Prevalence of prediabetes and risk factors in the general adult population of Croatia - EH-UH 2 study

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Abstract:

Introduction: Prediabetes is a state of elevated blood glucose, but not high enough to be classified as diabetes. The prevalence depends on the criteria used in the definition of prediabetes and on the observed populations. Known risk factors are obesity, age ≥ 45 years, positive family history of type 2 diabetes, insufficient physical activity, arterial hypertension, dyslipidaemia, and positive smoking status. The aim of our study was to determine the prevalence of prediabetes in a randomized, representative sample of the adult population of the Republic of Croatia and to determine the association and predictability of risk factors.

Materials and methods: Out of 1219 adult participants who were involved in the scientific research project EHUH-2, 687 met the final criteria. All participants underwent clinical examination. Personal and family history were obtained from the collected data in the questionnaire. The participants were instructed to fast for 12 hours before the blood draw and were given detailed instructions on collecting a 24-hour urine sample. According to the ADA criteria, prediabetes is defined as a fasting glucose value between 5.6, and 6.9 mmol/L.

Results: The prevalence of prediabetes in our sample was 11.1%. Predictive factors for prediabetes were older age, male gender, higher body weight, higher body mass index, larger waist circumference, higher systolic and diastolic blood pressure, larger body surface area, a higher percentage of visceral fat, decreased glomerular filtration rate, higher serum uric acid levels, and greater albuminuria (ACR). The final hierarchical regression model, which included body mass index, systolic and diastolic blood pressure, waist circumference, age, gender, eGFR, information on smoking, albuminuria, and urate, was statistically significant (p < ; 0.001; Nagelkerke R2=0,272).

Conclusion: Our study is the first in which the prevalence of prediabetes and its association with risk factors were determined in a representative randomized sample of the general adult population of Croatia. While further research is needed, our results shows that in the presence of multiple risk factors for prediabetes, the focus should be on age, systolic blood pressure, and albuminuria as the main predictive factors of prediabetes, especially in individuals with visceral obesity.

Keywords: prediabetes, prevalence, predictors, hierarchical regression analysis

Sažetak:

Prevalencija predijabetesa i čimbenici rizika u općoj odrasloj populaciji Hrvatske - EH-UH 2 studija

Uvod: Predijabetes je stanje povišene razine glukoze u krvi, ali nedovoljno visoke da se klasificira kao dijabetes. Učestalost ovisi o kriterijima koji se koriste u definiciji predijabetesa i promatranim populaci-

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jama. Poznati faktori rizika su pretilost, dob ≥ 45 godina, pozitivna obiteljska anamneza dijabetesa tipa 2, nedovoljna tjelesna aktivnost, arterijska hipertenzija, dislipidemija i pušenje. Cilj ovoga istraživanja bio je odrediti učestalost predijabetesa u randomiziranome, reprezentativnom uzorku odrasle populacije Republike Hrvatske te utvrditi povezanost i prediktivnost faktora rizika.
Materijali i metode: U znanstveno istraživačkome projektu EHUH-2 sudjelovalo je 1219 odraslih sudionika, od kojih je 687 ispunjavalo konačne kriterije. Svi sudionici su prošli klinički pregled. Osobna i obiteljska anamneza dobiveni su iz prikupljenih podataka u upitniku. Ispitanici su bili upućeni da budu 12 sati natašte prije pregleda na kojem je izvršeno vađenje krvi, te gdje su dobili detaljne upute kako skupiti 24-satnu mokraću. Prema kriterijima Američke udruge za dijabetes (ADA), predijabetes se definira kao vrijednost glukoze natašte između 5,6 i 6,9 mmol/L.
Rezultati: Prevalencija predijabetesa u našem uzorku iznosila je 11,1%. Prediktivni faktori za predijabetes uključuju stariju dob, muški spol, veću tjelesnu težinu, veći indeks tjelesne mase, veći opseg struka, viši sistolički i dijastolički arterijski tlak, veću površinu tijela, veći postotak visceralne masti, smanjenu glomerularnu filtraciju, višu razinu serumske mokraćne kiseline te veću albuminuriju (ACR). Završni hijerarhijski regresijski model u koji su ušli indeks tjelesne mase, sistolički i dijastolički arterijski tlak, opseg struka, dob, spol, eGFR, podatak o pušenju, albuminurija i urati bio je statistički značajan ($p < 0,001$; Nagelkerke $R2=0,272$).
Zaključak: Naša studija je prvo istraživanje na reprezentativnome randomiziranom uzorku opće odrasle populacije Hrvatske u kojem je određena učestalost predijabetesa i njegova povezanost s faktorima rizika. Iako su potrebna daljnja istraživanja, naš model ima kliničke implikacije jer pokazuje da u prisutnosti više faktora rizika za predijabetes, treba obratiti pozornost na dob, sistolički arterijski tlak i albuminuriju kao glavne prediktivne faktore predijabetesa, posebno kod osoba s visceralnom pretilošću.

Ključne riječi: predijabetes, prevalencija, prediktori, hijerarhijska regresijska analiza

Introduction

Prediabetes is a metabolic disorder characterized by impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) that can potentially progress to type 2 diabetes. It is described as a state of elevated blood glucose, but not high enough to be classified as diabetes (1). Currently, there is no consensus among international societies and associations on the lower limit of blood glucose as a diagnostic criterion for the onset of prediabetes, which explains the differences in the prevalence of prediabetes obtained in various studies and populations (Figure 1) (2). According to the World Health Organization (WHO), prediabetes is defined as a fasting plasma glucose (FPG) level of 6.1 to 6.9 mmol/L (IFG) or a blood glucose level after an oral glucose tolerance test (OGTT) of 7.8 to 11.0 mmol/L (IGT) (3). The latest guidelines from the American Diabetes Association (ADA) define prediabetes as an FPG between 5.6 and 6.9 mmol/L (IFG), OGTT between 7.8 and 11.0 mmol/L (IGT), or glycated haemoglobin (HbA1c) levels that must be between 5.7% and 6.4% (1). In 2021, the number of adults with prediabetes or IGT worldwide was estimated at 541 million people (10.6%) (Figure 2A), with the assumption that this number will increase to 730 million (11.4%) by 2045 (4). The number of adults with IFG was 319 million (6.2%) (Figure 2B), and it is predicted to increase to 441 million (6.9%) by 2045 (4). In 2019, the number of adults over 18 with prediabetes in the United States was 96 million (38%), and only 19% of them were informed of this by a healthcare provider (5). According to a study conducted in Croatia that included 5092 participants, 17.3% had prediabetes using HbA1c criteria (6). In a study conducted in 2008 using WHO-IFG criteria, the prevalence of prediabetes was 11.3% (7). The prevalence of prediabetes in other European countries varies from country to country depending on the criteria used and the population included. In Italy, the prevalence was 39.9% (ADA-IFG criteria) or 16.4% (WHO-IFG criteria), in the Czech Republic it was 27.8% (ADA-HbA1c criteria), in Slovakia 12.5%, in France 9.9% (WHO-IFG criteria), and 28.6% (ADA-IFG criteria) (8-11). In a meta-analysis from 2016 that used two criteria, the prevalence of prediabetes in Europe was 22.3% (12).

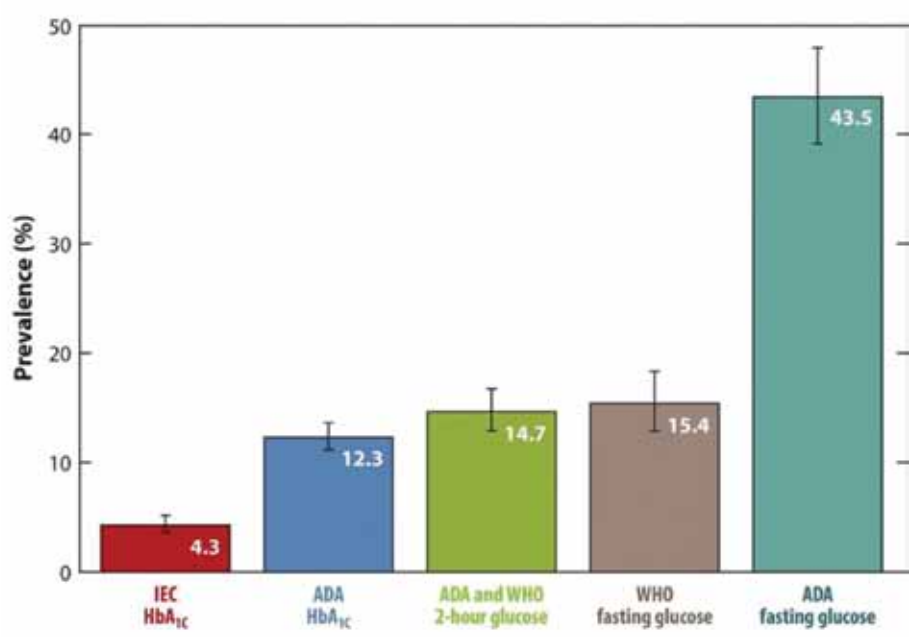

Figure 1. Prevalence of prediabetes in individuals over 20 years old in the US depending on the used definition of prediabetes (adapted from Echouffo-Tchegui, Selvin) (2); IEC: International Expert Committee; ADA: American Diabetes Association; WHO: World Health Organization.

A

B

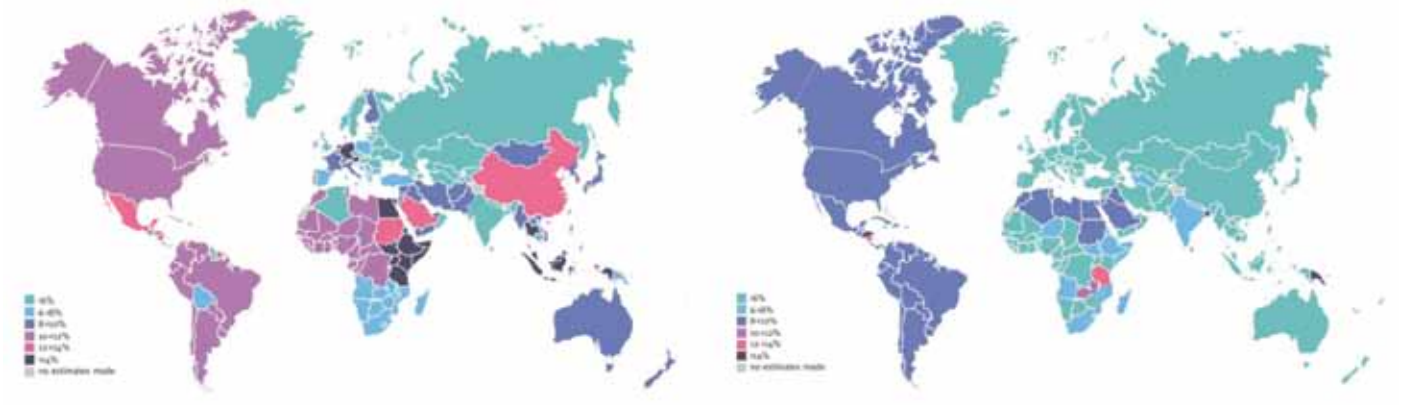

Figure 2. Prevalence of IGT (A) and prevalence of IFG (B) in adults in 2021 according to the International Diabetes Federation. IDF Diabetes Atlas, 10th Ed. Brussels, Belgium: 2021. (4)

Several mechanisms are involved in the pathophysiology of prediabetes. The fundamental disorder of homeostasis is increased insulin resistance, which can be present up to thirteen years before the diagnosis of diabetes (13-19) (Figure 3).

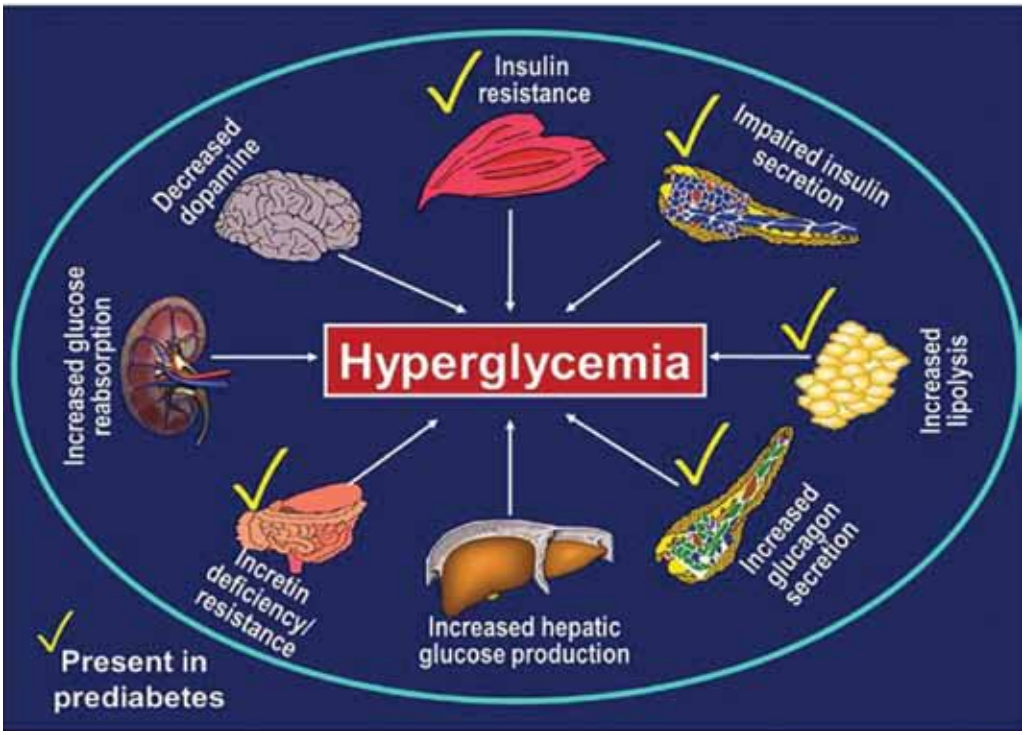

Figure 3. Pathophysiological mechanisms involved in the development of prediabetes and type 2 diabetes (From Dagogo-Jack et al.) (17)

Research has shown that prediabetes increases the risk of developing type 2 diabetes (T2D). The annual incidence of T2D development in prediabetic individuals is estimated at 5 to 10% (20-23). A 2018 meta-analysis including 103 cohort studies concluded that the risk of developing T2D is higher in prediabetic individuals compared to those with normoglycemia by 3.61 to 10.1 times, depending on the definition of prediabetes or IGT (24). Individuals with prediabetes also generally have a high prevalence of cardiovascular risk factors, leading to an increased risk of developing macrovascular complications (Figure 4) (25-28). Prediabetic individuals have an increased risk of developing cardiovascular disease and overall mortality compared to those with normoglycemia (29-31). In addition, there is evidence of a connection between prediabetes and kidney function, peripheral neuropathy, erectile dysfunction, and an increased incidence of cancer (32-38). Risk factors for prediabetes include obesity, age over 45, positive family history of T2D, physical activity less than 3 times per week, gestational diabetes in the past, and polycystic ovary syndrome (39). Risk factors also include hypertension, dyslipidemia, and positive smoking status (Figure 5) (9,25, 40). If not prevented through lifestyle changes, and in some cases treated, prediabetes can lead to various complications (Figure 6) (41).

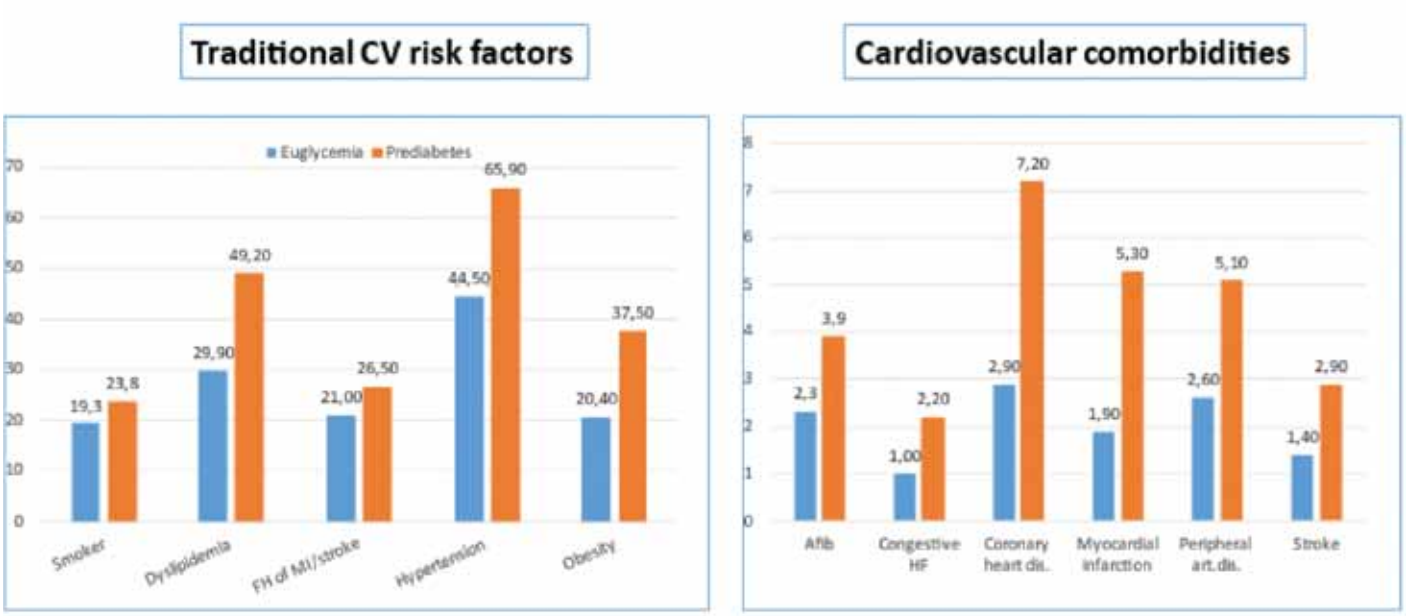

Figure 4. Frequency of cardiovascular risk factors and diseases in individuals with prediabetes; adapted from (25) Afib: atrial fibrillation, MI: myocardial infarction, HF: heart failure

Figure 5. Prediabetes risk factors; according to (25)

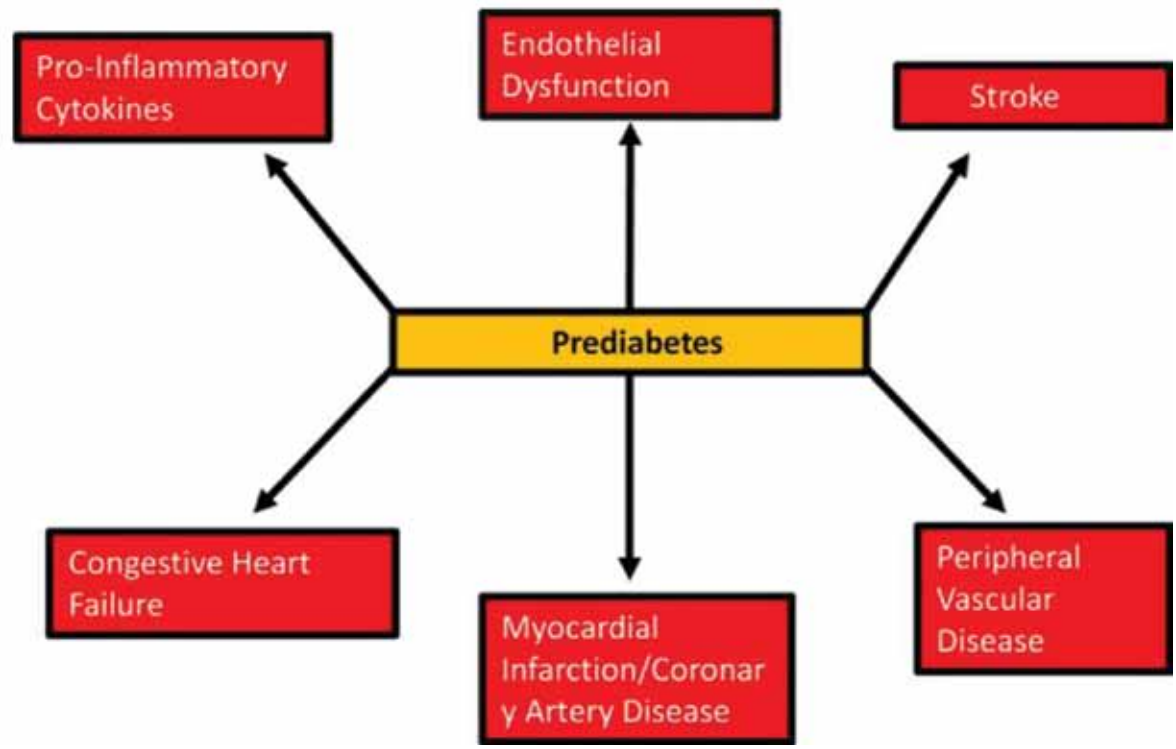

Figure 6. Macrovascular complications associated with prediabetes; from (41)

The presented data indicates a significant public health importance of prediabetes. Therefore, it is crucial to determine the prevalence of prediabetes in each specific population and analyse the risk factors and their predictivity to organize targeted screening and preventive programs. This is precisely one of the goals of the EHUH-2 project, as well as a stimulus for the preparation of this paper. This study aims to determine the prevalence of prediabetes in a randomized representative sample of the adult population of the Republic of Croatia and to analyse the predictive value of risk factors for the onset of prediabetes. The specific objectives are to compare the determined prevalence of prediabetes to the results from the literature, to analyse the characteristics of subjects with prediabetes, and to determine the association between risk factors and prediabetes and the strength of their predictive value for prediabetes.

Materials and Methods

Participants

In this cross-sectional study, 1219 adult participants were involved in the scientific research project EHUH-2. Figure 7 shows a diagram of the study, including the method of participant recruitment and group formation. All participants provided informed consent, underwent clinical examinations, and completed a large, structured questionnaire about their personal and family medical history. The clinical examinations, measurements, and tests were conducted by physicians and medical students involved in the EH-UH 2 project, who had received training to ensure standardized data collection and measurements. The study was approved by the ethics committee of the University of Zagreb School of Medicine.

Methods

All participants underwent clinical examination. Personal and family history, as well as age, were obtained from the collected data in the questionnaire. Height was measured in a standing position without shoes and expressed in centimeters, while body weight was measured using an Omron BF-511 scale without clothes and expressed in kilograms. Body mass index (BMI) was calculated as the ratio of body weight in kilograms to the square of height in meters. The percentage of body fat and muscle tissue, visceral fat, and basal metabolism were obtained by measur-

ing with the Omron BF-511 scale. In accordance with recent guidelines, arterial blood pressure (BP) was measured with an appropriate-sized Omron M6 oscillometric device. **Definitions:** Prediabetes was defined as a fasting glucose level between 5,6 and 6,9 mmol/L. Diabetes was defined as a positive history and/or antidiabetic therapy and/or fasting glucose level >7 mmol/L. Arterial hypertension (AH) was defined as a positive history and/or BP ≥ 140/90 mmHg and/or use of antihypertensive therapy. Pack years in current or former smokers were calculated as the number of cigarette packs smoked per day multiplied by the duration of smoking in years. Body surface area (BSA) was measured by the Moesteller formula using weight and height. After the measurements and completion of the questionnaire, a fasting blood sample was taken from the participants. Daily salt intake was determined from a 24-hour urine sample based on daily sodium excretion. The participants were instructed to fast for 12 hours prior to the blood draw and were given detailed instructions on how to collect a 24-hour urine sample. All laboratory analyses were performed at the central laboratory at the University Hospital Centre Zagreb. The following measurement methods were used to determine the biochemical parameters: uric acid: photometry with uricase and ascorbate oxidase standardized to ID/MS; instrument: Cobas c 501, Roche; creatinine: enzymatic with creatinine standardized to ID/MS, instrument: Cobas c 501, Roche; glucose: UV photometry with hexokinase standardized to ID/MS, instrument: Cobas c 501, Roche; cholesterol: photometry with cholesterol oxidase (CHOD-PAP) standardized to ID/MS, instrument: Cobas c 501, Roche; triglycerides: photometry with glycerol phosphate oxidase (GPO-PAP) standardized to ID/MS, instrument: Cobas c 501, Roche; HDL-cholesterol: enzymatic homogeneous with modified polyethylene glycol (PEG) and alpha-cyclodextran sulfate standardized to CDC reference method, instrument: Cobas c 501, Roche; LDL-cholesterol: homogeneous enzymatic colorimetry or calculated using Friedewald formula if triglyceride concentration is less than 4 mmol/L and chylomicrons are absent, instrument: Cobas c 501, Roche; albumin: nephelometry standardized with primary ERM DA470 calibrator and secondary Master calibrator, instrument: BN Prospec nephelometer, Siemens.

The basis for data collection is a structured questionnaire consisting of information about the researcher, basic information about the respondent, information about previous illnesses, medications, habits, information about home and outpatient visits, laboratory values, and a questionnaire for physicians. All data were entered into Microsoft Excel (Microsoft, USA), cleaned, and stored in a database. Statistical analysis was performed using SPSS v.29 (IBM Corp., USA). Adequate statistical methods were used in the data analysis. The normality of continuous variables was tested using kurtosis and skewness. Measures of central tendency used to display the variables were the mean and standard deviation, as well as the median and interquartile range. Normally distributed variables were compared using Student's t-test, and the Mann-Whitney test was used for variables with a non-normal distribution. Differences between three or more groups were tested using analysis of variance (ANOVA) and the Kruskal-Wallis test. Categorical variables will be displayed as absolute numbers and proportions. Fisher's exact $\chi 2$ test was used to compare categorical variables. Correlations were tested using Pearson's and Spearman's tests. The value of these tests' ranges from $-1 \leq r \leq +1$, where the sign (-) of the correlation indicates a negative (inverse) correlation, while the sign (+) indicates a positive correlation. The higher the correlation value, the more significant the correlation between variables. The associations of multiple independent variables with a single dependent continuous variable were examined using linear regression, and logistic regression was used for categorical variables. The effect size in logistic regression was the odds ratio (OR) with a 95% confidence interval (95% CI). Hosmer-Lemeshow's test was used as a measure of goodness-of-fit, and the regression coefficient was used as a measure of predictiveness. Hierarchical regression analysis was used to develop predictive models. Nagelkerke's R2 was used as a measure of the proportion of explained variance in the model. Prevalence was used as an indicator of the frequency of prediabetes in the population. A significant level of p-value less than 0.05 was used.

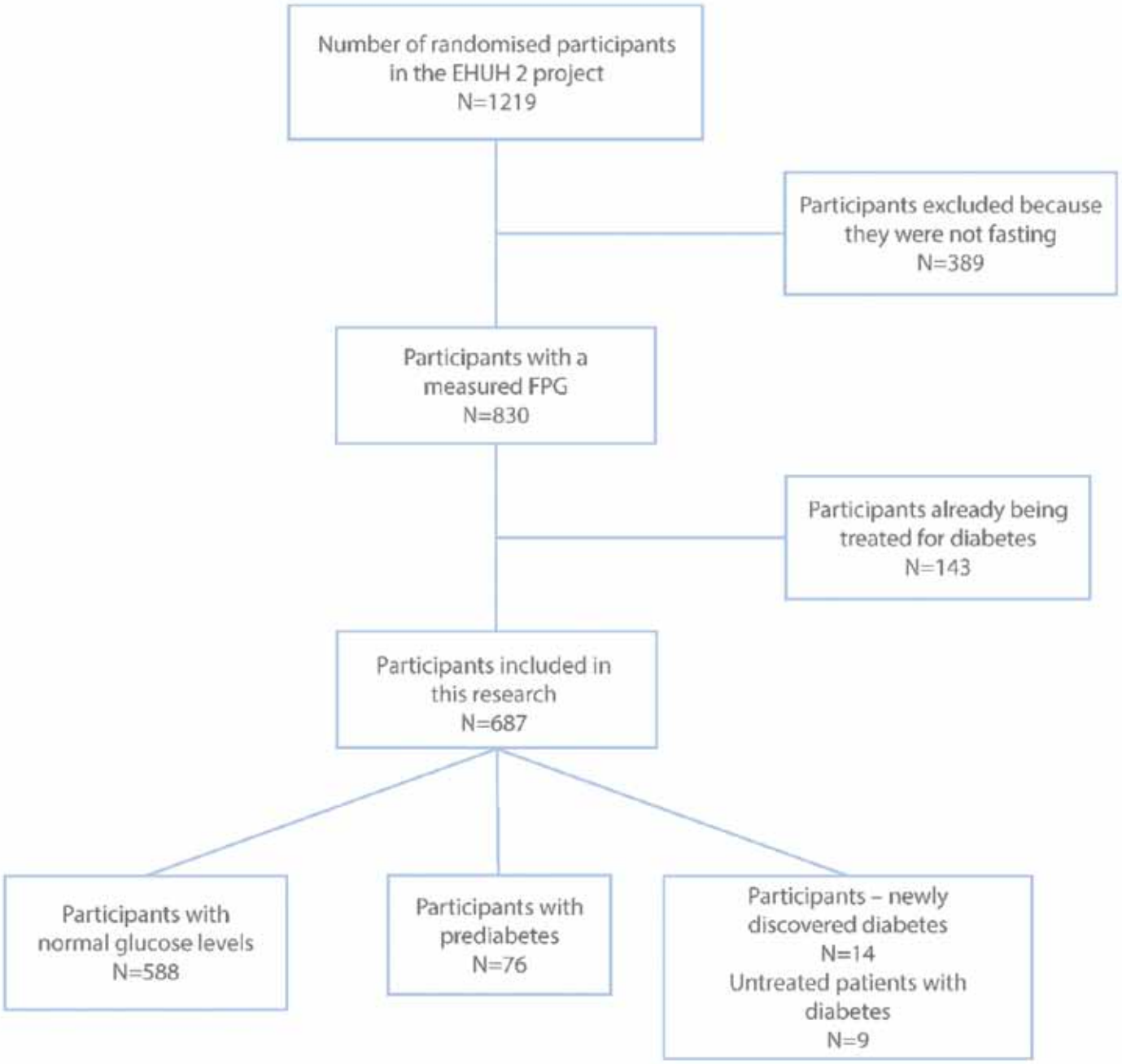

Figure 7. Flow chart showing methods of inclusion, exclusion and the formation of groups

Results

In our group with an average age of 56 ± 15 years, 33.9% were men. The prevalence of prediabetes was 11.1%. The prevalence was significantly higher in men than in women (15% vs. 9%; p < 0,001) (Figure 8). The characteristics of the participants classified by sex are shown in Supplementary Tables 1 and 2. Table 1 shows the characteristics of the participants classified based on their fasting blood glucose levels. Table 2 shows the results of Spearman's correlation between predictor variables and prediabetes status. Results of the univariate-binary logistic regression analysis are shown in table 3. Table 4 shows nine models of hierarchical regression analysis. Variables were entered into the hierarchical model in the order shown in Table 4. All models were statistically significant compared to the null model.

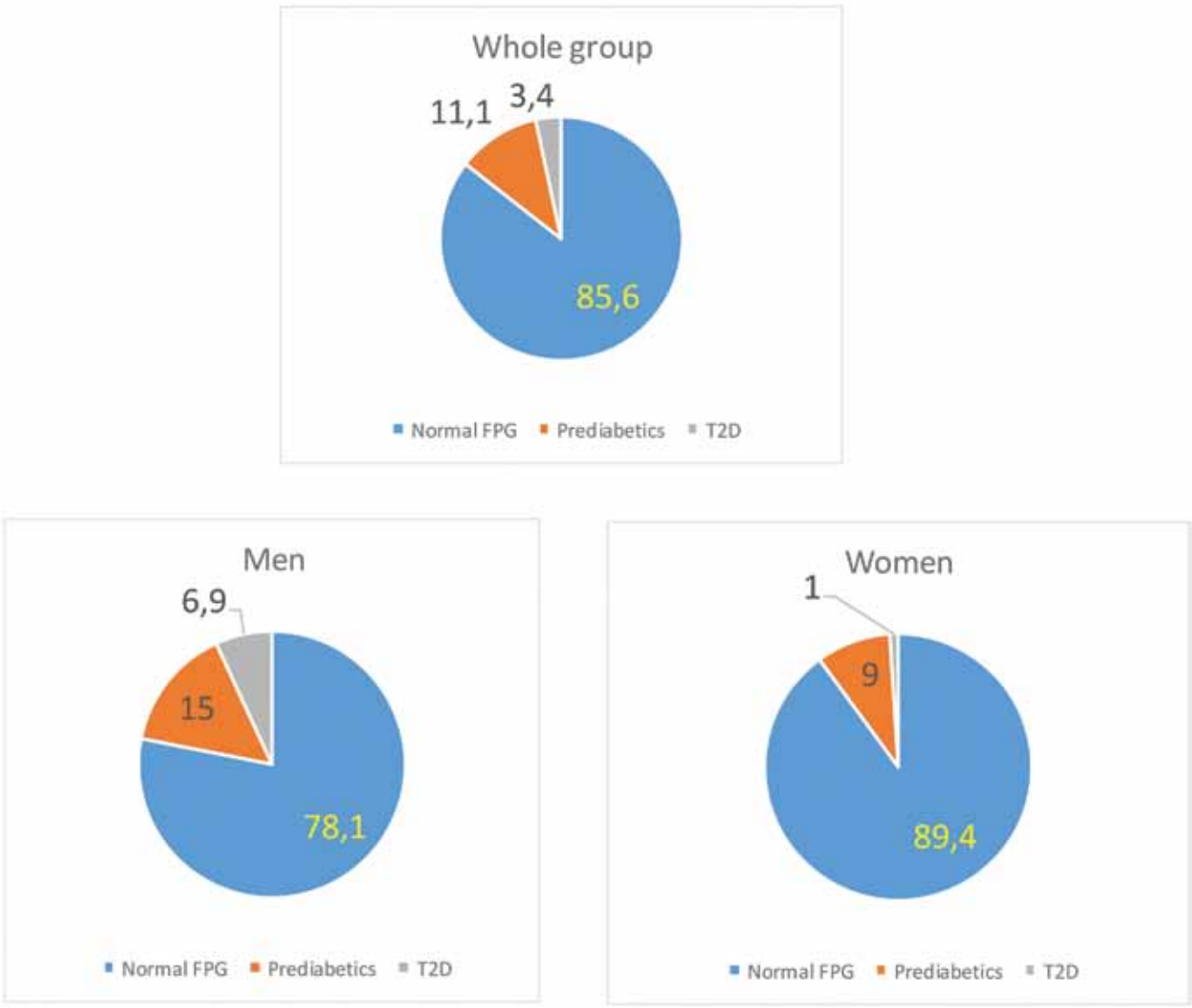

Figure 8. Prevalence of prediabetes in the whole group, and specifically in women and men; FPG: fasting plasma glucose; T2D: type 2 diabetes

Table 1. Demographic and clinical characteristics of participants classified according to FPG [1]

	Individuals with normal glucose values	Prediabetics	Untreated individuals with diabetes	p-value	Post hoc
% (n)	85,6 (588)	11,1 (76)	3,3 (23)	-	-
Men, % (n)	31 (182)	46,1 (35)	69,6 (16)	-	
Age (years)	54,51 ± 14,45	65,59 ± 10,58	66,78 ± 10,44	<0,001	a:b – p = <0,001; a:c – p = <0,001; b:c – p = 0,882
Height (cm)	166,56 ± 9,47	166,83 ± 9,20	170,26 ± 8,98	0,182	
Weight (kg)	79,11 ± 17,08	85,22 ± 13,41	85,86 ± 19,04	0,003	a:b – p = 0,012; a:c – p = 0,168; b:c – p = 0,987
BSA Moesteller (m^2)	1,90 ± 0,22	1,98 ± 0,19	2 ± 0,24	0,001	a:b – p = 0,009; a:c – p = 0,086; b:c – p = 0,924
BMI (kg/m^2)	28,34 ± 5,08	30,68 ± 4,44	28,75 ± 5,18	<0,001	a:b – p = <0,001; a:c – p = 0,931; b:c – p = 0,285
BMI categories					
BMI, <25 % (n)	28,5 (161)	6,7 (5)	9,1 (2)	<0,001	a:b – p = <0,001; a:c – p = 0,048; b:c – p = 0,405
BMI, 25 – 30 % (n)	35,9 (203)	45,3 (34)	59,1 (13)		
BMI, >30 % (n)	35,6 (202)	48 (36)	31,8 (7)		
Waist circumference (cm)	94,19 ± 14,08	100,81 ± 13,42	109,13 ± 14,14	<0,001	a:b – p = 0,002; a:c – p = <0,001; b:c – p = 0,117
SBP (mmHg)	131,49 ± 17,08	143,79 ± 18,2	143,13 ± 25,63	<0,001	a:b – p < 0,001; a:c – p = 0,100; b:c – p = 1,000
DBP (mmHg)	82,43 ± 9,69	85,76 ± 11,79	83,44 ± 13,95	0,026	a:b – p = 0,054; a:c – p = 0,937; b:c – p = 0,751
HR (bpm)	73,48 ± 10,8	74,71 ± 13,23	75,88 ± 10,8	0,424	
Body fat (%)	36,27 ± 9,46	37,27 ± 10,45	34,69 ± 12,37	0,587	
Muscle mass (%)	26,6 (23,8 – 30,5)	26,2 (23,2 – 31,3)	30 (23,4 – 32,9)	0,507	
BMR (kkcal)	1573,42 ± 248,53	1642,34 ± 212,95	1752 ± 223,31	0,003	a:b – p = 0,105; a:c – p = 0,021; b:c – p = 0,292
Visceral fat (%)	10,29 ± 4,41	13,86 ± 4,71	14,47 ± 3,29	<0,001	a:b – p = <0,001; a:c – p = 0,002; b:c – p = 0,892
Serum creatinine (umol/L)	70 (62 – 81)	76,5 (65,5 – 84,5)	86 (78 – 100)	<0,001	a:b – p = 0,011; a:c – p = <0,001; b:c – p = 0,009
CKD Epi (ml/min/1,73 m^2)	90,13 ± 17,69	80,36 ± 16,32	71,63 ± 25,7	<0,001	a:b – p = <0,001; a:c – p = 0,006; b:c – p = 0,289
CKD Mi (ml/min)	98,66 ± 22,86	94,22 ± 22	85,83 ± 34,51	0,024	a:b – p = 0,285; a:c – p = 0,250; b:c – p = 0,569
Urate levels (mmol/L)	282,68 ± 77,5	327,38 ± 75,56	356,59 ± 87,84	<0,001	a:b – p = <0,001; a:c – p = <0,001; b:c – p = 0,300
Total cholesterol (mmol/L)	5,3 ± 1,08	5,38 ± 1,32	5,3 ± 1,41	0,847	
Triglyceride (mmol/L)	1,19 (0,86 – 1,65)	1,25 (0,98 – 1,84)	1,34 (1,07 – 1,8)	0,05	a:b – p = 0,045; a:c – p = 0,127; b:c – p = 0,698
HDL cholesterol (mmol/L)	1,49 ± 0,39	1,45 ± 0,38	1,31 ± 0,5	0,088	
LDL cholesterol (mmol/L)	3,22 ± 0,99	3,28 ± 1,22	3,16 ± 1,19	0,847	
Sodium/potassium ratio	3,35 ± 1,32	3,12 ± 1,41	4,30 ± 1,51	0,002	a:b – p = 0,391; a:c – p = 0,006; b:c – p = 0,002
Daily salt intake (grams)	9,74 ± 4,69	9,49 ± 4,46	12,46 ± 5,43	0,028	a:b – p = 0,912; a:c – p = 0,002; b:c – p = 0,038

Table 1. Characteristics of participants classified according to FPG - continuation

Duration of hypertension (years)	9 (4 – 14)	10 (5 – 17)	14 (3 – 29,5)	0,376
AH yes, % (n)	47,4 (275)	74 (54)	76,2 (16)	<0,001
CKD yes, % (n)	2,5 (14)	5,4 (4)	9,1 (2)	0,096
Smokers, % (n)	28,1 (165)	27,3 (18)	17,4 (4)	0,404
PY	12 (5 – 25)	24 (8 – 40)	50 (12,5 – 75)	<0,001
Exercise intensity				
Low, % (n)	44,9 (264)	52,6 (40)	60,9 (14)	0,032
Medium, % (n)	35,9 (211)	19,7 (15)	26,1 (6)	
I don't know, % (n)	19,2 (113)	27,6 (21)	13 (3)	

[1]Continuous variables are expressed as mean ± SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Categorical variables are presented as percentages (number).
BSA: body-surface area; BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; bpm: beats pre minute; BMR: basal metabolic rate; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration; CKD EPI Mi: CKD EPI equation adjusted for individual body surface area calculated using the Mosteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; AH: arterial hypertension; CKD: chronic kidney disease; PY: pack-years.

Table 2. Statistically significant results of Spearman correlation between predictor variables and prediabetes status[a]

Independent variable	Correlation coefficient	p-value	95% CI
Age (years)	0,253	< 0,001	0,178 – 0,325
Average personal monthly income	-0,079	0,042	-0,156 – (-0,001)
Average family monthly income	-0,082	0,034	-0,160 – (-0,004)
Pack years	0,177	0,002	0,061 – 0,289
Weight (kg)	0,147	< 0,001	0,069 – 0,224
BMI (kg/m^2)	0,163	< 0,001	0,085 – 0,240
BSA Moesteller (m^2)	0,130	< 0,001	0,051 – 0,208
Waist circumference (cm)	0,168	< 0,001	0,077 – 0,257
SBP (mmHg)	0,206	< 0,001	0,129 – 0,280
DBP (mmHg)	0,121	0,002	0,042 – 0,198
BMR (kkcal)	0,122	0,006	0,032 – 0,210
Visceral fat (%)	0,254	< 0,001	0,167 – 0,336
Serum creatinine (mmol/L)	0,099	0,011	0,021 – 0,176
CKD Epi (ml/min/1,73m^2)	-0,178	< 0,001	-0,253 – (-0,101)
Serum Urate (mmol/L)	0,183	< 0,001	0,106 – 0,258
Triglycerides (mmol/L)	0,078	0,045	0,000 – 0,155
ACR	0,114	0,006	0,031 – 0,196

BMI: body mass index; BMR: basal metabolic rate; BSA: body surface area; SBP: systolic blood pressure; DBP: diastolic blood pressure; BMR: basal metabolism rate; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; CI: confidence interval

Table 3. Univariate binary logistic regression analysis[a]

	ß	p-value	OR	95% CI
Sex	-0,644	0,009	0,525	0,324 – 0,852
Age (years)	0,062	< 0,001	1,064	1,043 – 1,085
BMI (kg/m^2)	0,088	< 0,001	1,092	1,042 – 1,144
BMI categories:				
BMI 25-30 (kg/m^2)*	1,686	< 0,001	5,393	2,062 – 14,103
BMI ≥30 (kg/m^2)*	1,,747	< 0,001	5,739	2,202 – 14,958
BSA Moesteller (m^2)	1,690	0,002	5,422	1,820 – 16,152
Waist circumference (cm)	0,035	< 0,001	1,035	1,015 – 1,056
Weight (kg)	0,020	0,004	1,020	1,006 – 1,033
BMR (kkcal)	0,001	0,036	1,001	1,000 – 1,002
Visceral fat (%)	0,158	< 0,001	1,171	1,106 – 1,239
SBP (mmHg)	0,035	< 0,001	1,035	1,022 – 1,049
DBP (mmHg)	0,033	0,007	1,034	1,009 – 1,059
SBP categories	1,385	< 0,001	3,994	2,429 – 6,565
DBP categories	0,731	0,006	2,077	1,238 – 3,484
Serum creatinine (mmol/L)	0,015	0,025	1,015	1,002 – 1,028
CKD Epi (ml/min/1,73 m^2)	-0,030	< 0,001	0,971	0,958 – 0,984
Serum urate (mmol/L)	0,007	< 0,001	1,007	1,004 – 1,010
ACR	0,002	0,037	1,002	1 – 1,003
PY	0,028	< 0,001	1,029	1,013 – 1,045
AH	1,148	< 0,001	3,152	1,823 – 5,450
Physical activity	-0,757	0,017	0,469	0,252 – 0,873
Average personal monthly income	-0,569	0,025	0,566	0,345 – 0,931

[a]Sex: male vs. female; SBP categories: <140 vs. >140; DBP categories: <90 vs. >90; Arterial hypertension: yes vs. no; Physical activity: low vs. moderate; Average personal monthly income: <3500 vs. >3500 BMI: body mass index; BSA: body surface area adjusted for individual values calculated using the Mosteller equation; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; PY: pack-years; AH: arterial hypertension; OR: odds ratio; CI: confidence interval
*In relation to BMI <25 kg/m2

Table 4. Hierarchical regression models for prediabetes prediction

		ß	p-value	OR	95% CI	p-value	Nagelkerke R^2
Model 1	BMI (kg/m2)	0,083	0,003	1,086	1,028 – 1,147	0,003	0,038
Model 2	BMI (kg/m2)	-0,031	0,526	0,970	0,882 – 1,066	< 0,001	0,073
	Waist circumference (cm)	0,054	0,005	1,056	1,017 – 1,096		
Model 3	BMI (kg/m2)	-0,001	0,979	0,999	0,907 – 1,1	< 0,001	0,199
	Waist circumference (cm)	0,035	0,072	1,036	0,997 – 1,076		
	Age (years)	0,069	< 0,001	1,072	1,044 – 1,101		
Model 4	BMI (kg/m2)	0,049	0,378	1,050	0,942 – 1,17	< 0,001	0,215
	Waist circumference (cm)	0,011	0,618	1,011	0,968 – 1,056		
	Age (years)	0,074	0,000	1,076	1,047 – 1,106		
	Sex	-0,728	0,044	0,483	0,238 – 0,979		
Model 5	BMI (kg/m2)	0,039	0,480	1,040	0,933 – 1,16	< 0,001	0,227
	Waist circumference (cm)	0,012	0,606	1,012	0,968 – 1,057		
	Age (years)	0,066	< 0,001	1,068	1,039 – 1,099		
	Sex	-0,643	0,079	0,526	0,256 – 1,078		
	SBP (mmHg)	0,016	0,079	1,016	0,998 – 1,034		
Model 6	BMI (kg/m2)	0,037	0,515	1,038	0,928 – 1,161	< 0,001	0,231
	Waist circumference (cm)	0,013	0,574	1,013	0,968 – 1,06		
	Age (years)	0,060	< 0,001	1,062	1,031 – 1,094		
	Sex	-0,677	0,068	0,508	0,245 – 1,051		
	SBP (mmHg)	0,025	0,042	1,025	1,001 – 1,05		
	DBP (mmHg)	-0,024	0,265	0,976	0,935 – 1,019		
Model 7	BMI (kg/m2)	0,036	0,529	1,037	0,926 – 1,161	< 0,001	0,232
	Waist circumference (cm)	0,013	0,568	1,013	0,968 – 1,061		
	Age (years)	0,055	0,004	1,056	1,018 – 1,096		
	Sex	-0,682	0,067	0,506	0,244 – 1,048		
	SBP (mmHg)	0,025	0,039	1,026	1,001 – 1,051		
	DBP (mmHg)	-0,024	0,285	0,977	0,935 – 1,02		
	CKD Epi (ml/min/1,73 m2)	-0,005	0,653	0,995	0,973 – 1,017		

Table 4. Hierarchical regression models for prediabetes prediction - continued

Model 8	BMI (kg/m2)	0,053	0,358	1,055	0,941 – 1,182	< 0,001	0,262
	Waist circumference (cm)	0,005	0,816	1,005	0,96 – 1,053		
	Age (years)	0,055	0,005	1,056	1,017 – 1,098		
	Sex	-0,679	0,074	0,507	0,24 – 1,068		
	SBP (mmHg)	0,026	0,038	1,027	1,001 – 1,053		
	DBP (mmHg)	-0,021	0,344	0,979	0,937 – 1,023		
	CKD Epi (ml/min/1,73 m2)	-0,007	0,567	0,993	0,971 – 1,016		
	Smoking status	0,673	0,079	1,960	0,924 – 4,156		
	ACR	0,003	0,043	1,003	1 – 1,005		
Model 9	BMI (kg/m2)	0,034	0,564	1,035	0,921 – 1,163	< 0,001	0,272
	Waist circumference (cm)	0,006	0,811	1,006	0,961 – 1,053		
	Age (years)	0,058	0,003	1,059	1,02 – 1,101		
	Sex	-0,484	0,229	0,616	0,28 – 1,356		
	SBP (mmHg)	0,027	0,034	1,027	1,002 – 1,053		
	DBP (mmHg)	-0,023	0,295	0,977	0,936 – 1,02		
	CKD Epi (ml/min/1,73 m2)	0,002	0,900	1,002	0,977 – 1,027		
	Smoking status	0,691	0,073	1,995	0,937 – 4,246		
	ACR	0,003	0,042	1,003	1 – 1,005		
	Serum urate (mmol/L)	0,004	0,119	1,004	0,999 – 1,009		

[a]BMI: body mass index; SBP: systolic blood pressure; DBP: diastolic blood pressure; CKD EPI: Chronic kidney disease epidemiology collaboration; ACR: albumin-to-creatinine ratio; OR: odds ratio; CI: confidence interval

Discussion

This is the first prevalence study of prediabetes and its association with risk factors in a randomized sample of the general adult population in Croatia. The obtained data on the high prevalence of prediabetes and its significant association with several important risk factors indicate the need for prediabetes screening, especially in the part of the population with a high risk of prediabetes, and the necessity of systematic and permanent education of the population about the importance of changing bad lifestyle habits. The prevalence of prediabetes in our study was 11.1%, while the estimate for the entire world in the IDF Atlas was 6.2%, and for Croatia, it was 7.1% (4,42). This difference is likely due to the use of different criteria for diagnosing prediabetes, in addition to the differences in the characteristics of the populations included in the studies. In our study, we used the definition of prediabetes as a fasting blood glucose level between 5.6 and 6.9 mmol/L (IFG-ADA criteria), while the IDF Atlas used the WHO definition of fasting glucose levels between 6.1 and 6.9 mmol/L (IFG-WHO criteria). From studies that used only the IFG-ADA criteria, the prevalence of prediabetes was 12.5% in Slovakia, which is consistent with our results, while the prevalence was significantly higher in France (28.6%) and Italy (39.9%) (8, 10, 11). When comparing the prevalence of prediabetes of 11.1% obtained for our population with the results obtained in other countries that used IFG-WHO criteria, our results are in line with those obtained in France (9.9%), lower than the results obtained in Italy (16.4%), and higher than the results obtained in Hungary (4.4%) (8, 11, 43). Our results are consistent with previous reports for Croatia (11.3%) when the same criteria were used, but the prevalence is lower when compared to the data based on the criterion that includes HbA1C (17.3%) (6, 7). However, in addition to the differences in the criteria used, the higher prevalence in this other study conducted in Croatia may be explained by differences between the groups because that study did not analyse data obtained from a randomized sample of the general population, but included patients who were admitted to the emergency department or were examined by their family physicians. It is important to note that using only one of the three criteria stated by ADA or one of the two criteria stated by WHO is likely to underestimate the prevalence of prediabetes, as there are participants for whom one criterion may be negative while other criteria may be positive. This is evident from the results of a study conducted in Germany, where the prevalence of prediabetes was 33% according to the fasting glucose criterion, 16% according to the OGTT criterion, 26% according to the elevated HbA1c criterion, and when any of the three criteria were used, the prevalence was as high as 50% (44). However, it should be noted that the study only considered participants over the age of 37, which undoubtedly influenced the results, as it is well-known that the prevalence of prediabetes increases with age. Differences in the prevalence of prediabetes were also observed in a large European meta-analysis depending on the criteria used, i.e., definitions (12). The prevalence of prediabetes was 8.4% when using the IFG-WHO criterion and 11.4% when using the OGTT criterion, while the overlap was only 2.5%, which could indicate a true prevalence of around 22% (12). It is important to note that our results are also consistent with these data. A screening test must be simple, accessible, sensitive, and inexpensive because it is necessary to examine a large number of people to identify a small number of potential cases that must be subsequently confirmed with more specific diagnostic tests. In this study, we decided to use the IFG-ADA criteria, i.e., fasting glucose level, which we chose because it is very simple, accessible, and cheap. We are aware that it is not as sensitive as, for example, OGTT or HbA1C, which are, however, more demanding, and expensive for screening in the general population. To increase sensitivity, we opted for IFG-ADA rather than IFG-WHO criteria due to the wider range that includes subjects with lower fasting glucose values. This sample of the general adult population in Croatia, with older average age, a high frequency of hypertension, dyslipidemia, smokers, and obesity, is at high risk for developing prediabetes. The average BMI in prediabetics was 30.68 kg/m2, and only 6.7% of prediabetics had a BMI < 25 kg/m^2. Similar characteristics of prediabetics are described in various studies, such as those from Romania and Spain (45, 46). Using univariate binary logistic regression analysis, we examined the association of various risk factors with prediabetes status. Age, body weight, BMI, waist circumference, and hypertension were risk factors that showed a statistically significant positive correlation with prediabetes in our study. These are risk factors that have also been shown to be significant in other studies (40). The Czech cross-sectional study from 2014 and the German KORA (Cooperative Health Research in the Region of Augsburg) study also showed statistical significance for age, BMI, and waist circumference (9, 44), while SBP and DBP were not measured. Gender in the Czech study was not significant, while it showed a statistically significant effect on prediabetes in the German study. Our analysis also found that hypertension has a statistically significant effect on prediabetes, which has been shown in many studies (9, 40, 44, 47). All of the aforementioned risk factors, except waist circumference, are considered general risk factors for cardiovascular diseases and are included as such in numerous cardiovascular risk calculators. Thus, our study confirms that prediabetes, type 2 diabetes, and cardiovascular diseases share many similar risk factors that are crucial in the pathophysiology of these diseases. The American cross-sectional study conducted on a sample of MESA (Multi-Ethnic Study of Atherosclerosis) in 2015 showed that individuals with prediabetes in a population without previously known cardiovascular disease have a higher chance of developing unrecognized myocardial infarction, even after adjusting for multiple risk factors (48). Among other risk factors, BSA Moesteller and personal monthly income stood out.

BSA Moesteller shows a positive correlation with prediabetes, which is consistent with a study conducted in Finland in 2019 (49). In our study, as well as in the study from the Netherlands, low-income levels showed a positive correlation with prediabetes, but additional research in that direction is needed due to a lack of data on the impact of socioeconomic factors on prediabetes (50). According to a German study, low or no physical activity positively correlates with prediabetes, which was also significant in our study (44). Based on our results, we recommend increased focus by physicians in everyday clinical practice on reducing BMI and promoting increased physical activity as the main universal methods for preventing prediabetes. Furthermore, using hierarchical regression analysis, we developed predictive models of prediabetes. The final hierarchical model (model 9 in Table 4) was statistically significant with a predictive power of 27.2%. The model included 10 potential predictive factors of prediabetes, of which age and SBP were statistically the most significant. Due to a lack of similar hierarchical regression models for predicting prediabetes in the literature, we could not compare our final model. Our model has clinical implications because it shows that in the presence of multiple risk factors for prediabetes, the focus should be on age, SBP, and ACR as the main predictive factors of prediabetes, especially in individuals with visceral obesity.

Limitations and strengths of this study

Our research, like any other, has certain limitations: (i) we used only one criterion, fasting blood glucose, which may lead to an underestimation of the actual prevalence of prediabetes in the general population. However, in numerous other epidemiological studies, it was not possible to use more demanding or expensive tests, so our results can be compared with others, and the ADA states that all three methods are satisfactory for screening for prediabetes and diabetes; (ii) blood glucose measurement was done only once and not in two separate instances, but this is also the case in the majority of conducted cross-sectional epidemiological studies; (iii) this is a cross-sectional study, and therefore, we could not establish a causal relationship between observed risk factors and prediabetes, and there is a possibility of the influence of unknown risk factors.

Our research has several important and valuable strengths: (i) the prevalence of prediabetes and its association with risk factors were determined in a relatively large representative randomized sample of the general adult population of Croatia. This is the first such study conducted in Croatia and will be of great public health benefit; (ii) laboratory processing was done in one laboratory, so the possibility of inter-laboratory variability was excluded; (iii) blood glucose was determined only in participants who were fasting, as those who had eaten 12 hours before the examination were excluded, which reduces the probability of false-positive results; (iv) all anthropometric measurements were done uniformly following recent guidelines, and we also used a bioimpedance scale; (v) all demographic and clinical data were collected not only by self-reporting of participants but also by analysing medical records of family medicine physicians, so the possibility of recall bias was excluded; (vi) by using a simple, accessible, and inexpensive test, fasting blood glucose, we determined the most important predictors of prediabetes, which indicates subpopulations where it is necessary to conduct screening tests using more expensive and demanding methods, but it is also important in planning targeted education.

In conclusion, our research findings provide valuable insights into the prevalence and predictive factors of prediabetes in the Republic of Croatia. We observed an overall prevalence of 11.1%, which aligns with existing literature on the subject. Additionally, our study revealed a higher prevalence of prediabetes in men compared to women (15% vs. 9%). The identified predictive factors for prediabetes include older age, male gender, higher body weight, higher body mass index, longer waist circumference, high blood pressure, larger body surface area, a higher percentage of visceral fat percentage, decreased glomerular filtration rate, higher uric acid levels and greater albuminuria (ACR). Hypertension, smoking history, decreased physical activity, and lower personal monthly income are also associated with an increased risk of developing prediabetes. Furthermore, our final hierarchical multivariate regression model demonstrated that older age, systolic blood pressure, and albuminuria (ACR) were the most significant predictors of prediabetes, accounting for 27.2% of the predictive power. Overall, these findings emphasize the importance of early detection and intervention strategies targeting individuals with specific risk factors, such as older age, elevated blood pressure, and albuminuria (ACR), to effectively address the growing burden of prediabetes in the population. Future research and public health initiatives should consider these factors to develop targeted interventions and preventive measures to mitigate the progression of prediabetes to type 2 diabetes.

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Conflict of Interest

None.

Supplementary Materials

Table 1S. Clinical characteristics of participants categorized by sex[a]

	Whole group	Men	Women	p-value
%, (n)	100 (687)	33,9 (233)	66,1 (454)	-
(S) Glucose (mmol/L)	4,7 (4,3 – 5,2)	4,8 (4,4 – 5,4)	4,6 (4,2 – 5,1)	< 0,001
(S) Glucose categories				
Individuals with normal glucose levels	85,6 (588)	78,1 (182)	89,4 (406)	< 0,001
Prediabetics	11,1 (76)	15 (35)	9 (41)	
Untreated individuals with diabetes	3,4 (23)	6,9 (16)	1,5 (7)	
Age (years)	56,15 ± 14,51	56,75 ± 14,4	55,84 ± 14,57	0,719
Height (cm)	166,72 ± 9,44	175,28 ± 7,38	162,29 ± 7,03	< 0,001
Weight (kg)	80,04 ± 16,9	90,09 ± 16,46	74,87 ± 14,65	< 0,001
BMI (kg/m^2)	28,61 ± 5,07	29,09 ± 4,3	28,37 ± 5,41	0,036
BMI <25, % (n)	25,3 (168)	16,4 (37)	30 (131)	
BMI 25-30, % (n)	37,7 (250)	42,5 (96)	35,2 (154)	< 0,001
BMI ≥30, % (n)	37 (245)	41,2 (93)	34,8 (152)	
BSA Moesteller (m^2)	1,91 ± 0,22	2,08 ± 0,18	1,83 ± 0,19	< 0,001
Waist circumference (cm)	95,53 ± 14,35	101,92 ± 12,03	92,3 ± 14,37	< 0,001
Body fat (%)	36,35 ± 9,67	28,18 ± 6,97	40,20 ± 8,28	< 0,001
Muscle mass (%)	26,6 (23,7 – 30,85)	32,1 (30 – 34,95)	24,9 (22,73 – 27,3)	< 0,001
BMR (kkcal)	1587,32 ± 245,96	1813,53 ± 198,3	1480,68 ± 187,14	< 0,001
Visceral fat (%)	10,86 ± 4,61	14,16 ± 4,96	9,31 ± 3,49	< 0,001
SBP (mmHg)	133,17 ± 17,99	137,79 ± 17,26	130,82 ± 17,92	< 0,001
DBP (mmHg)	82,83 ± 10,15	85,89 ± 10,56	81,28 ± 9,58	< 0,001
Duration of hypertension (years)	9 (4 – 15)	9 (4 – 14)	10 (4 – 15)	0,266
HR (bpm)	73,70 ± 11,09	72,65 ± 11,85	74,24 ± 10,65	0,148
PY	12 (5,25 – 30)	20 (7,25 – 38,25)	10,4 (5 – 22,5)	< 0,001
AH				
Yes, % (n)	50,5 (345)	49,6 (115)	51 (230)	0,113
No, % (n)	48,2 (329)	47,9 (111)	48,3 (218)	
Don't know, % (n)	1,3 (9)	2,6 (6)	0,7 (3)	
CKD				
Yes, % (n)	2,9 (20)	4,7 (11)	2 (9)	0,102
No, % (n)	93,3 (637)	92,2 (214)	93,8 (423)	
Don't know, % (n)	3,8 (26)	3 (7)	4,2 (19)	

Table 1S. Clinical characteristics of participants categorized by sex - continued

Smoking status				
Never, % (n)	55,9 (384)	46,4 (108)	60,8 (276)	0,797
Ex smoker, % (n)	16,9 (116)	27 (63)	11,7 (53)	
Smoker, % (n)	27,2 (187)	26,6 (62)	27,5 (125)	
Exercise intensity				
Low, % (n)	46,3 (318)	41,2 (96)	48,9 (222)	
Medium, % (n)	33,8 (232)	42,9 (100)	29,1 (132)	0,001
High, % (n)	0 (0)	0 (0)	0 (0)	
Don't know, % (n)	19,9 (137)	15,9 (37)	22 (100)	

[a]Continuous variables are expressed as mean ± SD for normally distributed variables and as median and interquartile range for non-normally distributed variables. Categorical variables are expressed as percentages (number). BMI: body mass index; BSA: body surface area; SBP: systolic arterial pressure; BMR: basal metabolic rate; SBP: diastolic arterial pressure; HR: heart rate; bpm: beats per minute PY: pack-years; AH: arterial hypertension; CKD: chronic kidney disease

Table 2S. Laboratory characteristics of participants classified by sex[a]

	Whole group	Men	Women	p-value
Serum creatinine (mmol/L)	71 (63 – 82)	83 (76 – 91)	66 (60 – 74)	< 0,001
CKD Epi (ml/min/1,73 m^2)	88,43 ± 18,36	88,02 ± 18,03	88,64 ± 18,55	0,871
CKD Mi (ml/min/1,73 m^2)	97,74 ± 23,34	105,84 ± 24,56	93,48 ± 21,52	< 0,001
Serum urate (mmol/L)	290,01 ± 79,7	338,99 ± 72,76	264,81 ± 70,97	< 0,001
Total cholesterol (mmol/L)	5,31 ± 1,12	5,24 ± 1,2	5,35 ± 1,08	0,172
Triglycerides (mmol/L)	1,2 (0,88 – 1,68)	1,27 (0,93 – 1,83)	1,17 (0,87 – 1,6)	0,004
HDL cholesterol (mmol/L)	1,48 ± 0,39	1,33 ± 0,39	1,55 ± 0,37	< 0,001
LDL cholesterol (mmol/L)	3,22 ± 1,02	3,20 ± 1,06	3,24 ± 1	0,506
Sodium/potassium ratio	3,35 ± 1,35	3,62 ± 1,49	3,22 ± 1,25	0,002
Daily salt intake (grams)	9,8 ± 4,71	11,37 ± 5,18	8,98 ± 4,23	< 0,001
ACR	16,69 (7,3 – 39,64)	14,5 (6,02 – 35,4)	18,17 (8,11 – 38,82)	0,018

[a]Values of continuous variables are expressed as mean ± SD in case of normally distributed variables, and as median and interquartile range in case of non-normally distributed variables. CKD EPI: Chronic kidney disease epidemiology collaboration; CKD Mi: CKD-EPI equation adjusted for individual body surface area values calculated using the Mosteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; ACR: albumin-to-creatinine ratio

Table 3S. Statistically non-significant results of Spearman's correlation between predictor variables and prediabetes status (p > 0.05)[a]

Independent variable	Correlation coefficient	p-value	95% CI
Education	-0,038	0,324	-0,116 – 0,040
Professional qualification	-0,058	0,138	-0,135 – 0,021
Duration of hypertension	0,044	0,428	-0,068 – 0,155
Height (cm)	0,006	0,878	-0,073 – 0,085
HR (bpm)	0,031	0,436	-0,049 – 0,110
Body fat (%)	0,034	0,446	-0,056 – 0,124
Muscle mass (%)	-0,017	0,700	-0,108 – 0,073
CKD Mi (ml/min)	-0,051	0,221	-0,135 – 0,033
Total cholesterol (mmol/L)	0,000	0,996	-0,079 – 0,078
HDL cholesterol (mmol/L)	-0,036	0,355	-0,114 – 0,042
LDL cholesterol (mmol/L)	-0,009	0,813	-0,087 – 0,069
Sodium/potassium ratio	-0,076	0,054	-0,154 – (-0,004)
Daily salt intake (grams)	-0,015	0,697	-0,095 – 0,064

[a]HR: heart rate; bpm: beats per minute; CKD Mi: CKD EPI equation: adjusted for individual body surface area values calculated using the Moesteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein

Table 4S. Statistically non-significant results of univariate binary logistic regression analysis[a]

	ß	p-value	OR	95% CI
Duration of hypertension (years)	0,011	0,499	1,011	0,979 – 1,044
Height (cm)	0,003	0,816	1,003	0,978 – 1,029
HR (bpm)	0,010	0,373	1,010	0,988 – 1,032
Body fat (%)	0,011	0,430	1,011	0,984 – 1,039
Muscle mass (%)	-0,014	0,547	0,986	0,944 – 1,031
CKD Mi (ml/min)	-0,009	0,139	0,991	0,98 – 1,003
Total cholesterol (mmol/L)	0,063	0,562	1,065	0,861 – 1,318
Triglycerides (mmol/L)	0,165	0,183	1,180	0,925 – 1,504
HDL cholesterol (mmol/L)	-0,245	0,450	0,782	0,414 – 1,479
LDL cholesterol (mmol/L)	0,060	0,617	1,061	0,841 – 1,340
Sodium/potassium ratio	-0,136	0,169	0,873	0,72 – 1,059
Daily salt intake (grams)	-0,012	0,665	0,988	0,938 – 1,042
Average familiy monthly income	-0,336	0,168	0,714	0,433 – 1,153
Education	-0,366	0,172	0,693	0,410 – 1,173
Professional qualification	-0,152	0,596	0,859	0,491 – 1,504
CKD	0,803	0,167	2,233	0,715 – 6,972
Smoking status	-0,229	0,422	0,796	0,455 – 1,391

[a]Average family monthly income: <5000 vs. >5000; Education: <8 years vs. >8 years; Professional qualification: low and intermediate vs. high (high school, bachelor's, and master's degrees); CKD: yes vs. no; Smoking status: yes vs. no
HR: heart rate; bpm: beats per minute; CKD Mi: CKD EPI equation adapted for individual body surface area values calculated using Moesteller equation; HDL: high-density lipoprotein; LDL: low-density lipoprotein; CKD: chronic kidney disease