed the differences between predicting factors for T2DM preceded by IR, β-cell function deficits or both. For example, weight gain and adiposity were independently associated with increased occurrence of diabetes, which was primarily preceded by IR rather than poor β-cell function (Imamura, 2012). Hence, it is proposed that the diagnosis of individuals with prediabetes and further measures to prevent progression to the disease state should be based not only on blood glucose levels measurement but also on the assessment of insulin sensitivity, insulin secretion and CVR factors (Dimova et al., 2020; Haffner S.M., 2003; Weiss et al., 2003.

One of the approaches that could be used to evaluate insulin sensitivity and insulin secretion could be Homeostatic Model Assessment (HOMA). To date, not many studies have attempted to identify characteristics of the population with IFT and/or IGT using the HOMA-IR for insulin resistance and the HOMA-β for impaired β-cell function. (Cai et al., 2019; Khalili et al., 2023; Kim et al., 2018). There are some controversies about the practical application of HOMA-IR and HOMA-β values to evaluate metabolic state (Wallace et al., 2004). Still, it has been shown that there is a positive association of HOMA-IR with pre-diabetes subtypes and T2DM cases and HOMA- β with isolated IGT incidence (Khalili at al., 2023). Also, when used appropriately and not in isolation, HOMA models could help to receive valuable characteristics for general patient assessment (Wallace et al., 2004).

In addition to the lack of studies that used HOMA to characterize the prediabetic population, there is an unavailability of research that attempts to analyse prediabetes in Central Asian countries, including Kazakhstan. However, according to IDF (2021) report, the prevalence of T1DM and T2DM among the Kazakhstani population aged between 20-79 is expected to rise from 6.6% in 2021 to 7.3% by 2030 and to 7.7 % by 2045. A large cross-sectional study conducted by Orazumbekova et al. (2022), which included 4,753 participants from four geographically remote regions of Kazakhstan, has shown that 8% of participants had T2DM and 1.9% were diagnosed with prediabetic conditions based on WHO criteria. Still, no studies attempted to identify the characteristics of the population with prediabetes in Kazakhstan, although it could possibly be done through usually collected data from blood glucose and insulin measurements and CVR factors, as they were found to be associated with prediabetes (Beulens et al., 2019; Hu et al., 2018; Huang et al., 2016)

The data obtained from International Hoca Ahmet Yesevi Turkish-Kazakh University employees will be analysed in this study.

Specific aim(s):

1. To describe the prevalence of prediabetes in the population;
2. To identify the characteristics of people with prediabetes, including age, BMI, CVD risk factors, and glucose metabolism indexes HOMA-IR and HOMA-β;
3. To examine how IR, poor β-cell function, and CVD risk factors affect prediabetes;
4. To examine the effect of CVD risk factors on IR and impaired β-cell function.

Materials and Methods

Study population.

The data analysed in this research was an anonymised dataset collected from the Clinical Diagnostic Center of the Khoja Akhmet Yassawi International Kazakh-Turkish University (Turkistan, Kazakhstan) in 2019 and 2020. The workers from the Khoja Akhmet Yassawi International Kazakh-Turkish University comprised the study group. The criteria for involvement in the research were written informed consent to participate in the study and age between 27 and 69 years. Already diagnosed T1 or T2DM, kidney disease, or diagnosis of diabetes with the fasting blood or OGTT tests during this study were the exclusion criteria from participation. The selection process of the study group from the whole dataset is demonstrated in Figure 1.

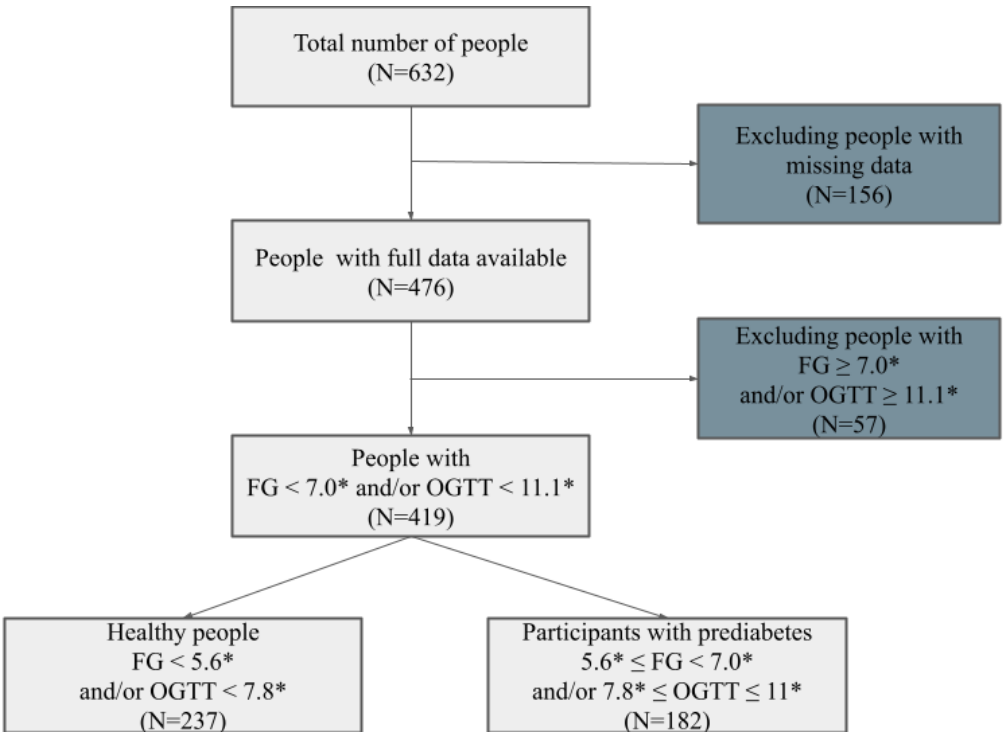


Figure 1. Study participants flow chart

Note. * - mmol/L

Data collection

Anamnesis and other information about each participant of the study were collected in a participant's summary card that included a passport, written voluntary informed consent form, demographic data, a summary of the study, and completed surveys about lifestyles (included

Firestorm test and the Alcohol Use Disorders Identification Test), as well as anthropometric studies and the results of laboratory tests. The detailed data collection process for the study has been published by Saruarov et al. (2023).

In this study, criteria for prediabetes were chosen as 5.6–6.9 mmol/L for fasting glucose and 7.8-11.0 mmol/L after 2h-OGTT (ADA, 2022).

Homeostasis model assessment

The HOMA-IR and HOMA-β were computed using fasting glucose and insulin values and split into IR and impaired function of β-cells (Saha, 2022). The following formulas were used to calculate HOMA models. HOMA-IR = (fasting insulin (μU/mL) x fasting glucose (mmol/L))/22.5, and HOMA-β = (20 x fasting insulin (μU/mL))/(fasting glucose (mmol/L) − 3.5). Generally, participants having HOMA-IR ≥ 2.5 were considered as having IR, and values of HOMA-β ≤ 50 as having a poor β-cell function.

Statistical analysis

The numerical variables were evaluated for normality using Kolmogorov-Smirnov and skewness tests, and the clinical, biochemical and metabolic characteristics of the study participants were described. Since the continuous data was distributed non-normally, the median (IQR) was used. The categorical variables were described using frequency distribution. Pearson's Chi-square test was used to compare characteristics between the healthy and the prediabetic populations, while Kruskal Wallis tests were used to compare indices of groups divided based on HOMA indexes.

Multivariable logistic regression analyses were used to create the models to examine the association of prediabetes with IR and poor function of β-cells (model 1a); the association of IR (model 2a) and poor function of β-cells (model 3a) with CVD risk factors in prediabetes population. Multivariable stepwise logistic regression analyses were used to identify predicting factors for prediabetes, IR, and poor β-cells function. In the analyses, the odds ratios (OR) were calculated. Receiver operating characteristics (ROC) curves were used to compare the forward and backward selection results in stepwise logistic regression analyses. A value of 0.2 was used for selection. Model 1a was adjusted by age and sex, while models 2a and 3a were adjusted by age, sex, and BMI. In all tests, a value of $P < 0.05$ was considered significant.

The study performed analyses using the Stata version 17.0 package (Stata Corporation, Stata Press, Texas, USA).

This study was approved by the Nazarbayev University School of Medicine Research Ethics Committee.

Results

Initially, the dataset contained records of 632 participants, but HOMA-IR and HOMA-β were calculated only for 476 individuals who had fully completed data. The total sample comprised 419 subjects, of which 237 (56.6% of the study population) were healthy participants and 182 (43,4% of the study population) were compatible with prediabetes criteria. The general characteristics of the study population are shown in Table 1. A higher prevalence of obesity, high BMI, and age of 50 and older should be noted in the prediabetes population (Table 1). The comparison of the median, interquartile ranges, and density of BMI and age groups is depicted in Figure 2 and Figure 3, respectively.

Table 1. General characteristics of the study population

Characteristics		**Healthy**		**Prediabetes**		**P value**
		Frequency	**%**	**Frequency**	**%**	
Sex	Men	59	24.9	59	32.4	NS
	Women	178	75.1	123	67.6	
Age groups (years)	20-29	8	3.40	0	0	<0.000
	30-39	75	31.6	21	11.5	
	40–49	66	27.8	38	20.9	
	50-59	61	25.7	62	34.1	
	60-69	27	11.4	61	33.5	
Kazakh		204	86.1	166	91.2	NS
Other ethnicities		33	13.9	16	8.8	
Smoking		27	11.4	23	12.6	NS
Alcohol intake		64	27.0	50	27.4	NS
BMI (kg/m2)	Normal	97	41.0	27	14.8	<0.000
	Overweight	75	31.6	70	38.5	
	Obesity	65	27.4	85	46.7	
Waist Circumference (cm)	M: < 94; F: < 80	91	38.4	27	14.8	<0.000
	M: 94–102; F: 80–88	47	19.8	33	18.1	
	M: 102 <; F: 88 <	99	41.7	122	67.0	
Insulin Resistance		38	16.0	58	31.9	<0.000
Poor beta cell function		22	9.28	87	47.8	<0.000
Total number of participants		**237**	**56.6**	**182**	**43.4**	

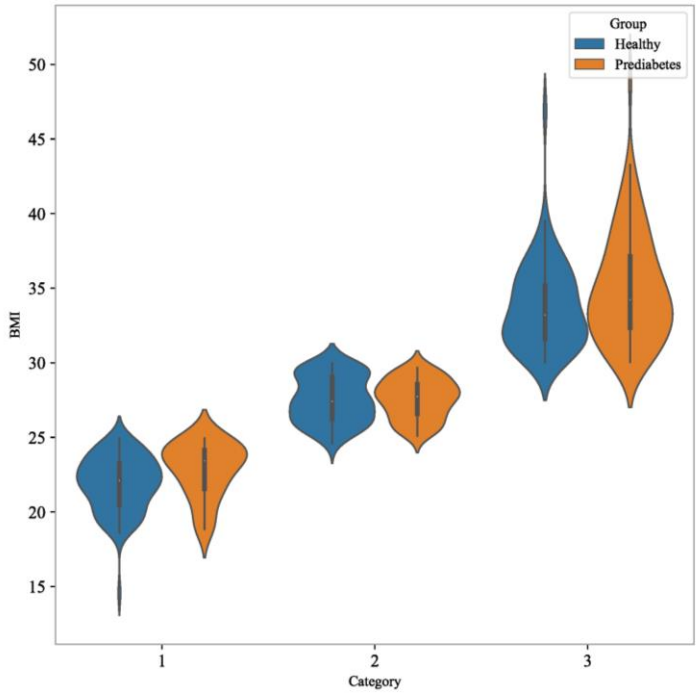


Figure 2. Violin plots of BMI

Note. Group 1 (BMI 18.5 to 24.9 kg/m2) is the population with normal weight, Group 2 (BMI 25 to 29.9 kg/m2) is the overweight population, and Group 3 (BMI ≥ 30 kg/m2) is the population with obesity.

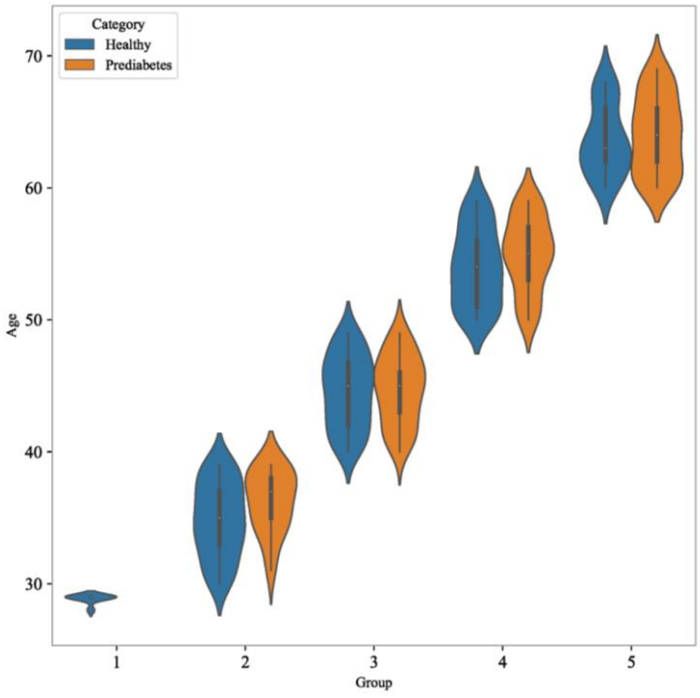


Figure 3. Violin plots of age

Note. Group 1 - 20-29 years, Group 2 - 30-39 years, Group 3 - 40-49 years, Group 4 - 50-59 years, and Group 5 - 60-69 years.

The biochemical, clinical and metabolic characteristics of the study group are demonstrated in Table 2. The median fasting (6.2 (0.7) vs. 5.0 (0.54) mmol/L, P < 0.00001) and 2-h (5.8 (1.85) vs. 5.3 (0.8) mmol/L, P < 0.0000) plasma glucose levels after oral glucose challenge in the prediabetic group were higher significantly than those of healthy respectively (Table 2).

Table 2. Clinical, biochemical, and metabolic characteristics of the study population

Characteristics	Healthy		Prediabetes		P value
	Median	IQR	Median	IQR	
Age (years)	45	14	55	16	< 0.000
BMI	26.30	7.89	29.38	7.30	< 0.000
Waist circumference (cm)	89	20	97	15	< 0.000
Hip circumference (cm)	101	14	108	13	< 0.000
SBP (mmHg)	110	30	140	40	< 0.000
DBP (mmHg)	80	20	82.5	10	< 0.000
Total cholesterol (mmol/L)	4.80	0.8	5.10	1.10	< 0.000
LDL - cholesterol (mmol/L)	2.10	0.71	2.36	0.69	< 0.000
HDL - cholesterol (mmol/L)	1.26	0.24	1.17	0.25	0.009
TG (mmol/L)	1.97	1.21	2.07	0.92	0.034
Fasting glucose (mmol/L)	5.0	0.54	6.20	0.7	< 0.000
OGTT (mmol/L)	5.3	0.8	5.80	1.85	< 0.000
Fasting Insulin (μU/mL)	7.73	4.77	7.52	5.02	NS
HOMA-IR	1.67	1.02	2.02	1.36	< 0.000
HOMA-beta	114.0	92.99	52.84	45.69	< 0.000

Note. SBP systolic blood pressure, DBP diastolic blood pressure, LDL low-density lipoprotein, HDL high-density lipoprotein, TG triglycerides, OGTT oral glucose tolerance test.

Based on HOMA values, the prediabetes group was subdivided into three subgroups: no IR with proper beta-cell function, isolated IR, and isolated poor β-cell function. The first group included participants with HOMA-IR < 2.5 and HOMA-β > 50, the second group HOMA-IR > 2.5 and HOMA-β > 50, and the third group HOMA-IR < 2.5 and HOMA-β < 50. The clinical, biochemical, and metabolic characteristics of all three subgroups are demonstrated in Table 3. The mean and median for fasting glucose were not computed because subgroups include only the prediabetic population and the difference between subgroups was not significant. Only one participant had HOMA-IR > 2.5 and HOMA-β < 50, but the data from one participant cannot be used for comparison. Thus, the data is not shown.

Table 3. Subgroups of the prediabetes population based on HOMA values

	Group with no IR and proper beta-cell function	Group with isolated IR	Group with isolated poor β-cell function	p-value
Individuals (n, %*)	38, 21	57, 31	86, 47	
Male/Female (n)	19/19	14/43	26/60	0.058
Age (years)				
Mean (SD)	50.92 (8.77)	50.86 (9.78)	56.72 (9.49)	0.002
Median (IQR)	50 (12)	52 (13.5)	59 (10)	
Insulin (µU/mL)				
Mean (SD)	7.87 (0.96)	12.28 (3.12)	4.69 (1.41)	< 0.000
Median (IQR)	7.93 (0.72)	11.38 (3.24)	4.62 (2.43)	
BMI				
Mean (SD)	29.437 (5.835)	29.961(5.582)	30.967 (5.035)	NS
Median (IQR)	28.465 (5.737)	29 (8.534)	30.209 (7.294)	
Waist Circumference (cm)				
Mean (SD)	95.157 (13.980)	96.771 (12.467)	99.116 (12,434)	NS
Median (IQR)	96 (12)	96 (18)	98 (14)	
Systolic Blood Pressure (mmHg)				
Mean (SD)	131.289 (18.499)	126.368 (18.688)	135.114 (19.244)	0.034
Median (IQR)	137 (20)	120 (30)	140 (35)	
Diastolic Blood Pressure (mmHg)				
Mean (SD)	82.026 (9.835)	81.877 (9.030)	85.070 (9.644)	NS
Median (IQR)	80 (20)	80 (17.5)	90 (10)	
Total Cholesterol (mmol/L)				
Mean (SD)	4.858 (0.786)	4.902 (0.748)	5.157 (0.743)	0.003
Median (IQR)	4.8 (1.1)	4.90 (0.92)	5.4 (0.8)	

Table 3 *continued*

LDL-cholesterol (mmol/L)				
Mean (SD)	2.175 (0.634)	2.179 (0.677)	2.450 (0.618)	0.002
Median (IQR)	2.16 (0.46)	2.14 (0.695)	2.47(0.69)	
HDL - cholesterol (mmol/L)				
Mean (SD)	1.318 (0.368)	1.233 (0.229)	1.182 (0.222)	0.024
Median (IQR)	1.26 (0.29)	1.18 (0.255)	1.14 (0.2)	
Triglycerides (mmol/L)				
Mean (SD)	1.884 (0.876)	2.047 (0.598)	2.023 (0.693)	NS
Median (IQR)	1.86 (1.12)	2.070 (0.635)	2.115 (0.96)	

Note. * This is the percentage of the prediabetes population

The model for the association of IR and poor β-cell function with prediabetes showed that both factors strongly correlate with prediabetes (Table 4). After adjusting for age and sex, the population with IR had 7.3 (95% CI 4.21; 13.48) times the odds of having prediabetes, while those with poor β-cell function had 13.4 (95% CI 7.61; 26.84). The OR of IR remained approximately the same, while the OR of poor β-cell function decreased by 4.83 (Table 4).

The results of stepwise forward and backward logistic regressions for factors predicting diabetes are demonstrated in Table 5. Figure 4 depicts the forward and backward selection ROC curves for this model.

Table 4. Model for the association of IR and poor β-cell function with prediabetes

Variables	**Coefficient (95% CI)**	
	Unadjusted	**Adjusted***
IR	7.005 (4.086, 12.011)	7.312 (4.154, 12.872)
Impaired β-cell function	18.26 (10.183, 32.763)	13.434 (7.285, 24.770)

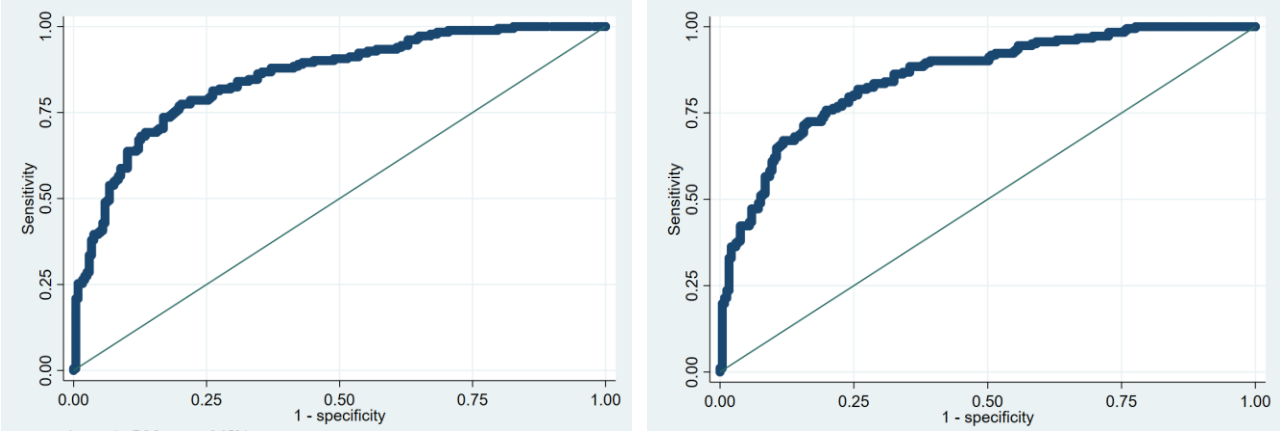
Note. *Adjusted by age and sex

The areas under the ROC curves (AUC) for forward and backward selection are approximately the same (Figure 4). On the desirability of parsimony, the results of the forward selection are preferred over the backward for the prediabetes risk factors model. Hence, age, waist circumference, systolic blood pressure, IR, and impaired β-cell function are positively associated with prediabetes.

Table 5. Model for stepwise logistic regression for prediabetes risk factors

Variables	Forward selection		Backward selection	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.03 (1.00-1.06)	0.042	1.03 (1.00-1.06)	0.022
Gender	-		0.60 (0.34 - 1.05)	NS
BMI	-		1.08 (1.03-1.14)	0.003
Waist circumference	1.03 (1.01-1.05)	0.011	-	
SBP	1.02 (1.00-1.03)	0.038	1.01 (0.99-1.03)	NS
IR	7.34 (4.12-13.08)	<0.000	7.67 (4.28-13.76)	<0.000
Poor β-cell function	13.75 (7.34-25.75)	<0.000	14.45 (7.65-27.26)	<0.000

Note. IR insulin resistance, SBP systolic blood pressure, OR odds ratio, 95% CI confidence interval, NS not significant



A. AUC = 0.8524 B. AUC = 0.8552

Figure 4. ROC curve for predicting prediabetes using forward stepwise (A) and backward stepwise (B) logistic regression models

Note. AUC area under the curve

Table 6 shows the models for the association of prediabetes with IR and poor function of β-cell. Prediabetes is positively associated with IR and with poor β-cell function. The adjusted Model IR had a higher OR (3.16, 95%CI 1.86-5.37) than the unadjusted (2.45, 95% CI 1.536-3.905). However, it was the opposite for the adjusted Model poor β-cell function, which OR decreased after the adjustment (8.95, 95% CI 5.29-15.15 vs. 6.64, 95 % CI 3.78-11.68).

Considering the risk factors for IR in the study population, neither the forward stepwise logistic regression model nor the backward found any significant correlation between CVR factors

and IR (Table 7). The ROC curves also demonstrated that no model could be applied to describe the association of CVR factors and IR in this selected population group (Figure 5).

Table 6. Models for the association of prediabetes with IR and with poor β-cell function

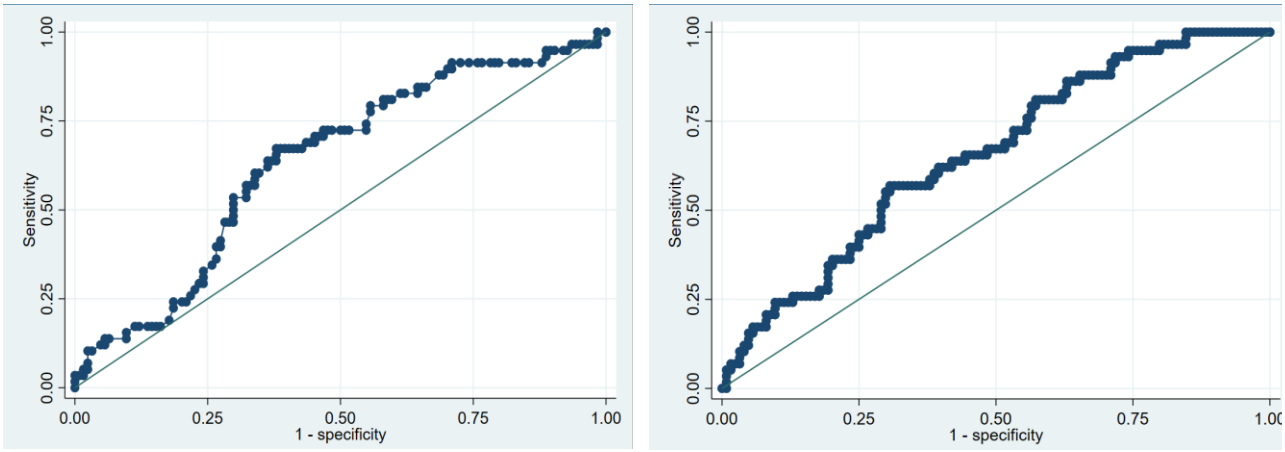
Variables	Coefficient (95% CI)			
	Model IR		Model poor β-cell function	
	Unadjusted	Adjusted*	Unadjusted	Adjusted*
Prediabetes	2.45 (1.54-3.91)	3.16 (1.86-5.37)	8.95 (5.29-15.15)	6.64(3.78-11.68)

Note. *Adjusted by age, sex, and BMI

Table 7. Model for stepwise logistic regression models for IR risk factors in the prediabetes population

Variables	Forward model		Backward model	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	0.97 (0.94-1.00)	NS	0.97 (0.93-1.00)	NS
SBP	0.99 (0.97-1.01)	NS	0.97 (0.94-1.01)	NS
DPB	-		1.05 (0.98-1.12)	NS
Total cholesterol	-		0.70 (0.42-1.17)	NS
TG	-		1.56 (0.91-2.68)	NS

Note. SBP systolic blood pressure, DBP diastolic blood pressure, TG triglycerides, OR odds ratio, 95% CI confidence interval, NS not significant



A. AUC = 0.6342 B. AUC = 0.6545

Figure 5. ROC curve for predicting IR using forward stepwise (A) and backward stepwise (B) logistic regression models

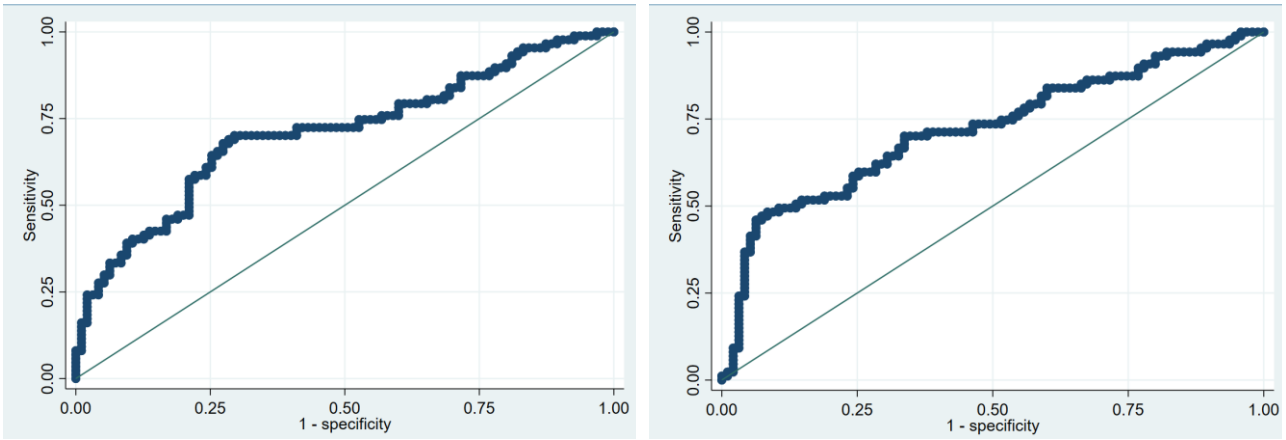
Note. AUC area under the curve

As for the model for poor β-cell function risk factors, the backward selection had a higher AUC than the forward (0.7205 vs. 0.7091) (Figure 6). Thus, backward stepwise logistic regression analysis was chosen to describe the model for IR risk factors in prediabetes. According to the model, age and total cholesterol are positively associated with poor β-cell function.

Table 8. Stepwise logistic regression models for poor β-cell function risk factors in prediabetes population

Variables	Forward selection		Backward selection	
	OR (95% CI)	P-value	OR (95% CI)	P-value
Age	1.06 (1.01-1.10)	0.001	1.06 (1.03-1.10)	0.000
Total cholesterol			1.72 (1.05-2.85)	0.031
LDL-cholesterol	1.59 (0.96-2.62)	NS		
HDL-cholesterol	0.31 (0.68-1.36)	NS	0.27 (0.07-1.10)	NS
TG			0.71 (0.42-1.19)	NS

Note. LDL low-density lipoprotein, HDL high-density lipoprotein, TG triglycerides, OR odds ratio, 95% CI confidence interval, NS not significant



A. AUC = 0.7091 B. AUC = 0.7205

Figure 6. ROC curve for predicting poor β-cell function using stepwise forward (A) and stepwise backward (B) logistic regression models

Discussion

The overall prevalence of prediabetes in the study population is 43.4 %. The prediabetic population, in general, has a significantly higher prevalence of obesity (46.7 vs. 27.4 %, $P < 0.000$), including abdominal obesity (67.0 vs. 41.7 %, $P < 0.000$) than the healthy population (Table 1). This corresponds to the previous studies that also demonstrated higher proportions of overweight or obese people among prediabetic and diabetic patients (Akter et al., 2014; Satman et al., 2013). Also, the proportion of people at age 50 and older was considerably greater in the population with prediabetes (Figure 3). This is in agreement with the earlier nationwide study from Bangladesh that showed the risk of prediabetes rises with age (Akter et al., 2014). Other studies, which accessed the prevalence of T2DM, observed that it increased with age (Decode-Decoda Study Group et al., 2003; Satman et al., 2013; Suastika et al., 2012, p.73).

Earlier findings have also demonstrated that prediabetes is correlated with abnormal irregular fluctuations in blood pressure (Gupta et. al., 2008) and elevated risk of CVD (Hu et al., 2018; Huang et al., 2016). High blood pressure and dyslipidemia are considered factors associated with CVD (Bays et al., 2022). In the study population, the median systolic blood pressure in the population with prediabetes is 140 mmHg, which is significantly higher ($P < 0.000$) than in the healthy population and is compatible with the diagnosis of hypertension (Melichnova et al., 2023). Dyslipidemia characteristics were also observed in the prediabetes group. Total cholesterol, LDL-cholesterol, and triglyceride levels were noticeably higher, while median HDL-cholesterol levels were noticeably lower (Table 2).

Considering the glucose metabolism characteristics of the prediabetic group, the IR and poor β-cell function were much more prevalent in this group (Table 1). Median HOMA-IR is significantly higher and median HOMA-β is significantly lower than in the healthy group (Table 2). The model for the association of IR and poor β-cell function with prediabetes demonstrated that both factors have a positive correlation with prediabetes (Table 4). Interestingly, IR is associated independently from age and sex, while β-cell function had a decreased effect on prediabetes after adjustment (Table 4). Nevertheless, in this study population, the impaired β-cell function serves as the stronger predictor for prediabetes than IR. The general model used to describe all possible risk factors for prediabetes showed that waist circumference, age, systolic blood pressure, IR, and poor β-cell function are strong predictors of prediabetes in this study population.

When the group was subdivided by HOMA values (Table 3), 21% of the prediabetic population showed neither IR nor poor β-cell function. These individuals could be considered to have the lowest risk of progressing to T2DM. The possible explanation for this finding could be using a lower threshold according to ADA criteria to diagnose prediabetes. On average, individuals who are identified as having prediabetes according to the ADA criteria are less likely to develop T2DM and CVD compared to those diagnosed by WHO criteria (Ford et al., 2010).

Among the three subgroups, the individuals from the IR group had the highest mean and median insulin levels. In the presence of IR, pancreatic β-cells respond by increasing the production and release of insulin to overcome cellular resistance and compensate for the deficiency of insulin (Gołacki et al., 2022). However, none of the factors, including CVR factors, showed a significant

association with IR, so the model cannot be used for predicting IR in the study group. Still, prediabetes is independently positively correlated with IR.

Regarding the subgroup with isolated poor β-cell function, participants from this group had the lowest mean and median insulin levels, the oldest age, the highest systolic and diastolic pressure, and the characteristics of dyslipidemia (Table 3). Prediabetes is positively correlated with impaired β-cell function. Age and total cholesterol levels have been found to be positively associated with poor β-cell function within the prediabetes population. The model suggests that with each year the risk of having an insufficient function of β-cell increases by 6%. Earlier findings revealed that insulin secretion reduces with age even in a nondiabetic population (Iozzo et al., 1999). Pancreatic islet studies have also shown that insulin secretion dynamics declined with age (Westacott et al., 2017). The accumulation of cholesterol has been shown to affect the deterioration of β-cell function (Perego et al., 2019). High cholesterol levels induce oxidative stress on the cells and further activation of phosphorylated-p38 mitogen-activated protein kinase signaling, which provokes β-cell apoptosis (Lu et al., 2011). Furthermore, Chin et al. (2021) have demonstrated that the overall pancreatic fat content is negatively associated negatively with the β-cell function.

This study has several limitations. Firstly, the study is based on data from a small, selected population, so further validation is required in a larger sample size to check if the results could be generalized. Secondly, the cross-sectional design of the study limits the ability to make a causal interference from the correlations observed, although earlier studies have demonstrated a significant association of IR, poor β-cell function, and CVR factors with prediabetes. There are no standardized values for IR or beta-cell deficit; having selected other values, results of this work may have been different. Regardless of these limitations, this study is among the first which attempted to identify the characteristics and risk factors of the prediabetes population in Kazakhstan, as well as used the preliminary approach to stratify and analyse the prediabetes population based on HOMA indices. Further research is needed to be done to evaluate the incidence of T2DM in this study group after several years and check whether the approach used in this study could be applied in future studies.

To conclude, this study has revealed that IR and impaired β-cell function are associated with prediabetes. Waist circumference, age, systolic blood pressure, IR, and poor function of β-cell could be used to predict prediabetes in this study population. Prediabetes is positively associated with IR and poor β-cell function. Though the study has not identified the model for IR risk factors among the prediabetes population, the study has revealed that age and total cholesterol levels could be used to predict poor β-cell function in prediabetic individuals of the study group.

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